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Influencing Factors in the Survival of Dialysis Patients in El Salvador

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Content/Índice

Editorial

The importance of Regional Integration and Cooperation in the Development of Science

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Dear readers of Alerta journal, in this new issue we are pleased to present a wide range of content comprising six case reports featuring unusual and challenging clinical situations. These reports offer a detailed overview of diagnoses and treatments that can be helpful for healthcare professionals in their daily practice. Among them are: "Eisenmenger Syndrome Associated with an *ostium secundum* Atrial Septal Defect in an Adult Woman," "Mesenteric Heterotopic Ossification as a Cause of Intestinal Obstruction" and "Kartagener Syndrome and Rheumatoid Arthritis. Case Report," among others, for scientific or educational purposes. At the same time, they stimulate and open windows to conduct research studies in the future with a higher level of evidence.[i]

We present four original articles: "Factors that influence the survival of dialysis patients in El Salvador," which is highlighted on the cover, given the importance of adopting preventive and control measures in chronic kidney disease. In addition, "Somatoform Disorders and Personality Traits in Hospitalized Patients with Chronic Back Pain in El Salvador" is a relevant topic that generates evidence on healthcare in the Salvadoran Social Security Institute. Furthermore, two other articles showed novel research in diverse scientific areas, offering a unique perspective on the most recent developments in their respective disciplines.

There are included five narrative reviews with emerging topics such as "Genetic Alterations Associated with Parkinson's and Alzheimer's Disease: Evolution and Response to Treatment," related to the evolution and response to treatment; "Burnout Syndrome in Health Care Personnel During the COVID-19 Pandemic," and "Intermittent Fasting and Caloric Restriction as an Adjunctive Treatment in Alzheimer's Disease and Multiple Sclerosis," among others. These narrative reviews are based on extensive literature searches and explore specific topics from different angles, providing an overview and critical analysis of the existing literature responding to a knowledge gap. They are, therefore, valuable for those who wish to keep up to date with advances in their field of study.[ii]

Finally, I encourage you to read the three letters to the editor. One of them calls for nutritional education for parents and caregivers to promote healthy lifestyles in children. In addition another letter mentions the importance of effective communication as a contribution of linguistics applied to healthcare services; and finally, the "Regional Integration in Health in Central America and Dominican Republic: Achievents and Opportunities."

The latter is of great relevance for the editorial line of Alerta, as it is the product of the Annual Meeting of the Latin American Regional Network of the International Association of National Public Health Institutes, IANPHI/LatAm, which was held in El Salvador from October 16 to 18, 2023. The National Institutes of Public Health, homonymous to ours, play a fundamental role in the mitigation of health inequities and contribute from a scientific perspective to promote the transition to a rights-based, sustainable, and harmonized development model with policies to reduce the carbon footprint to address climate change, food insecurity, and

La importancia de la integración y la cooperación regional en el desarrollo de la ciencia

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malnutrition, as well as health emergencies at the global, regional and national levels, topics addressed at the annual meeting.[iii]

This letter examines the relevant aspects that should be included in a regional strategy that, based on the analysis of information on public health issues, will make it possible to develop a proposal to strengthen regional integration to address the main social determinants of health. At the same time, it provides a route to continue promoting relevant opportunities identified in Central American health integration. At the same time, it represents a challenge that shows that this integration would facilitate the exchange of epidemiological information, the harmonization of health policies and regulations, and access to medicines and medical supplies at better prices. In the current global context, where communicable diseases such as HIV/AIDS are a threat to public healthcare, this integration becomes even more significant and crucial to improve people's wellness since working together would bring significant progress in terms of prevention, medical care, and promotion of healthy lifestyles.[iv]

I want to highlight that the number of letters to the editor Alerta receives increases with each issue published. These letters encourage debate and discussion among our readers, which allows a dynamic exchange of ideas. It is an open space where readers have the opportunity to express their opinions on relevant topics in science, medicine, and public policy.

We hope you enjoy reading the latest edition of Alerta and find its content both informative and stimulating for the development of science. As always, we thank everyone for the continued support of this publication, an invaluable jewel for the National Institute of Health.

References

i. Pineda-Leguízamo R, Miranda-Novales G, Villasís-Keever MA. La importancia de los reportes de casos clínicos en la investigación. Rev. alerg. Méx. 2018;65(1):92-98. DOI: 10.29262/ram.v65i1.348

ii. Guirao Goris Silamani JA. Utilidad y tipos de revisión de literatura. 2015;9(2). DOI: 10.4321/S1988-348X2015000200002

iii. Instituto Nacional de Salud. El Salvador fue sede de la Reunión anual de IANPHI Latinoamérica. Instituto Nacional de Salud. 2023. Date of citation: January 21, 2024. Available at: https://ins.salud.gob.sv/el-salvador-fue-sede-de-la-reunion-anual-de-ianphi-latinoamerica/

iv. Sistema de la Integración Centroamericana. Consejo de Ministros de Salud de Centroamérica (COMISCA). Agenda de Salud de Centroamérica y República Dominicana 2019-2030. Placencia. SICA. 2018. 42 p. Available at: https://www.sica.int/busqueda/busqueda_archivo.aspx?Archivo=odoc_120455_1_22112019.pdf

Case report

Mesenteric Heterotopic Ossification as a Cause of Intestinal Obstruction in a Patient with a Septic Abdomen

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Abstract

Case presentation. A 49-year-old male, with a history of blunt abdominal trauma with a blunt object without hemodynamic alterations. The focused trauma ultrasound was positive for free fluid in the abdominal cavity in three windows. **Treatment.** The patient underwent multiple exploratory laparotomies with peritoneal lavage after presenting a septic abdomen (Björk 4), who after 38 days of intrahospital stay presented an enteroatmospheric fistula that caused a large nutritional deficit. In a surgical intervention, the enteroatmospheric fistula was closed, with the finding of trabecular bone tissue in the abdominal cavity, corresponding to intra-abdominal heterotopic ossification of recent formation. **Outcome.** After the small intestine anastomosis, he presented signs of intestinal obstruction, because of this, a new exploratory laparotomy was performed, in which bone tissue was found adhered to the mesentery of the small intestine that generated a complete obstruction. The bone material was removed and the intestinal flow was reestablished, freeing the obstruction in the small intestine.

Keywords
Ossification, Heterotopic, Mesentery, Intestinal Obstruction, Sepsis.

Resumen

Presentación del caso. Se trata de un masculino de 49 años, con historia de un trauma abdominal cerrado con un objeto contuso sin alteraciones hemodinámicas. La ecografía focalizada de traumatismos resultó positiva a líquido libre en la cavidad abdominal en tres ventanas. **Intervención terapéutica.** Fue sometido a múltiples laparotomías exploratorias con lavados de cavidad abdominal posterior a presentar un cuadro de abdomen séptico Björk 4, quien después de 38 días de estancia intrahospitalaria presentó una fístula enteroatmosférica que causaba un déficit nutricional. En una intervención quirúrgica se realizó el cierre de la fístula enteroatmosférica, con el hallazgo de tejido óseo trabecular en cavidad abdominal, correspondiente a osificación heterotópica intraabdominal de formación reciente. **Evolución clínica.** Luego de la anastomosis del intestino delgado presentó signos de obstrucción intestinal, a causa de esto, se realizó una nueva laparotomía exploratoria, en la que se encontró tejido óseo adherido al mesenterio del intestino delgado que generó una obstrucción completa, se extirpó el material óseo y se logra restablecer el flujo intestinal liberando la obstrucción en el intestino delgado.

Palabras clave
Osificación Heterotópica, Mesenterio, Obstrucción Intestinal, Sepsis.

Introduction

Heterotopic ossification is a benign process consisting of the formation of bone tissue in tissue other than the skeletal system. It is classified as an infrequent and incidental finding in most cases, that occurs most frequently as a complication of orthopedic surgery and may be observed during the healing process of midline abdominal incisions. Bone formations have been evidenced in the greater omentum, abdominal wall and rarely in the mesentery.[i]

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Osificación heterotópica mesentérica como causa de obstrucción intestinal en un paciente con abdomen séptico

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Although the mechanism of tissue formation is unclear, some authors describe it as a reactive process with an exuberant response to a traumatic or surgical stimulus. Although studies have attributed this mechanism to infectious and tumor processes, it has also been associated with genetic alterations.[ii] Other authors suggest that osteoblasts are released into the surrounding tissues when a surgical wound injures the xiphoid appendix.[iii] The presence of foreign bodies, such as non-absorbable threads, mesh, gauze, abscesses, necrotic tissue, or iodopovidone, can serve as a nidus for heterotopic ossification.[iv]

Case presentation

A 49-year-old man with no known medical history, who consulted with a history of closed abdominal trauma with a blunt object; he was hit in the hypogastrium with a metal bar. After the event, he was taken to the emergency unit of the regional hospital of San Miguel. He presented diffuse abdominal pain, without alteration in neurological status, alert, oriented, grunting, hemodynamically stable, with blood pressure of 130/95 mmHg, heart rate of 95 beats per minute and weighing of 85 kg. On physical evaluation, he presented moderate abdominal pain.

Focused assesment with sonography in trauma was positive for free fluid in the abdominal cavity in three windows.

Laboratory tests reported leukocytosis with neutrophilia and mild anemia; he underwent an emergency exploratory laparotomy. In this procedure, 2500 mL of blood were found in the abdominal cavity, a small bowel lesion with vascular compromise at the mesentery level, as well as an intestinal segment of 80 cm with ischemic changes. These changes started at 2.90 meters from the angle of Treitz, ending about 10 cm from the ileocecal valve, and a resection and confection of the terminal ileostomy was performed. The abdominal cavity was managed as an open abdomen, utilizing a Bogotá bag, with plans for a second abdominal exploration, subsequently.

After 48 hours, the patient remained stable with a blood pressure of 125/80 mmHg and a heart rate of 88 L/min. A new surgical procedure was undertaken to evaluate the cavity; the abdomen was found to be clean and free of any intestinal leaks. There was no evidence of any free liquid, and the closure was performed by layers using caliber 1 braided multifilament sutures to close the aponeurosis and nylon 1 as retention sutures. Additionally, a Penrose drain was placed. On the tenth day of the hospitalization, a culture of the abdominal cavity revealed the presence of *Escherichia coli*. The infection was promptly treated with ceftriaxone 1 g every 12 hours and metronidazole 500 mg every eight hours administered intravenously. After 13 days of hospital stay, he presented deterioration of hemodynamic status with blood pressure of 100/60 mmHg and increased heart rate up to 120 beats per minute. Also, there was evidence of leakage of intestinal material through the surgical wound, and leukocytosis with neutrophilia was reported (Table 1). Consequently, an exploratory laparotomy was performed, which confirmed a septic abdomen with leakage of intestinal material through a perforation in the small intestine of approximately 2 cm, which failed to be categorized at the space from the angle of Treitz due to the presence of a frozen abdomen; the macroscopic characteristics of the intestinal fluid generated the suspicion of localization in the ileum (Figure 1a).

After 21 days of hospitalization, the culture of the abdominal cavity was reported positive for *Pseudomonas aeruginosa*, and antimicrobial therapy was initiated with imipenem cilastatin at a dose of 500 mg intravenous every six hours for 21 days.

Treatment

The patient underwent nine exploratory laparotomies over a period of 38 days, in which cavity washouts were performed with 0.9 % saline solution with an average of four to six liters in each intervention to control the leakage of intestinal material and reduce abdominal contamination. Multiple maneuvers were attempted, such as splinting of the fistula with Foley type catheter (Figure 1b), techniques such as Rivera´s condom suture[v] (Figure 1c), and placement of a negative pressure system to avoid contamination of the abdominal cavity. In addition, he was given nutritional support with the use of total parenteral nutrition and transferred to the intensive care unit. The use of noradrenaline at a dose of 20 µg/h was necessary, with a gradual reduction of the dose as the septic focus was controlled.

After the control of the enteroatmospheric fistula (Figure 2), it was determined that the patient had a septic abdomen Björk 4,[vi] with a proximal lesion in the small intestine that generated an approximate output of 2 to 3 L per day; consequently, he presented a nutritional deterioration, with a weight loss of 25 kg, in addition to frequent episodes of dehydration with periods of hypovolemic shock that reverted with the administration of 0.9 % saline solution. For

Table 1. Sequence of laboratory tests

Laboratory test	Days								
	1	3	14	20	43	55	69	74	77
Leukocytes /mm^3	23 100	14 900	25 000	9480	12 800	13 100	12 260	15 000	8830
Neutrophils %	86 %	87 %	87 %	74 %	65 %	64 %	85 %	82 %	65 %
Hemoglobin g/dL	9.7	11	11.7	11.1	11.9	13.4	11.3	8.7	11.2
Platelets /µL	184 000	139 000	680 000	423 000	202 000	178 000	252 000	274 000	326 000
Albumin g/dL	-	2.1	3.2	2.1	3.1	3.3	3.2	2.8	2.2
Sodium meq/L	137	138	127	137	134	135	135	139	142
Potassium meq/L	5.1	3.5	4.8	4.1	3.6	4	4	3.5	3.8
Magnesium mg/dL	1.5	1.8	1.8	1.2	2	2	1.4	2	2
Calcium mg/dL	7.2	6.7	9	7.8	8.8	9.4	8.2	7.7	7.9
Chlorine meq/L	103	-	89.7	106	95.5	98.4	100	106	105
Creatinine mg/dL	1.36	1.22	1.1	1.03	0.99	1.06	0.97	0.89	0.87
Glucose mg/dL	145	120	113	125	103	88.7	157	122	107
Urea nitrogen mg/dL	18.5	18.8	25.1	24.2	34.9	35.9	13.8	25.4	11.5

Fuente: Data obtained from the clinical record.

Figure 1. A. Leakage of intestinal material. It is evident when removing the retention stitches, opening of the abdominal cavity with leakage of intestinal material and dehiscence of the aponeurosis. B. Fistula splinting with Foley catheter. C. Rivera´s condom technique

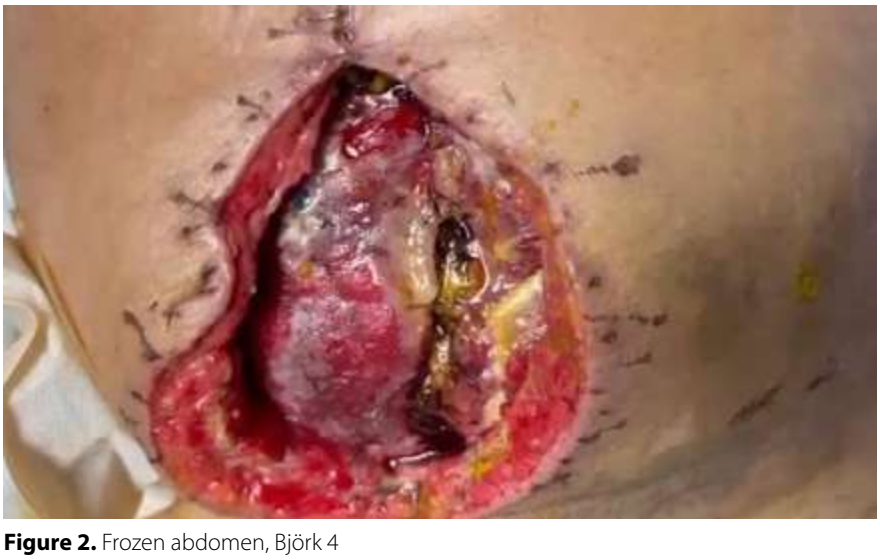

Figure 2. Frozen abdomen, Björk 4

this reason, it was decided to use octreotide at a dose of 0.1 mg subcutaneous every eight hours and loperamide 2 mg orally every eight hours.

Due to the complexity of the case, it was decided to transfer the patient to a specialized center (Medical Surgical Hospital) on the 65th day of in-hospital stay, where he was evaluated by the complex abdominal team and by the nutrition specialty of that hospital. It was decided to perform the tenth exploratory laparotomy with intestinal resection of the fistula segment (Figure 3a) and a manual small bowel anastomosis was performed. The distance from the Treitz angle was not determined because the abdomen was still partially frozen. During this intervention, while the release of the firm adhesions was being performed, a fragment of tissue was found that resembled a bone structure with trabecular appearance located between the intestinal loops and adhered to the mesentery of the terminal ileum that, when extracted, showed scarce bleeding and texture similar to cancellous bone (Figure 3b), and surgical intervention was completed by closing the abdominal wall in layers, including skin.

Forty-eight hours after the surgery, he presented intestinal obstruction, characterized by marked abdominal distention and the absence of output by terminal ileostomy. As a result, an emergency surgery was conducted. During the procedure, multiple firm adhesions were identified between small bowel loops and multiple transition zones between intestinal dilatation and segments with collapsed intestinal lumen. Additionally, a structure resembling bone tissue in the mesentery that conditioned the intestinal obstruction was found. This generated some areas of complete stenosis without passage of intestinal material through the small intestine, the integrity of the anastomosis performed in previous surgery was confirmed. In light of the findings, the adhesions were dislodged, the segmental regions of heterotopic ossification of the small bowel were extracted, and consequently, the intestinal passage was reestablished (Figure 3c).

On the 72nd day of in-hospital stay, forty-eight hours after surgery, a new surgical intervention was performed in which the abdominal cavity was evaluated, followed by definitive closure of the abdominal wall; the abdomen was found to be clean, without intestinal adhesions, without edema of the intestinal loops, with the anastomosis intact, the aponeurosis retracted and a functional ileostomy, for this reason, definitive closure of the abdominal cavity was performed (Figure 3d).

Outcome

The removal of bone tissue from a portion adjacent to the mesentery of the terminal ileum managed to reverse the obstruction, observing intestinal material outflow through the ileostomy in the transoperative period.

Ileostomy output measurements, which at the beginning was 1300 mL in 24 hours, decreased to output between 800 and 1100 mL in 24 hours after the last intervention, parenteral nutrition was suspended with adequate tolerance to the oral route.

After 75 days of intrahospital stay, the culture of the abdominal cavity was reported positive for *Morganella morganii spp*; for this reason, treatment was started

Figure 3. A. Small intestine segment. B and C. Bone fragments. D. Abdominal cavity closure

with ciprofloxacin 0.4 g intravenous every 12 hours for 14 days.

Complementary imaging and laboratory studies were performed that could be associated with heterotopic ossification. Abdomino-pelvic computed tomography on the 78th day of in-hospital stay identified bony formations adhered to the small bowel mesentery (Figure 4a). Thyroid ultrasonography described it within normal limits. Parathyroid hormone was reported at 32.5 pg/mL.

The macroscopic histopathological study recorded the finding of irregular bone fragments that together measured 8 cm. The microscopic findings corresponded to fragments of mature trabecular and medullary bone tissue, mesenchymal metaplasia composed of mature bone tissue, with no atypia or malignancy on examination (Figure 4b).

The patient had an adequate clinical evolution, with adequate tolerance to the oral route, the abdomen was soft and depressible, functional ileostomy with peristalsis present and normal, with no signs of intestinal obstruction, the operative wound with approximated edges, without secretions, due to this, discharge was decided after 79 days of admission with good clinical condition, with the follow-up plan by the complex abdomen team of the Medical Surgical Hospital (Figure 5).

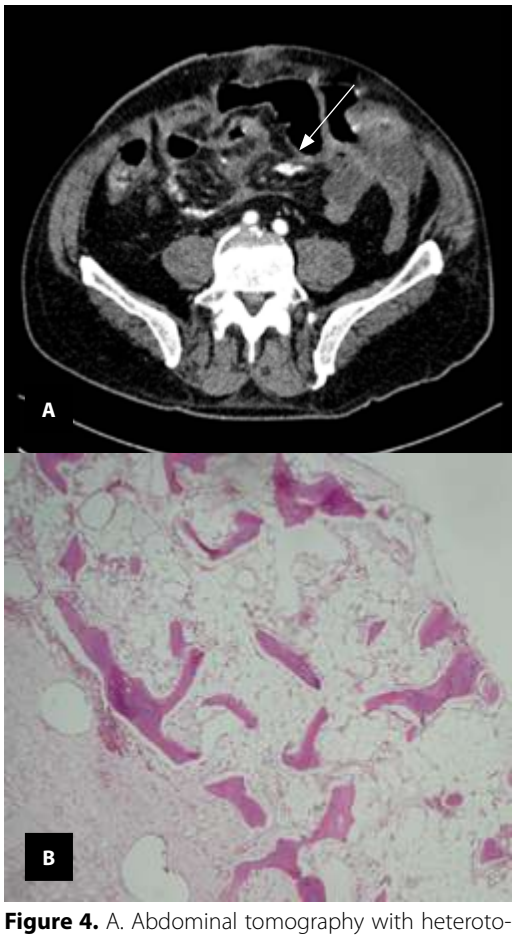

Figure 4. A. Abdominal tomography with heterotopic osteogenesis indicated by arrow. B. Fragments of mature trabecular and medullary bone tissue

Clinical diagnosis

Histopathological diagnosis confirms mesenteric heterotopic ossification as the cause of intestinal obstruction following resolution of the enteroatmospheric fistula.

Discussion

Heterotopic osteogenesis is a rare pathology with very few reports;[vii] currently, there are about 75 cases reported according to searches in EMBASE and PUBMED,[iii,viii-xii] reviews have found that this entity occurs mostly in patients of middle to late adulthood, with a predominance of male patients.[xiii] In the majority of patients with

Figure 5. Timeline

septic abdomen who have undergone multiple abdominal surgical interventions,[xiv] according to the results of pathological studies, the presence of mature bone formations with trabecular structure similar to that of cancellous bone has been determined.[xv] These findings inside the abdominal cavity being the cause of intestinal obstruction are a rarely described pathology.

The pathophysiology of the formation of this bone tissue in the abdominal cavity is still unknown. It is theorized that heterotopic osteogenesis is due to stimulation of pluripotential mesenchymal stem cells in response to inflammation, causing differentiation of these stem cells into osteoblasts.[xi] Multiple cases of intestinal obstruction associated with heterotopic ossification have been reported over the years, in addition to other symptomatologies, such as early satiety and epigastralgia.[xvi]

After the removal of this bone structure, the permeability of the intestinal tract was achieved, improving the passage of intestinal contents, which makes this pathology one more complication that a patient who has undergone multiple abdominal surgeries may suffer, as detailed by Althaqafi *et al.* in their review of cases.[xv]

As detailed in the timeline (Figure 5), the patient's evolution was satisfactory for the resolution of the intestinal obstruction; the symptoms of this entity may not be specific, with vague abdominal symptoms, such as vague abdominal pain, nausea, and vomiting. Due to the limited research on these cases, it is challenging to identify this entity as the root cause of the issue. Typically, the diagnosis is made incidentally. In this case, serial measurements of calcium and parathyroid hormone were conducted, but they did not reveal any alterations, thus preventing any correlation with endocrinological entities to date.

Medical therapies, including bisphosphonates and NSAIDs, may help mitigate recurrence, but further research is needed to determine the efficacy.[xvii] Some authors have advocated surgical resection, while others suggest that this may induce further heterotopic mesenteric ossification formation.

Heterotopic mesenteric ossification must be considered in those patients in whom mineralization of the mesentery is detected on CT scans, especially if there has been major surgery or previous trauma. As presented in this case, ossification can develop within a few weeks of major surgery and can progress and evolve to form wide or irregular ossification laminae, leading to bowel obstruction and perforation. Radiologists and surgeons must not dismiss early signs of ossification as surgical or other foreign material to avoid misdiagnosis.[xii]

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References

i. Choi H, Choi J-W, Ryu DH, Woo CG, Kim KB. Spontaneous heterotopic mesenteric ossification around the pancreas causing duodenal stenosis: A case report with literature review. International Journal of Surgery Case Reports. 2021;81:105702. DOI: 10.1016/j.ijscr.2021.105702

ii. Amalfitano M, Fyfe B, Thomas SV, Egan KP, Xu M, Smith AG, *et al.* A case report of mesenteric heterotopic ossification: Histopathologic and genetic findings. Bone. 2018;109:56-60. DOI: 10.1016/j.bone.2018.01.006

iii. Bahmad HF, Lopez O, Sutherland T, Vinas M, Ben-David K, Howard L, *et al.* Heterotopic mesenteric ossification: a report of two cases. JPTM. 2022;56(5):294-300. DOI: 10.4132/jptm.2022.07.23

iv. Cao G, Zhang S, Wang Y, Quan S, Yue C, Yao J, *et al.* Pathogenesis of acquired heterotopic ossification: Risk factors, cellular mechanisms, and therapeutic implications. Bone. 2023;168:116655. DOI: 10.1016/j.bone.2022.116655

v. Muñoz-Ruiz EO, Bravo-Flórez NM, Herrera Chaparro JA, Vallejo-Vallecilla G. Nueva técnica para control de contaminación de fístulas enteroatmosféricas en abdomen abierto Björck 4. Método de Capilaridad (MECA). Rev Colomb Cir. 2021;37(1):90-95. DOI: 10.30944/20117582.939

vi. Björck M, Kirkpatrick AW, Cheatham M, Kaplan M, Leppäniemi A, De Waele JJ. Amended Classification of the Open Abdomen. Scand J Surg. 2016;105(1):5-10. DOI: 10.1177/1457496916631853

vii. Louis EM, Nicolaou S. Bowel obstruction and perforation secondary to progressive heterotopic mesenteric ossificans. Radiology Case Reports. 2022;17(10):3651-3654. DOI: 10.1016/j.radcr.2022.06.010

viii. Andrea Aurelio R, Nicola DR, Stefani C, Francesco S, Alberto F, Anna Vittoria M, *et al.* An unusual case of bowel obstruction in emergency surgery: The heterotopic mesenteric ossification. SAGE Open Medical Case Reports. 2020;8:2050313X2092604. DOI: 10.1177/2050313X20926042

ix. Ferreira C, Gomes C, Melo A, Tenreiro N, Pinto B, Moreira H, *et al.* Heterotopic mesenteric and abdominal wall ossification - Two case reports in one institution.

International Journal of Surgery Case Reports. 2017;37:22-25. DOI: 10.1016/j.ijscr.2017.06.004

x. Hansen Ø, Sim F, Marton PF, Grüner O-PN. Heterotopic Ossification of the Intestinal Mesentery. Pathology - Research and Practice. 1983;176(2-4):125-130. DOI: 10.1016/S0344-0338(83)80004-1

xi. Koolen PGL, Schreinemacher MHF, Peppelenbosch AG. Heterotopic Ossifications in Midline Abdominal Scars: A Critical Review of the Literature. European Journal of Vascular and Endovascular Surgery. 2010;40(2):155-159. DOI: 10.1016/j.ejvs.2010.03.010

xii. Navarro-Briceño Y, Villalba-Meneses CP. Osificación heterotópica intraabdominal: reporte de caso. RCHRAD. 2021;27(4):7700. DOI: 10.24875/RCHRAD.M21000012

xiii. Lai H-J, Jao S-W, Lee T-Y, Ou J-J, Kang J-C. Heterotopic Mesenteric Ossification After Total Colectomy for Bleeding Diverticulosis of the Colon—A Rare Case Report. Journal of the Formosan Medical Association. 2007;106(2):S32-S36. DOI: 10.1016/S0929-6646(09)60350-8

xiv. Çelik SU. Heterotopic mesenteric and omental ossification incidentally found in a patient with multiple abdominal surgical operations because of gunshot injury. Ulus Travma Acil Cerrahi Derg. 2018. DOI: 10.5505/tjtes.2018.44014

xv. Althaqafi RMM, Assiri SA, Aloufi RA, Althobaiti F, Althobaiti B, Al Adwani M. A case report and literature review of heterotopic mesenteric ossification. International Journal of Surgery Case Reports. 2021;82:105905. DOI: 10.1016/j.ijscr.2021.105905

xvi. Oroian T. S2994 History of Parachuting as Cause of Heterotopic Mesenteric Ossification in an Elderly Male. Am J Gastroenterol. 2021;116(1):S1239-S1240. DOI: 10.14309/01.ajg.0000785508.41498.e8

xvii. Honjo H, Kumagai Y, Ishiguro T, Imaizumi H, Ono T, Suzuki O, *et al.* Heterotopic Mesenteric Ossification After a Ruptured Abdominal Aortic Aneurism: Case Report With a Review of Literatures. International Surgery. 2014;99(4):479-484. DOI: 10.9738/INTSURG-D-13-00074.1

Case report

Eisenmenger Syndrome Associated with an *ostium secundum* Atrial Septal Defect in an Adult Woman

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Síndrome de Eisenmenger secundario a comunicación interatrial tipo *ostium secundum* en mujer adulta

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Abstract
Eisenmenger syndrome is the most severe form of pulmonary arterial hypertension secondary to an unrepaired congenital heart disease. Despite the low prevalence, it remains a challenge for the public health service of developing countries due to the complexity of the treatment. **Case presentation.** A female patient without known medical history, who consults with dyspnea on exertion and polycythemia. **Treatment.** A transesophageal echocardiogram was performed, showing an *ostium secundum* atrial septal defect and severe pulmonary arterial hypertension with a right-left shunt. Supplemental oxygen was administrated and pharmacological treatment was started. **Outcome.** The patient presented remarkable clinical improvement to dyspnea, she was discharged with medical reference to the Adult Congenital Heart Disease clinic at Rosales National Hospital.

Keywords
Eisenmenger Complex, Pulmonary Arterial Hypertension, Heart Defects, Congenital, Polycythemia.

Resumen
El síndrome de Eisenmenger es la forma más severa de presentación de hipertensión arterial pulmonar secundaria a defectos cardíacos congénitos no reparados, aunque su prevalencia es baja, continúa siendo un reto para los sistemas de salud de los países en vías de desarrollo por su complejidad en el manejo. **Presentación del caso.** Paciente femenina sin antecedentes médicos conocidos quien consulta por disnea relacionada a los esfuerzos y policitemia. **Intervención terapéutica.** Se realiza ecocardiograma transesofágico que arroja la presencia de defecto interatrial tipo *ostium secundum* e hipertensión arterial pulmonar severa, con cortocircuito de derecha a izquierda, se inicia oxigenoterapia y terapia farmacológica. **Evolución clínica.** Paciente permaneció ingresada presentando notable mejora a la disnea, se le dio de alta con referencia a la clínica de cardiopatías congénitas del adulto en Hospital Nacional Rosales.

Palabras clave
Complejo de Eisenmenger, Hipertensión Arterial Pulmonar, Cardiopatías Congénitas, Policitemia.

Introduction

Eisenmenger syndrome (ES) is the most severe presentation of pulmonary arterial hypertension; clinically, it is characterized by the presence of an unrepaired congenital heart defect (CHD) that allows the presence of a shunt between the systemic and pulmonary circulation as a ventricular septal defect and atrial septal defect.[i]

In Europe, ES shows a reported prevalence of 1 to 5.6 % in cohorts of patients with CHD.[ii] In El Salvador, there was a registry of 70 000 newborns during 2017, and 1173 presented CHD, which implies a risk for the development of ES.[iii]

It is considered a systemic disease with multi-organ involvement, which explains the various manifestations presented by patients suffering from it, such as exercise intolerance, erythrocytosis, dyspnea, central and peripheral cyanosis, digital clubbing, headaches, cerebrovascular accidents, brain abscesses, hemorrhages, thrombosis, iron deficiency, anemia, hyper-viscosity syndrome, among others.[iv]

The treatment of patients with ES is limited to palliative management due to the difficulty of accessing cardiopulmonary transplantation as a curative treatment; however, there are advances in pharmacological management with antiarrhythmic drugs, prostacyclin analogs, and diuretics, among others.[v]

Case presentation

This report is about a 37 year-old woman who consulted with a month history of dyspnea related to moderate physical exertion that decreased with repose, and during the last 24 hours, had progressed to dyspnea on minimal exertion and was accompanied by acrocyanosis, fatigue, generalized weakness, oppressive precordial pain associated with physical activity, which improved with rest. Palpitations, syncope, or other symptoms, were ruled out. The patient went to a private practice and was referred to the San Rafael National Hospital for inpatient management due to the identification of polycythemia.

There was a history of two previous pregnancies, with no other diagnosed medical conditions. On exploring the health medical history, the patient described episodes of perioral cyanosis since childhood that subsided without having received specific treatment.

In the physical evaluation, tachypnea was identified, with diaphoresis and perioral cyanosis. In addition, the patient exhibited a heart rate of 100 bpm, respiratory rate of 22 rpm, blood pressure of 90/60 mmHg, oxygen saturation of 70 % at room temperature; There was perioral cyanosis, acrocyanosis and hippocratic fingers (Figure 1), neck with bilateral jugular ingurgitation at 90° to the edge of the jaw, decreased vesicular murmur was auscultated, with bilateral basal crepitant rales in lung fields, regular heart rhythm, end-systolic murmur in mitral focus III/IV with Rivero-Carvallo sign, flat abdomen, painful on palpation in the right upper quadrant, liver 1 cm below the costal margin, positive hepatojugular reflux.

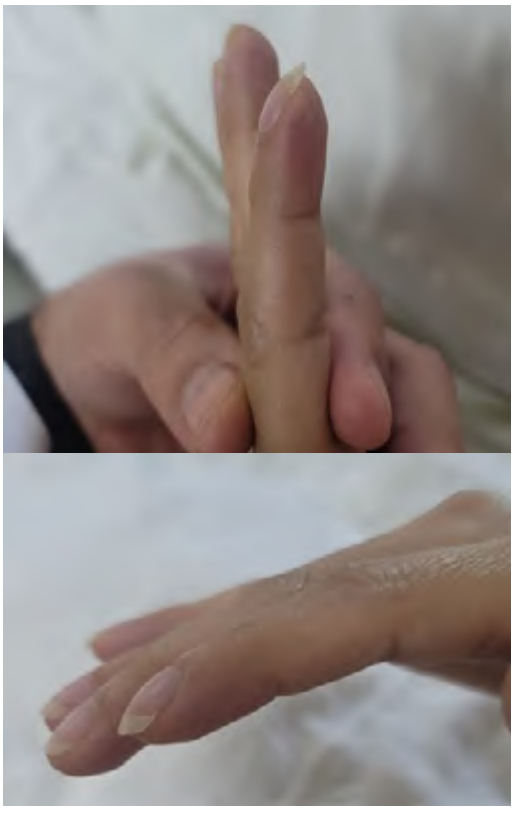

Figure 1. Finger clubbing

Therapeutic intervention

The patient was transferred to the area of maximum urgency, where management began with supplemental oxygen at 15 L/min with a reservoir mask; a hemogram was taken (Table 1), polycythemia was detected, and an electrocardiogram (Figure 2) (Figure 3) reflected an enlarged cardiac silhouette.

Table 1. Admission hemogram taken at the maximum urgency unit of the San Rafael National Hospital

Results	
Red line	
Hemoglobine	18.5 g/dL
Hematocrit	55.6 %
Mean corpuscular volume	89.5 µg
Mean corpuscular hemoglobin	29.8 pg
Erythroblasts	0.75 %
White line	
White blood cells	5.91 $\times 10^3$ µL
Neutrophils	72.7 %
Lymphocytes	22.0 %
Platelet line	
Platelets	247x10^3/µl
Mean platelet volume	10.7 fL

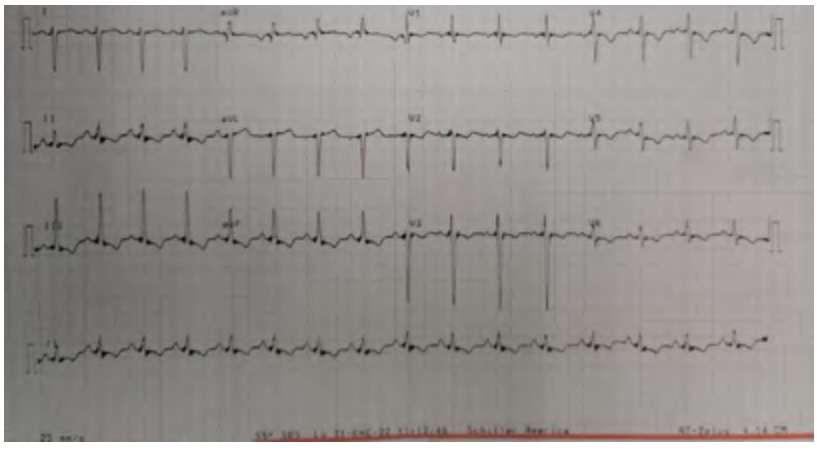

Figure 2. Electrocardiogram of 12 leads. Taken in maximum urgency unit. Reports: sinus rhythm, heart rate 100 bpm, electrical axis deviation to the right, high voltage P wave, R wave > 6 mm in V1, Lewis index = -25, Cabrera index = 0.87, suggestive of right ventricular hypertrophy

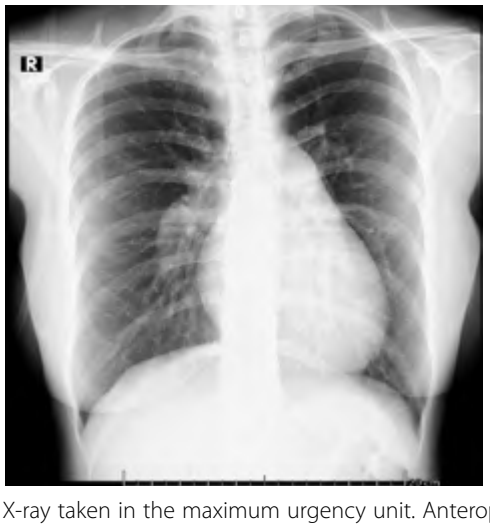

Figure 3. Chest X-ray taken in the maximum urgency unit. Anteroposterior projection, showing magnification of the cardiac silhouette by projection. Dilatation of the pulmonary artery trunk and prominent right interlobar artery with decreased peripheral pulmonary vasculature. Pattern of pulmonary hypertension

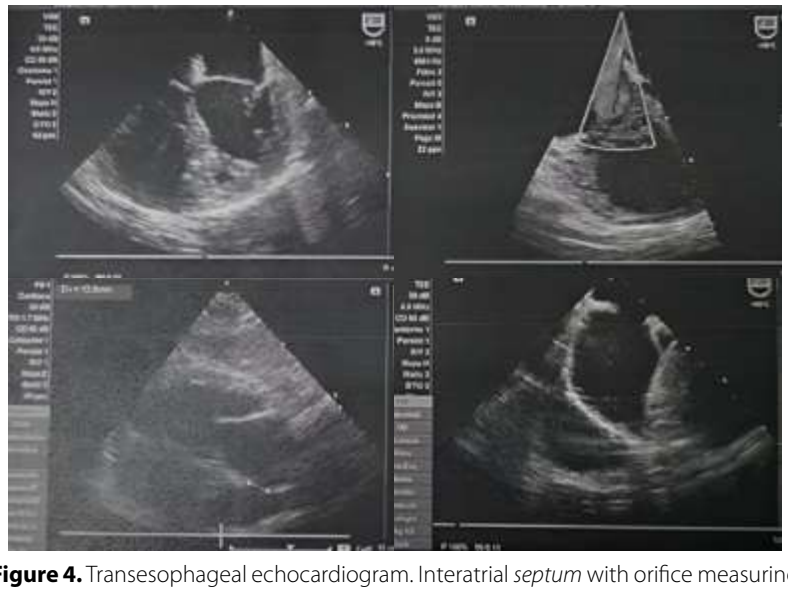

Figure 4. Transesophageal echocardiogram. Interatrial *septum* with orifice measuring 22 mm, with wide right-to-left shunt, *osteum secundum* type. Tricuspid valve with wide regurgitation jet that goes to the interatrial *septum* and reaches the septal defect

After the patient was stabilized, she was transferred to the intermediate care unit, with heart rate of 87 bpm, respiratory rate of 16 rpm, blood pressure of 100/60 mmHg, oxygen saturation of 85 % with O_2 with reservoir mask with FIO_2 100 %. Arterial blood gases reported moderate respiratory distress syndrome (Table 2), due to which furosemide 20 mg intravenous (IV) every eight hours and acetylsalicylic acid 100 mg orally every day were started.

Table 2. Arterial blood gas

Parameter	Value
pH	7.45
$paCO_2$	17 mmHg
pO_2	39 mmHg
SO_2	77 %
HCO_3	11.8 mmHg
BE	-9.6 mmol/L
TCO_2	12.6 mmol/L

The transthoracic echocardiogram taken on the second day of admission reported left chambers with normal diameters, dilated right chambers. It was not possible to define the continuity defect in the interatrial *septum*, and it was also difficult to define a shunt due to the presence of severe tricuspid regurgitation that collided with the septum. The pericardium was reported normal, and the aortic and mitral valves were functional with moderate pulmonary valve dysfunction; normal systolic function, left ventricular ejection fraction of 53 %, and pulmonary artery systolic pressure of 88 mmHg, were found

After four days, a transesophageal ultrasound was performed, which showed an *ostium secundum*-type lesion (Figure 4).

Clinical evolution

The patient was maintained on supplemental oxygen through a reservoir mask at 15 L/min, and treatment was started with sildenafil 25 mg orally every eight hours in the second day of admission, as well as a single dose of digoxin (0.25 mg IV). The patient presented favorable evolution with improved dyspnea at rest, and oxygen saturation between 85 and 90 %.

The patient continued with furosemide 20 mg IV every eight hours and acetylsalicylic acid 100 mg orally every day. Phlebotomies of 200 mL were administered with a volume replacement of 200 mL of 0.9 % saline solu-

tion every day for five days. Subsequently, after 11 days of hospital stay, the patient was transferred to the intermediate care unit, where oxygen therapy was reduced to a minimum of 3 L/min. After fifteen days of management, she was discharged from the hospital with furosemide 40 mg orally every 12 hours, sildenafil 25 mg every eight hours, and supplemental oxygen at 3 L/min with nasal cannula. Finally, the patient was referred to the Adult Congenital Heart Disease Clinic of the Rosales Nacional Hospital for follow-up.

Clinical diagnosis

Eisenmenger syndrome associated with an unrepaired *ostium secundum* atrial septal defect.

Discussion

Eisenmenger's syndrome consists of a variety of symptoms such as dyspnea, cyanosis, precordial pain, clubbed fingers, syncope, hemoptysis, etc., which are the result of untreated CHD. Any CHD that leads to the development of pulmonary arterial hypertension can cause SE. It usually occurs in atrioseptal defects, ventricular septal defects, atrioventricular defects, and persistent ductus arteriosus.[v]

ES is a rare clinical entity that affects patients who do not have adequate access to health services in rural areas or developing countries, in which large CHD can go undetected for years.[iv] In the case presented, the patient presented symptomatology congruent with ES without a history of CHD, which delayed the diagnosis, with the social risk factors described.

The pathophysiology that leads to the ES development is a consequence of left-to-right shunts, which cause an increase in pulmonary vascular resistance and the alteration of vasoactive mediators triggering vasoconstriction and vascular remodeling, which consists of smooth muscle proliferation and thrombosis caused by an increase in blood flow resistance. Consequently, there is a chronic increase in pulmonary pressure and right ventricular pressure when pulmonary artery pressure exceeds systemic pressure, thus reversing to a right-to-left shunt and establishing ES.[v]

The right-to-left shunt allows deoxygenated blood to enter the systemic circulation, causing systemic manifestations such as erythrocytosis, cyanosis, exercise intolerance, palpitations, acropaquia, jugular ingurgitation, lower limb edema, livedo reticularis, among others.[vi]

Hypoxia and chronic cyanosis generate multiorgan compromise, which produces secondary erythrocytosis as a maladaptive response to hypoxemia; this adaptation triggers iron deficiency and hyper-viscosity syndrome that increases morbidity and the frequency of patient hospitalization.[vii]

On the other hand, compensated erythrocytosis generates a balance in iron and ferritin levels with elevated hematocrit; in these patients VHS symptoms are mild or nonexistent, and the risk of presenting thrombotic events is low, as long as hematocrit levels do not exceed 70 %.[viii] Whereas, in patients with decompensated erythrocytosis, a balance between increased hematocrit levels and iron reserves is not achieved causing moderate to severe VHS symptoms.[ix] The highest hematocrit recorded in the case presented was 56.9 %, with a low risk of VHS and thrombotic events. Iron and ferritin levels were not identified.

In terms of diagnosis, some studies, such as the electrocardiogram, have a complementary role, allowing early detection of arrhythmias, right ventricular hypertrophy, and the presence of right bundle branch block. Frequently, the following can be identified: right axis deviation, presence of pulmonary P wave, QTc prolongation, ST depression/T inversion in the right precordial leads V1-V4, and leads DII, DIII, and aVF.[x] Similarly, transthoracic echocardiography, which is the most relevant monitoring tool, allows identification of cardiac morphology and function.[x] In this case in question, an atrial septal defect was suspected at the level of its middle portion with right-to-left shunt, which was confirmed by transesophageal echocardiography.

In the same way, cardiac magnetic resonance imaging allows the evaluation of ventricular function and its volumes, being a useful non-invasive tool to determine the pulmonary flow to systemic flow ratio, it is not available in all healthcare centers. It should not be conducted on unstable, dyspneic or oxygen-dependent patients.[xi]

Finally, right cardiac catheterization, which is considered the gold standard, allows confirmation of the diagnosis and differentiation between pulmonary hypertension of other origin since it is a direct hemodynamic evaluation; patients with SE have a higher mean pulmonary artery pressure and pulmonary vascular resistance than patients with idiopathic pulmonary arterial hypertension.[xii]

The key to the treatment of patients with ES lies in avoiding alteration of the balance of the pathophysiological state, which implies close monitoring by a multidisci-

plinary team focused on the prevention and management of complications.[xiii] Supplemental oxygen does not reduce the risk of mortality or increase tissue oxygenation, and can cause dry mucous membranes in the upper airway, predisposing patients to epistaxis and hemoptysis. It is recommended when an increase in oxygen saturation in the bloodstream and a consistent improvement in symptoms are present.[xiv]

Elevated hemoglobin values in these patients should not be treated like other types of polycythemia; routine phlebotomies are associated with adverse outcomes such as iron deficiency and increased risk of thrombotic events. Selected patients may benefit from occasional phlebotomies with isovolumetric replacement, for example, patients with moderate to severe symptoms of hyperviscosity or hematocrit > 65 %.[xv]

Anticoagulation therapy is not recommended for all patients as it has not been shown to reduce mortality and may increase the risk of bleeding. Hence, it is recommended only for patients with hemostatic risk factors such as atrial fibrillation, atrial flutter, prosthetic valves, blood stasis, and absence of hemoptysis.[xvi]

Drug therapy is based on three different metabolic pathways, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclins. Bosentan, an endothelin receptor antagonist, is the first drug to improve exercise tolerance and decrease mean pulmonary arterial pressure and pulmonary vascular resistance. It is considered first-line treatment, a result comparable to those shown by phosphodiesterase-5 inhibitors such as sildenafil[xvii]. Also, prostacyclins, a third-line treatment, prevent the risk of infection and paradoxical thrombotic events.[xviii]

Surgical intervention to repair CHD is recommended in the terminal phase of the disease, with variable results.[xix] On the other hand, cardiopulmonary transplantation is the definitive treatment accompanied by pharmacological treatment.[xvii]

Early detection of CHD and intervention before the onset of irreversible alterations lead to a better quality of life; in this regard, it is recommended that adequate cardiac screening be implemented in newborns and children who present symptoms suggestive of heart disease, and adequate education to parents or caregivers to identify the warning signs and symptoms.[xx]

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References

i. Benlamkaddem S, Bouyermane F, Doughmi D, Berdai MA, Harandou M. Fatal Association of Eisenmenger Syndrome and Severe Preeclampsia. Cureus. 2023 Apr 19. DOI: 10.7759/cureus.37836

ii. Flores Molina V. Perfil Epidemiologico y Clinico de las Malformaciones Cardiacas Congenitas, en pacientes ingresados en el servicio de Neonatologia del Hospital Nacional de Niños Benjamin Bloom del 1° de Enero del 2016 al 31 de Diciembre del 2018. Tesis de posgrado. San Salvador: Universidad de El Salvador; 2019. Available at: https://docs.bvsalud.org/biblioref/2020/10/1127641/13-11106181.pdf

iii. Calderón-Colmenero J, Sandoval Zárate J, Beltrán Gámez M. Hipertensión pulmonar asociada a cardiopatías congénitas y síndrome de Eisenmenger. Arch. Cardiol. México. 2015;85(1):32-49. DOI: 10.1016/j.acmx.2014.11.008

iv. Arvanitaki A, Gatzoulis MA, Opotowsky AR, Khairy P, Dimopoulos K, Diller G-P, *et al.* Eisenmenger Syndrome. J. Am. Coll. Cardiol. 2022;79(12):1183-1198. DOI: 10.1016/j.jacc.2022.01.022

v. Basit H, Wallen TJ, Sergent BN. Eisenmenger Syndrome. National Library of Medicine. 2023. Date of citation: 2 de agosto de 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507800/

vi. Kellish AS, Hakim A, Soal V, Hassinger G, Gable B. Where on the Differential Is Eisenmenger Syndrome in a Patient Without Prior Cardiopulmonary Disease? Cureus. 2020 Jun 8. DOI: 10.7759/cureus.8509

vii. Martin-Garcia AC, Arachchillage DR, Kempny A, Alonso-Gonzalez R, Martin-Garcia A, Uebing A, *et al.* Platelet count and mean platelet volume predict outcome in adults with Eisenmenger syndrome. Heart. 2018;104(1):45-50. DOI: 10.1136/heartjnl-2016-311144

viii. Moons P, Canobbio MM, Budts W. Eisenmenger Syndrome: A Clinical Review. Eur. J. Cardiovasc. Nurs. 2009;8(4):237-245. DOI: 10.1016/j.ejcnurse.2009.05.004

ix. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R, *et al.* Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur. Heart

J. 2011;32(22):2790-2799. DOI: 10.1093/eurheartj/ehr130

x. Valkovicova T, Kaldararova M, Reptova A, Bohacekova M, Bacharova L, Hatala R, Simkova I. Eisenmenger syndrome - an electrocardiographic and echocardiographic assessment of the right ventricle. Bratisl. Med. J. 2018;119(06):321-329. DOI: 10.4149/BLL_2018_060

xi. Arvanitaki A, Giannakoulas G, Baumgartner H, Lammers AE. Eisenmenger syndrome: diagnosis, prognosis and clinical management. Heart. 2020;106(21):1638-1645. DOI: 10.1136/heartjnl-2020-316665

xii. Gong C, He S, Chen X, Wang L, Guo J, He J, *et al.* Diverse Right Ventricular Remodeling Evaluated by MRI and Prognosis in Eisenmenger Syndrome With Different Shunt Locations. J. Magn. Reson. Imaging. 2022;55(5):1478-1488. DOI: 10.1002/jmri.27791

xiii. Diller G-P, Lammers AE, Oechslin E. Treatment of adults with Eisenmenger syndrome—state of the art in the 21st century: a short overview. Cardiovasc. Diagn. Ther. 2021;11(4):1190-1199. DOI: 10.21037/cdt-21-135

xiv. Chaix M-A, Gatzoulis MA, Diller G-P, Khairy P, Oechslin EN. Eisenmenger Syndrome: A Multisystem Disorder—Do Not Destabilize the Balanced but Fragile Physiology. Can. J. Cardiol. 2019;35(12):1664-1674. DOI: 10.1016/j.cjca.2019.10.002

xv. Dulac Y. Traitements conventionnels et prise en charge globale. Presse Médicale. 2009;38:1S14-1S17. DOI: 10.1016/S0755-4982(09)73419-0

xvi. Giannakoulas G, Boutsikou M. The Gordian knot of thromboembolism in congenital heart disease: Table 1. Heart. 2015;101(19):1523-1524. DOI: 10.1136/heartjnl-2015-308045

xvii. Gatzoulis MA, Landzberg M, Beghetti M, Berger RM, Efficace M, Gesang S, *et al.* Evaluation of Macitentan in Patients With Eisenmenger Syndrome: Results From the Randomized, Controlled MAESTRO Study. Circulation. 2019;139(1):51-63. DOI: 10.1161/CIRCULATIONAHA.118.033575

xviii. Hjortshøj CS, Gilljam T, Dellgren G, Pentikäinen MO, Möller T, Jensen AS, *et al.* Outcome after heart-lung or lung transplantation in patients with Eisenmenger syndrome. Heart. 2020;106(2):127-132. DOI: 10.1136/heartjnl-2019-315345

xix. Manuel L, Freeman L, Nashef SA. Surgery for Eisenmenger syndrome: time for a rethink? J. R. Soc. Med. 2019;112(12):512-513. DOI: 10.1177/0141076819877551

xx. Barradas-Pires A, Constantine A, Dimopoulos K. Preventing disease progression in Eisenmenger syndrome. Expert Rev. Cardiovasc. Ther. 2021;19(6):501-518. DOI: 10.1080/14779072.2021.1917995

Case report

Kartagener Syndrome and Rheumatoid Arthritis. Case Report

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Abstract
Case presentation. A 26-year-old woman, under follow-up by the rheumatology specialty since she was 17 years old, when she consulted with a history of one year of evolution of polyarticular disease of large and small joints, additive, symmetrical, accompanied by fatigue and morning stiffness for more than one hour. Positive rheumatoid factor was also reported. Additionally, the patient had a history of repeated sinobronchial processes since childhood. Medical examination revealed sinus pain in the paranasal sinuses, dextrocardia, and bronchiectasis, confirmed by imaging studies, which led to the diagnosis of Kartagener's syndrome. **Treatment.** The patient presented the severe clinical activity of rheumatoid arthritis. The treatment was started with methotrexate 10 mg orally one day a week, prednisone 5 mg a day, and folic acid 5 mg a week and periodic appointments, controlling the activity data and adverse effects of the drugs, with liver tests, hemogram, and transaminases. The pneumology department recommended the inclusion of the patient in a respiratory rehabilitation program as well as the use of azithromycin 500 mg every day for three days during periods of exacerbation. **Outcome.** The treatment was successful in maintaining a mild activity of the rheumatoid arthritis and without exacerbation of respiratory symptoms.

Keywords
Kartagener Syndrome, Dextrocardia, Ciliary Motility Disorders, Arthritis, Rheumatoid.

Resumen
Presentación del caso. Se trata de una mujer de 26 años de edad, en seguimiento por la especialidad de reumatología desde los 17 años, cuando consultó con historia de un año de evolución de síndrome poliarticular de grandes y pequeñas articulaciones, aditivo, simétrico acompañado de fatiga, rigidez matutina mayor de una hora. Se reportó además factor reumatoide positivo. La radiografía de ambas manos presentó erosiones, que confirmó el diagnóstico de artritis reumatoide. Adicionalmente, la paciente tenía el antecedente de procesos sinobronquiales a repetición desde su infancia. En la evaluación médica se identificó dolor en los senos paranasales, dextrocardia y bronquiectasias, confirmados por los estudios de imágenes, que permitió concluir en el diagnóstico de síndrome de Kartagener. **Intervención terapéutica.** La paciente presentaba actividad clínica severa de la artritis reumatoide, se inició el tratamiento con metotrexato 10 mg vía oral un día a la semana, prednisona 5 mg al día y ácido fólico 5 mg a la semana y citas periódicas, controlando los datos de actividad y efectos adversos de los medicamentos, con pruebas hepáticas, hemograma y transaminasas. La especialidad de neumología recomendó la inclusión de la paciente en un programa de rehabilitación respiratoria, así como el uso de azitromicina 500 mg cada día por tres días en los períodos de agudización. **Evolución clínica.** El tratamiento logró mantener una actividad leve de la artritis reumatoide y sin exacerbación de los síntomas respiratorios.

Palabras clave
Síndrome de Kartagener, Dextrocardia, Discinesia Ciliar Primaria, Artritis Reumatoide.

Introduction

Kartagener syndrome (KS) is an autosomal recessive disorder consisting of the triad of sinusitis, bronchiectasis and *situs inversus* with dextrocardia and represents a subgroup of primary ciliary dyskinesia (PCD). It is a genetically heterogeneous respiratory disorder characterized by chronic upper and lower respiratory tract disease.[i,ii] The estimated worldwide prevalence is 1/15 000 to 1/30 000 live births.[i]

Approximately 50 % of patients with SCD have laterality defects (including *situs inversus totalis* and, less frequently, heterotaxy and congenital heart disease), reflecting dysfunction of embryologic nodal cilia.[i-iii]

Most mutations identified as causes of PCD involve the heavy (DNAH5) or intermediate (DNAI3) mutation, which chains dynein genes in the ciliary outer dynein arms, although some mutations in other genes have been observed. Clinical molecular genetic testing is available for the most common mutations.[iv,v] Ciliary ultrastructural analysis reveals defective dynein arms in more than 80 % of patients, although defects in other axonemal components have also been observed.[vi,vii]

The respiratory manifestations of PCD are chronic bronchitis, bronchiectasis, chronic rhinosinusitis, chronic otitis media, and less frequently infertility and are the result of impaired mucociliary clearance due to a defective axoneme structure.[vi,vii] Cases of KS with glomerular alterations and neoplasms[viii] and rheumatoid arthritis (RA) have been reported. Several theories have been proposed on pathogenesis, one of them accepts that environmental factors such as smoking, repeated infections and periodontitis play an important role in the development of the disease in a genetically susceptible person.[ix]

Case presentation

The patient is a 26-year-old, nulliparous woman with no family history of autoimmune diseases who has been under follow-up by the rheumatology specialty since she was 17 years old due to mild to moderate intensity joint pain in the wrist, metacarpophalangeal, proximal interphalangeal, elbow and knee joints, of one year of evolution, which presented with greater intensity in the mornings and improved with exercise, accompanied by systemic manifestations, including unquantified weight loss, morning stiffness lasting more than one hour and fatigue when carrying out her activities; she had received treatment with non-steroidal anti-inflammatory drugs that did not generate clinical improvement.

During a routine examination, the patient was diagnosed with sinobronchial syndrome, characterized by frequent crises since she was two years old, which had been treated with antibiotics and expectorants. On physical evaluation, the patient was found to be thin, tachycardic, with a nasal voice, pain on palpation of the maxillary regions, expiratory wheezing, and palpable liver 2 cm below the left costal ridge. In addition, she had synovial hypertrophy in the elbows, wrists, metacarpophalangeal and proximal interphalangeal joints with swan neck deformity (Figure 1 and 2), flexion contracture at 30 degrees, and nodules in the right elbow. She also had a heart rate of 109 bpm, respiratory rate of 18 rpm, ambient air oxygen saturation of 97 % of 81 pounds, height of 1.50 m, and a body mass index of 16.4 kg/m^2.

Laboratory tests and imaging studies reported moderate anemia with elevated erythrocyte sedimentation rate and rheumatoid factor (RF) (Table 1).

Treatment

Due to the detection of a moderate clinical index of disease activity, she was given outpatient treatment with methotrexate 7.5 mg and folic acid 5 mg weekly, prednisone 5 mg and calcium carbonate 1200 mg daily. This treatment was based on the recommendations of the American College of Rheumatology guidelines for patients with RA.[x]

After two months, she was evaluated by rheumatology, where a slight improvement in hemoglobin was identified, and she presented with mild leukocytosis (Table 1).

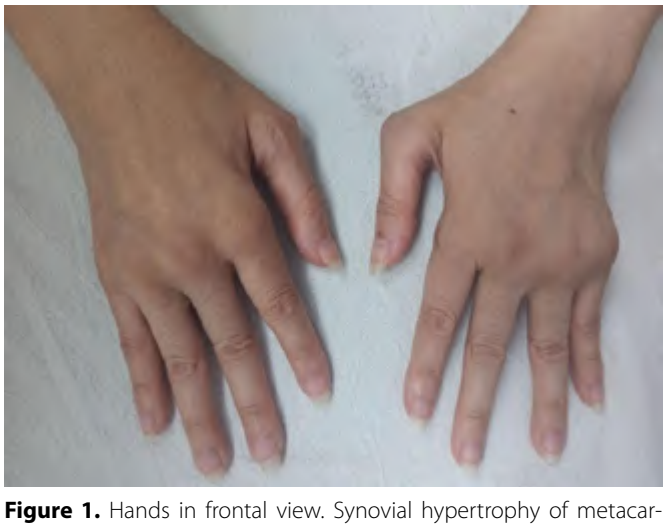

Figure 1. Hands in frontal view. Synovial hypertrophy of metacarpophalangeal joints, proximal, ulnar deviation

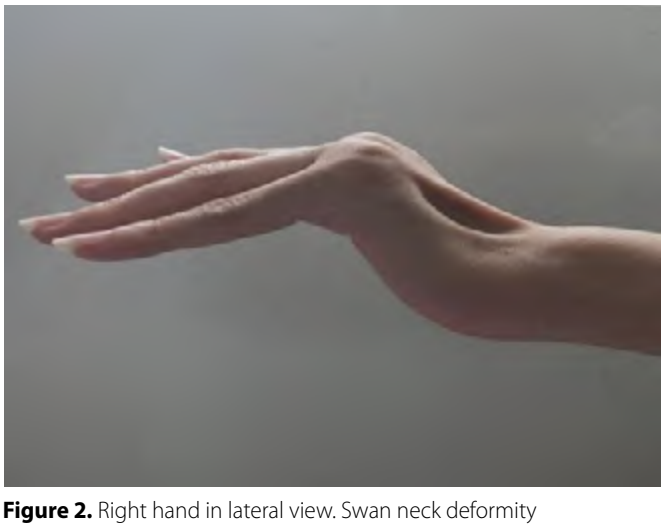

Figure 2. Right hand in lateral view. Swan neck deformity

Posteroanterior chest X-ray reported dextrocardia, with a gastric bubble displaced to the right and bilateral basal bronchial dilatations (Figure 3).

Sinus radiography identified opacity of the frontal and maxillary sinuses, which confirmed the diagnosis of chronic sinusitis. At the same time, posteroanterior radiography of both hands reported soft tissue enlargement with joint space narrowing in the proximal interphalangeal areas, metacarpophalangeal, carpal, and radiocarpal joints, and juxta-articular osteopenia and erosions, which led to the diagnosis of erosive rheumatoid arthritis radiological grade III.

The echocardiogram described the left atrium within normal diameters and the left ventricle with preserved thickness, diameters, and systolic function (left ventricular ejection fraction: 66 %) with normal right cavities and dextrocardia. Computed tomography also reported dextrocardia and multiple moderate-caliber basal bronchiectasis (Figure 4 and 5).

After four months, no adverse effects to methotrexate were identified, and she continued with moderate activity, so the dose of methotrexate was increased to 12.5 mg every week without changes in the prednisone, folic acid, and calcium carbonate.

The pneumology department recommended the inclusion of the patient in a respiratory rehabilitation program, along with the administration of azithromycin 500 mg daily for three days during periods of exacerbation.

Clinical evolution

After six months of treatment, a mild activity of rheumatoid arthritis was identified. Therefore, it was indicated to continue the treatment and periodic specialty follow-up.

Table 1. Laboratory tests

Examination performed	Medical Follow-up 1	Medical Follow-up 2
Hemoglobin	9.4 gr/dL	11.0 gr %
Hematocrit	31.4 %	-
White blood cells	7000 mm^3	11 700/mm^3
Lymphocytes	26.3 %	-
Neutrophils	65 %	-
Monocytes	9 %	-
Platelets	323 000 mm^3	-
Erythrocyte sedimentation rate	56 mm/h	-
Rheumatoid factor	128 UI/mL	-
Total proteins	8.3 gr %	-
Albumin	3.9 gr %	-
Globulin	4.4 gr %	-
Aspartate aminotransferase (AST)	12 UI/mL	30 UI/l.
Alanine aminotransferase (ALT)	9 UI/mL	28 UI/l
Serum creatinine	-	0.8 mg %

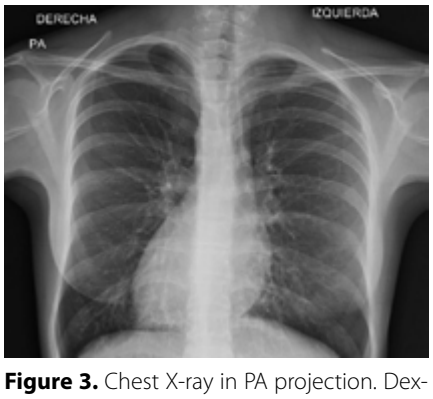

Figure 3. Chest X-ray in PA projection. Dextrocardia, parahilar dlation with parahilar and basal bronchiectasis

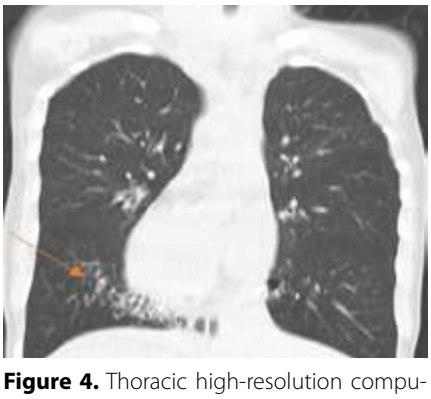

Figure 4. Thoracic high-resolution computed tomography, sagittal section. Cylindrical bronchial and tram-track bronchiectasis (indicated with arrow)

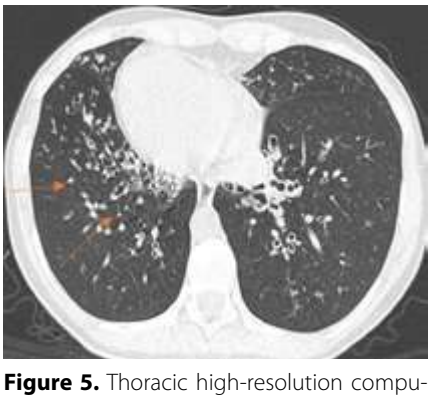

Figure 5. Thoracic high-resolution computed tomography, coronal section. Dextrocardia, multiple basal bronchiectasis of moderate caliber (indicated with arrows)

Clinical diagnosis

The diagnoses of sinusitis, dextrocardia, and bronchiectasis that constitute the triad of Kartagener's syndrome were integrated. Likewise, in this case, it was associated with rheumatoid arthritis due to the additive and symmetrical involvement of more than four joints, elevated erythrocyte sedimentation, positive rheumatoid factor at high titers, and the presence of erosions in hand radiographs.

Discussion

The diagnosis of KS is based on clinical features of persistent wet cough, *situs* abnormalities, congenital heart defects, persistent rhinitis, chronic otitis media with or without hearing loss, history in term newborns of neonatal upper and lower respiratory symptoms or neonatal intensive care.[iii] Diagnostic methods include transmission electron microscopy that identifies specific ciliary ultrastructural defects in biopsy specimens and high-speed video microscopy to evaluate cilia waveform and beat frequency. Another method is the study through diagnostic immunofluorescence microscopy and electron microscopy, which helps to identify individual defects of the ciliary structure. Molecular genetic testing of the causative genes can confirm the diagnosis. Currently, 33 mutations in more than 40 genes associated with PCD have been identified.[iv-vi]

The characteristic clinical findings of CPD are repeated bronchial processes since infancy, and the radiological findings are chronic sinusitis, dextrocardia, left liver, and bronchiectasis, characteristic of KS.[ii,iii] This case highlights the importance of timely diagnosis of CPD in patients with chronic respiratory tract infections since birth or infancy, and ideally, early diagnosis to prescribe timely treatment, thus avoiding permanent sequelae such as chronic sinusitis and bronchiectasis.

On the other hand, the diagnosis of RA was confirmed by clinical analysis, additive symmetrical involvement of large and small joints, and the detection of erythrocyte sedimentation disturbances, positive rheumatoid factor, and the presence of erosions on radiographic images.[xi]

Treatment is on measures to prevent the frequency and severity of respiratory infections. Aggressive treatment to improve mucus clearance, such as physical therapy and inhalation therapy, as well as intranasal steroids and nasal lavage are recommended as a treatment for sinusitis.[iv,v,vii]

The presentation of KS and RA is rare and there is no evidence available to support a causal relationship between both diseases. Some cases have been reported, including an 11-year-old adolescent with a diagnosis of juvenile idiopathic arthritis and negative RF, who evolved with good response after treatment with methotrexate and prednisone; a 60-year-old woman, diabetic and hypertensive, with non-erosive RA, positive RF, who was in remission due to this received chloroquine phosphate and methylprednisolone; a 38-year-old woman with positive RF, erosive, treated with prednisone 7.5 mg daily and methotrexate 15 mg once a week; a 35-year-old man with positive RF due to erosive arthritis who had a good evolution with prednisone 10 mg daily and methotrexate 15 mg every week; finally, an 18-year-old adolescent with RA, non-erosive and negative RF, who received methotrexate at 20 mg/ once a week and prednisone 5 mg daily.[ix,xii,xiii]

Certain environmental factors are considered to play an important role in the development of RA in genetically susceptible individuals. Among them, repeated infections and periodontitis are mentioned, two factors that were found to be present in the patient.[xi,xiv,xv] Increasing evidence suggests that autoimmunity in RA patients is initiated outside the joint. This theory is supported by the observation that circulating autoantibodies, including RF and anti-citrullinated protein antibodies, can be detected in many subjects years before the development of initial joint symptoms, leading to a diagnosis of RA. Of the possible extra-articular sites implicated in disease onset, mucosal tissues have captured increasing attention. Several lines of research have separately implicated mucosal tissues from different anatomical locations as possible sites of RA onset, including those of the lung and oral cavity.[xvi,xvii]

One of the main bacteria implicated in the development of periodontal disease is Porphyromonas gingivalis. Gingival tissue affected by periodontitis has been shown to trigger a citrulline-specific autoimmune response characterized by an antibody response to citrullinated proteins, accelerated by increased expression of neutrophil extracellular traps.

These citrullinated proteins and their related antibodies have been detected in the blood and joints of RA patients, as well as in the inflamed gingiva of patients with periodontitis.[xix,xx]

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References

i. Cogollo M, Rincón-Alvarez E. Síndrome de Kartagener. Acta Med Col. 2021;47(1). DOI: 10.36104/amc.2022.2280

ii. Sahu S, Ranganatha R, Batura U, Choubey U, Meghana DR, Menon VR, *et al.* A Case of Unusual Presentation of Kartagener's Syndrome in a 22-Year-Old Female Patient. Cureus. 2022 Aug 17. DOI: 10.7759/cureus.28119

iii. Queiroz RM, Bernardes Filho F. Kartagener's syndrome. Pan Afr Med J. 2018;29. DOI: 10.11604/pamj.2018.29.160.14927

iv. Lucas JS, Burgess A, Mitchison HM, Moya E, Williamson M, Hogg C. Diagnosis and management of primary ciliary dyskinesia. Archives of Disease in Childhood. 2014;99(9):850-856. DOI: 10.1136/archdischild-2013-304831

v. Mirra V, Werner C, Santamaria F. Primary Ciliary Dyskinesia: An Update on Clinical Aspects, Genetics, Diagnosis, and Future Treatment Strategies. Front. Pediatr. 2017;5:135. DOI: 10.3389/fped.2017.00135

vi. Rubbo B, Lucas JS. Clinical care for primary ciliary dyskinesia: current challenges and future directions. Eur Respir Rev. 2017;26(145):170023. DOI: 10.1183/16000617.0023-2017

vii. Shapiro AJ, Davis SD, Polineni D, Manion M, Rosenfeld M, Dell SD, *et al.* Diagnosis of Primary Ciliary Dyskinesia. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;197(12):e24-e39. DOI: 10.1164/rccm.201805-0819ST

viii. Oka K, Sugase T, Akimoto T, Murakami T, Nagayama I, Kaneko M, *et al.* Kartagener syndrome complicated by immunoglobulin A nephropathy. IMCRJ. 2018;Volume 11:359-362. DOI: 10.2147/IMCRJ.S185887

ix. Romão VC, Fonseca JE. Etiology and Risk Factors for Rheumatoid Arthritis: A State- of-the-Art Review. Front. Med. 2021;8:689698. DOI: 10.3389/fmed.2021.689698

x. Fraenkel L, Bathon JM, England BR, St.Clair EW, Arayssi T, Carandang K, *et al.* 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis & Rheumatology. 2021;73(7):1108-1123. DOI: 10.1002/art.41752

xi. Roos Ljungberg K, Joshua V, Skogh T, Eklund A, Sköld CM, Karimi R, *et al.* Secretory anti-citrullinated protein antibodies in serum associate with lung involvement in early rheumatoid arthritis. Rheumatology. 2020;59(4):852-859. DOI: 10.1093/rheumatology/kez377

xii. Takasaki S, Yamakage S, Fukase S, Takahashi T. Kartagener's Syndrome and Rheumatoid Arthritis. Intern. Med. 2014;53(3):269-274. DOI: 10.2169/internalmedicine.53.1262

xiii. Halabi H, Mulla I. Rheumatoid Arthritis, Kartagener's Syndrome, and Hyperprolactinemia: Who Started It? Case Reports in Rheumatology. 2016;2016:1-5. DOI: 10.1155/2016/7367232

xiv. Friedlander HM, Ford JA, Zaccardelli A, Terrio AV, Cho MH, Sparks JA. Obstructive lung diseases and risk of rheumatoid arthritis. Expert Review of Clinical Immunology. 2020;16(1):37-50. DOI: 10.1080/1744666X.2019.1698293

xv. Cheng Z, Do T, Mankia K, Meade J, Hunt L, Clerehugh V, *et al.* Dysbiosis in the oral microbiomes of anti-CCP positive individuals at risk of developing rheumatoid arthritis. Ann Rheum Dis. 2021;80(2):162-168. DOI: 10.1136/annrheumdis-2020-216972

xvi. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. Journal of Autoimmunity. 2020;110:102400. DOI: 10.1016/j.jaut.2019.102400

xvii. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. Clinical and Experimental Immunology. 2018;195(1):74-85. DOI: 10.1111/cei.13158

xviii. Kronzer VL, Davis JM. Etiologies of Rheumatoid Arthritis: Update on Mucosal, Genetic, and Cellular Pathogenesis. Curr Rheumatol Rep. 2021;23(4):21. DOI: 10.1007/s11926-021-00993-0

xix. Kozak M, Pawlik A. The Role of the Oral Microbiome in the Development of Diseases. IJMS. 2023;24(6):5231. DOI: 10.3390/ijms24065231

xx. Kobayashi T, Bartold PM. Periodontitis and periodontopathic bacteria as risk factors for rheumatoid arthritis: A review of the last 10 years. Japanese Dental Science Review. 2023;59:263-272. DOI: 10.1016/j.jdsr.2023.08.002

Case report

Imported Case of Malaria by *Plasmodium vivax* in El Salvador. An Epidemiological Approach

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Abstract
Case presentation. Male patient of Guatemalan origin with history of intermittent high fever, myalgia, arthralgia, generalized weakness, dizziness, and vomiting of gastric contents. He was initially treated in a private hospital with a diagnosis of acute febrile illness and referred to a national network hospital with a diagnosis of dengue with warning signs. On the third day of hospital stay a diagnosis of an imported malaria case by Plasmodium vivax was presented. **Treatment.** The patient was given antimalarial treatment consisting of chloroquine and primaquine. **Outcome.** The patient presented clinical improvement, and control laboratory tests were negative for Plasmodium vivax.

Keywords
Malaria, Plasmodium vivax, Vector Borne Diseases, Diagnosis, Case Study.

Resumen
Presentación del caso. Paciente masculino de origen guatemalteco con historia de fiebre alta de tipo intermitente, mialgias, artralgias, debilidad generalizada, mareo y vómito de contenido gástrico. Fue tratado inicialmente en un hospital privado con diagnóstico de síndrome febril agudo y referido a un hospital de la red nacional con diagnóstico de dengue con signos de alarma, al tercer día de estancia hospitalaria se diagnostica como un caso de malaria importado por *Plasmodium vivax*. **Intervención terapéutica.** Se le dio tratamiento antimalárico con cloroquina y primaquina. **Evolución clínica.** Presentó mejoría clínica y las pruebas de laboratorio de control reportaron resultados negativos para *Plasmodium vivax*.

Palabras clave
Malaria, *Plasmodium vivax*, Enfermedades Transmitidas por Vectores, Diagnóstico, Estudio de Caso.

Introduction

Malaria is a potentially fatal infectious disease caused by parasites transmitted to humans by the bite of female mosquitoes of the genus *Anopheles*, infected by obligate intracellular protozoa of the genus *Plasmodium*. Mainly four species cause disease: *P. vivax*, *P. falciparum*, *P. malariae, and P. ovale*.[i,ii]

P. vivax has an incubation period of 12 to 17 days after mosquito bite,[iii] although cases with incubation periods of more than 90 days have been documented.[iv]

Its cycle consists of two main stages. In the schizogonic stage, also called the intrinsic incubation period, which occurs in the vertebrate host, two cycles can be distinguished: one in the liver and the other in the red blood cells. In the hepatic cycle, the parasite reproduces in the liver cells for six to eight days. It then moves to the erythrocyte cycle, where it multiplies inside the red blood cells for two days before they rupture and release new parasites into the bloodstream.[i]

OPEN ACCESS

Caso importado de malaria por *Plasmodium vivax* en El Salvador. Un abordaje epidemiológico

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The sexual or sporogonic stage occurs in the mosquito and lasts eight to ten days. During this period, the sexual parasites fuse in the mosquito's stomach, forming sporozoites that migrate to the salivary glands. When the mosquito feeds on blood, the sporozoites can be transmitted to a new vertebrate host and transmit malaria.[i]

Plasmodium vivax is the most common parasite that causes malaria in humans, found primarily outside Africa.[v] In the Americas, it is responsible for 76 % of malaria cases.[v] For the 21st epidemiological week of the year 2023, Guatemala reported a total of 1276 cases in the country.[vi]

Malaria cases worldwide increased in 2021 from 245 million to 247 million.[vii] In the Americas during 2021, the World Health Organization (WHO) estimated 597 000 malaria cases and approximately 334 deaths.[v] Paraguay, Argentina, and El Salvador were certified malaria-free by WHO in 2018, 2019, and 2021, respectively.[v]

In 1980, El Salvador contributed 37 % of all reported cases in the region, while today, its contribution is less than 0.1 %.[viii] The last recorded case of locally transmitted *Plasmodium falciparum* occurred in 1995, whereas the latest death from *Plasmodium* infection occurred in 1984.[viii] In 2017, four cases of *Plasmodium vivax* were registered in the Country; three of them were imported, and the last was a relapse case from the previous year. [viii] El Salvador is the first Country in Central America to be certified malaria-free by WHO in 2021.[v] To prevent the recurrence of indigenous malaria transmission, the Country has increased its efforts through a multidisciplinary approach aimed at capturing cases, notifying them, providing timely treatment, and thoroughly investigating each case to carry out the necessary control actions.[ix]

The objective of this article is to underline the importance of epidemiological guidance in case management for an accurate and timely diagnosis based on the description of a malaria case in a patient of foreign origin.

Case presentation

This case is about a 23-year-old man from the poqomchí linguistic community in the rural area of Guatemala. He communicated through an interpreter. He entered El Salvador by land to work as a construction assistant in Santa Tecla, municipality of La Libertad. Six days after he arrived in the country, he consulted at the first aid station of his workplace with a history of one day of fever of moderate intensity of intermittent type, quantified at 38.1 °C, accompanied by lumbar pain and myalgias. He had no contributing medical history. Due to his clinical condition, the patient was referred to a private hospital where he was diagnosed with pharyngitis and given outpatient management with acetaminophen 500 mg orally every six hours and amoxicillin 500 mg every eight hours for seven days.

The patient consulted a private hospital after nine days, given that he presented intensified symptoms, such as a high intermittent fever of 39.4 °C, myalgias, arthralgias, generalized weakness, dizziness, and vomiting of gastric content of 500 mL on one occasion. He mentioned that he lives in a house with wooden walls, a tin roof, a dirt floor, only one room, and water obtained from a well and stored in containers with lids; also, he added that there are no health services nearby.

Laboratory tests reported mild anemia, low hematocrit, severe thrombocytopenia, elevated C-reactive protein, and COVID-19 was ruled out (Table 1); he was diagnosed with acute febrile syndrome. The patient was referred to a public network hospital, where he presented blood pressure of 110/60 mmHg, heart rate of 91 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 91 %. Pulmonary, cardiovascular, or hepatic alterations were not identified. Based on the above, dengue with alarm signs was suspected.

Follow-up examinations conducted after two days, reported hyperbilirubinemia and moderate anemia (Table 1). An abdominal ultrasound also reported splenomegaly with a longitudinal axis of 13 cm, with a volume of 480 mL, without solid or cystic focal lesions, with scarce free fluid in the abdominal cavity and right pleural effusion (Figure 1). In addition, the general stool examination reported the presence of *Ascaris lumbricoides*.

By the third day of hospital admission (day 12 of illness), dengue, chikungunya, and zika were excluded through laboratory tests, and *Plasmodium vivax* was identified by gross drop microscopy, with a parasite density of 5467 parasites/µL (Table 1 and Figure 2). A summary of the relevant events is shown in a timeline (Figure 3).

Therapeutic intervention

The patient was isolated with the use of a mosquito net and treatment was started with intravenous saline solution 1 L every eight hours, paracetamol 1 g intravenously every six hours, oxygen by nasal cannula at 3 L per minute, and mebendazole 100 mg orally every 12 hours; the latter was suspended due to the detection of *Plasmodium vivax*. Antimalarial therapy was indicated[x,xi] with

Tabla 1. Laboratory tests results

Laboratory tests results	Day 9*	Day 11*	Day 12*
Hemoglobin	10.8 g/dL	-	7.8 g/dL
Hematocrit	31 %	-	22.7 %
Leukocytes	-	-	6390/µL
Neutrophils	68.7 %	-	47.7 %
Lymphocytes	18.6 %	-	39.9 %
Platelets	28 000/mL	-	114 000/mm^3
COVID-19 antigen	Negative	-	-
C-reactive protein	320 mg/dL	-	-
Mean Corpuscular Volumen	-	-	80.8 fL
Mean Corpuscular Hemoglobin	-	-	27.8 fL
General stool test	*Ascaris lumbricoides*	-	-
Total Bilirubin	-	2.14 mg/dL	-
Indirect Bilirubin	-	1.18 mg/dL	-
Aspartate aminotransferase (AST)	-	61.2 UI/L	-
Alanine aminotransferase (ALT)	-	60.7 UI/L	-
Sodium	-	133.3 mEq/L	-
PCR Dengue	-	-	Negative
PCR Zika	-	-	Negative
PCR Chikungunya	-	-	Negative
Thick drop	-	-	*Plasmodium vivax*: Parasitic density 5467 parasite/µL blood

* Sick days.

Source: Data obtained from clinical records.

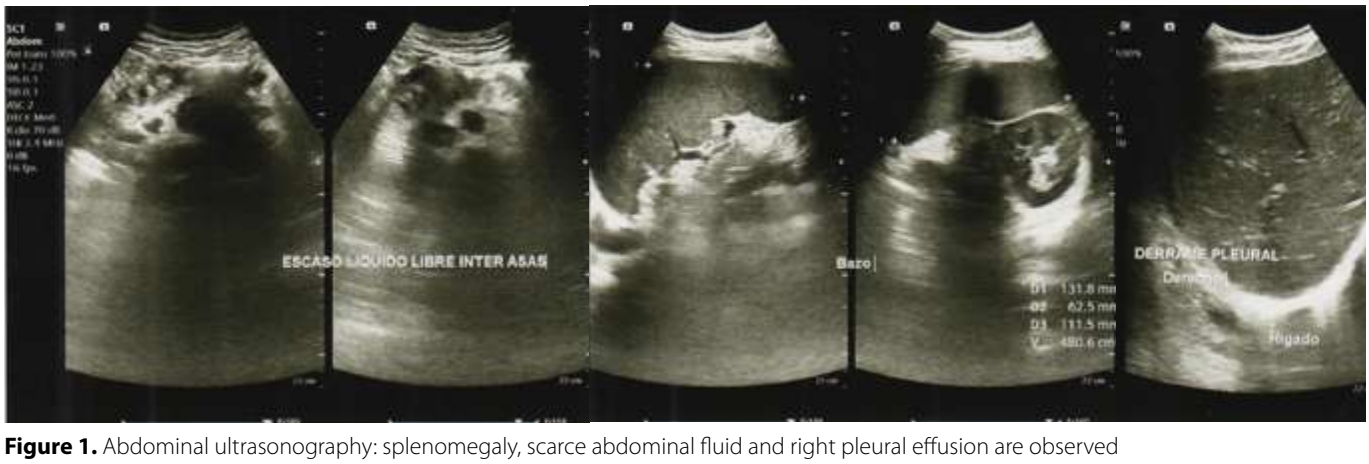

Figure 1. Abdominal ultrasonography: splenomegaly, scarce abdominal fluid and right pleural effusion are observed

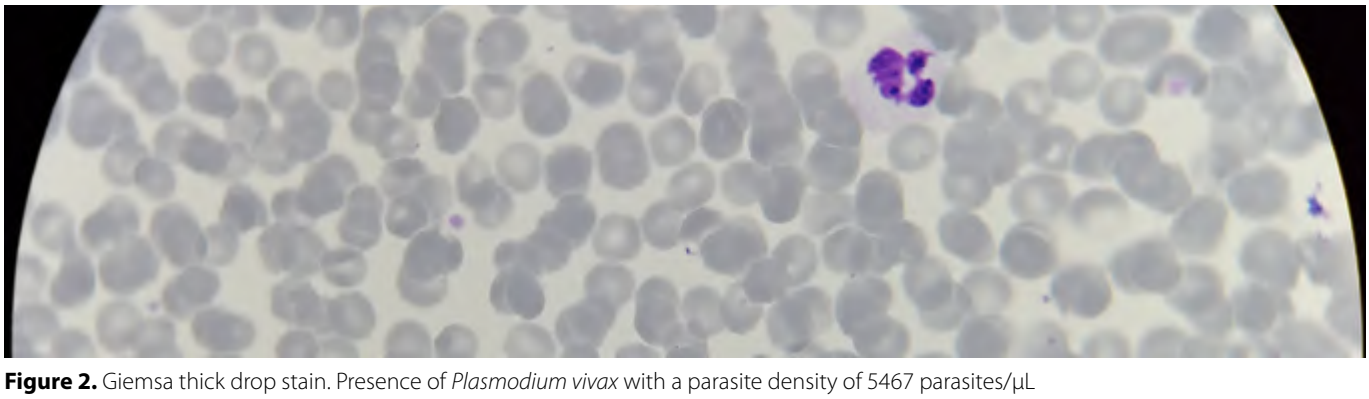

Figure 2. Giemsa thick drop stain. Presence of *Plasmodium vivax* with a parasite density of 5467 parasites/µL

chloroquine 750 mg orally every day (at a dose of 10 mg/Kg) for two days; then, 375 mg orally on the third day (at a dose of 5 mg/Kg), accompanied by primaquine 15 mg orally every day for seven days, and acetaminophen 500 mg orally every six hours, if the body temperature was higher than 37.5 °C; however, fever was not reported again. The case was reported to the epidemiological authorities through the epidemiological surveillance system of El Salvador.

Health authorities received notification as part of the epidemiological management. A sample was sent to the National Public Health Laboratory for quality control and confirmation. Thick blood smear tests collected from workers in contact with the patient, were obtained for analysis. A total of 30 samples were reported among the contacts, all with negative results.

Several vector and entomological surveillance measures, including inspection of the entomological situation within a two-kilometer radius, spraying the area with deltamethrin (adulticide), and application of larvicide with temephos in specific areas to detect possible vectors, were applied. In addition, domiciliary visits to treat water containers with 1 % temephos granules. In addition, water areas were inspected, but no transmitting vector was found.

Clinical evolution

After seven days of treatment, the patient was discharged from the hospital, and during the home visit made two days after discharge, clinical improvement presented; three thick blood smear microscopies were performed as a follow-up control for *Plasmodium vivax*, at 14, 21, and 28 days after the diagnosis of malaria, all with negative results.

Clinical diagnosis

The diagnosis of severe *Plasmodium vivax* malaria was confirmed by thick blood smear microscopy tests, due to the following complications: hyperbilirubinemia, splenomegaly, right pleural effusion, and anemia due to hemolysis.[xii]

Discussion

El Salvador has been certified as a malaria-free country since 2021;[iv] however, malaria-imported cases are still reported.[viii] This situation is also present in China certified during the same year.[ix] As a result, the recurrence of indigenous malaria transmission continues to be a potential risk. Therefore, all cases should be detected, reported, treated, and investigated in a timely manner.[ix]

In 2015, the United Nations Organization, in partnership with the Bill & Melinda Gates Foundation, published a framework for malaria eradication.[xiii] Similarly, the WHO published a technical strategy for the eradication of *P. vivax*.[xiii] However, public health tools for diagnosis, treatment, prevention, and control are sub-optimal in many endemic areas,[xiii] and a special effort is required in malaria-free countries to strengthen the national response and prevent the recurrence of indigenous malaria transmission.[vii,ix,xiv]

In the Americas, Paraguay and Argentina have been certified as malaria-free countries by the WHO since 2018 and 2019, respectively.[v] It gives some cause for optimism, as several endemic countries have shown progress in this regard;[vii] malaria control and elimination in endemic areas may assert impacts on the prevalence of imported cases and measures to prevent

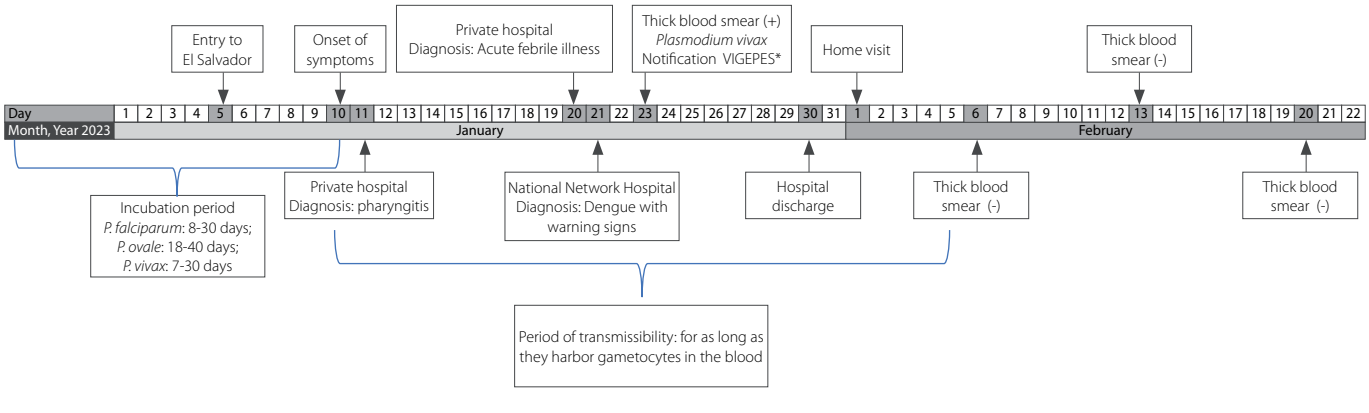

Figure 3. Timeline with key events in the development of the case

*VIGEPES: Epidemiological Surveillance System of El Salvador

the return of indigenous cases to malaria-free areas.[vii] To improve surveillance of *Plasmodium spp.*, contribute to the effective diagnosis of malaria and treatment in both endemic and non-endemic areas.[vii]

The increase in total global cases and deaths during 2020 and 2021 is partially traceable to the COVID-19[vii] pandemic, as the shutdown and movement restriction of healthcare providers during the pandemic disrupted the continuity of malaria control and elimination programs.[xv]

In the case described, symptoms began on the sixth day after the patient entered El Salvador; if considering the minimum incubation period (12 days),[iii] the patient became infected outside El Salvador. Therefore, this is an imported case of malaria, given that the patient had been in an endemic country and was in the incubation period at the time of his arrival in El Salvador.

Population movement and international travel lead to tourism and work opportunities in non-endemic areas that increase the risk of case import,[i] which, in turn, highlights the need for adequate surveillance and early detection.[ix] According to data collected in a systematic review of malaria outbreaks in China from 1990 to 2013, more than half of all outbreaks are traced to population movements.[xvi] This information is consistent with the findings of this case.

Efforts to control and eliminate *P. vivax* may not present the expected impact due to emerging drug resistance.[xvii] Endemic countries should regularly evaluate the therapeutic efficacy of antimalarial drugs to adjust their therapeutic guidelines.[xvii] In this case, the patient responded to conventional treatment, demonstrating the sensitivity of the parasite.

For the initial approach to the patient and a timely diagnosis of febrile infectious diseases in foreigners, it is advisable to guide the diagnosis considering the clinical symptoms, laboratory, and epidemiological criteria according to their country of origin.[xiv] In this specific case, tests were performed to rule out arbovirosis, due to the prevalence of these diseases in the country. Dengue, Zika, and chikungunya diseases were suggested as presumptive diagnoses; as these were discarded, malaria diagnosis was adopted, based on epidemiological criteria, including the characteristics of the patient's home, which favored the survival and reproduction of the vector,[xviii] as well as the endemicity and characteristics of the disease in neighboring countries.[xiv]

In the patient's hematologic findings, thrombocytopenia[xix] and anemia stand out. These alterations were the most common in a study published in 2019,[xx] in which the authors suggest as diagnostic support criteria for malaria the presence of thrombocytopenia in cases of acute febrile illness, whether or not accompanied by anemia, and recommend taking the management of these abnormalities into account to reduce the associated complications, thus suggesting considering the possibility of malaria in these patients.[xx]

Emphasis is placed on the importance of continuous education of health personnel to consider and diagnose malaria promptly, especially in imported cases. In addition, to implement prioritized vector control measures in endemic areas.[vii,xiii]

In this case, the importance of epidemiological surveillance and proper management of malaria, even in non-endemic areas, is highlighted, and emphasis is placed on the need to address the environmental and social risk factors that play a fundamental role in the patient's clinical condition and subsequent recovery.[vii,xiii,xiv]

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References

i. Heymann D. El control de las enfermedades transmisibles. 20th ed. Washington D.C.: American Public Health Association; 2017.
ii. Nemhauser JB, editor. CDC yellow book 2024: health information for international travel. New York, NY: Oxford University Press; 2023.
iii. Orish V, Afutu L, Ayodele O, Likaj L, Marinkovic A, Sanyaolu A. A 4-Day Incubation Period of *Plasmodium falciparum* Infection in a Nonimmune Patient in Ghana: A Case Report. Open Forum Infect. Dis. 2019;6(1):ofy169. DOI: 10.1093/ofid/ofy169
iv. Brasil P, De Pina Costa A, Pedro RS, Da Silveira Bressan C, Da Silva S, Tauil PL, *et al.* Unexpectedly long incubation period of

Plasmodium vivax malaria, in the absence of chemoprophylaxis, in patients diagnosed outside the transmission area in Brazil. Malar. J. 2011;10(1):122. DOI: 10.1186/1475-2875-10-122

v. Organización Mundial de la Salud. World Malaria Report. 2022. Available at: https://reliefweb.int/report/world/world-malaria-report-2022?gad_source=1&gclid=CjwKCAiA-vOsBhAAEiwAIWR0TSo6Fb-i1CtMAZwmqu-hAW0ZBY5hmZeSNDzWrhTn39WvAg4aet-o5BoCAjkQAvD_BwE

vi. Dirección epidemiológica y gestión de riesgos, Situación epidemiológica de malaria a la semana epidemiológica 21, Ministerio de Salud Ministerio de Salud Pública y Asistencia Social , Guatemala. 2023. Date of citation: 27/06/2023. Available at: https://epidemiologia.mspas.gob.gt/informacion/vigilancia-epidemiologica/salas-situacionales/6-vectoriales-parasitarias

vii. González-Sanz M, Berzosa P, Norman FF. Updates on Malaria Epidemiology and Prevention Strategies. Curr. Infect. Dis. Rep. 2023;25(7):131-139. DOI: 10.1007/s11908-023-00805-9

viii. Burton RA, Chévez JER, Sauerbrey M, Guinovart C, Hartley A, Kirkwood G, *et al.* Factors Associated with the Rapid and Durable Decline in Malaria Incidence in El Salvador, 1980-2017. Am. J. Trop. Med. Hyg. 2018;99(1):33-42. DOI: 10.4269/ajtmh.17-0629

ix. Zhu M, Zhang C, Zhang Y, Wang Z, Ma X, Dai S, *et al.* An epidemiological analysis of imported malaria in Shanghai during a COVID-19 outbreak. Malar. J. 2022;21(1):245. DOI: 10.1186/s12936-022-04273-9

x. Chu CS, White NJ. The prevention and treatment of *Plasmodium vivax* malaria. PLOS Med. 2021;18(4):e1003561. DOI: 10.1371/journal.pmed.1003561

xi. Kaur D, Sinha S, Sehgal R. Global scenario of *Plasmodium vivax* occurrence and resistance pattern. J. Basic Microbiol. 2022;62(12):1417-1428. DOI: 10.1002/jobm.202200316

xii. Sandoval De Mora M. Manejo clínico-terapéutico de la malaria grave. Bol. Venez. Infectol. 2022. DOI: 10.54868/BVI.2022.33.1.3

xiii. Lover AA, Baird JK, Gosling R, Price RN. Malaria Elimination: Time to Target All Species. Am. J. Trop. Med. Hyg. 2018;99(1):17-23. DOI: 10.4269/ajtmh.17-0869

xiv. Paquet D, Jung L, Trawinski H, Wendt S, Lübbert C. Fever in the returning traveler. Dtsch. Ärztebl. Int. 2022 Jun 7. DOI: 10.3238/arztebl.m2022.0182

xv. Tu H, Feng J, Yu C, Lin K, Peiyu W, Shaomi X, *et al.* Asymptomatic malaria infection at the China-Vietnam border: Knowledge and implications for the cross-border migrant population during the COVID-19 pandemic. Travel Med. Infect. Dis. 2022;47:102307. DOI: 10.1016/j.tmaid.2022.102307

xvi. Lu G, Zhou S, Horstick O, Wang X, Liu Y, Müller O. Malaria outbreaks in China (1990-2013): a systematic review. Malar. J. 2014;13(1):269. DOI: 10.1186/1475-2875-13-269

xvii. Ferreira MU, Nobrega De Sousa T, Rangel GW, Johansen IC, Corder RM, Ladeia-Andrade S, *et al.* Monitoring *Plasmodium vivax* resistance to antimalarials: Persisting challenges and future directions. Int. J. Parasitol. Drugs Drug Resist. 2021;15:9-24. DOI: 10.1016/j.ijpddr.2020.12.001

xviii. Botero D. Parasitosis humanas. 5° Edición. Medellin, Colombia: Corporación de Investigaciones Biológicas; 2012.

xix. Castilla Herrera N, González A. Paludismo falciparum y trombocitopenia severa. Rev. Latinoam. Infectol. Pediátrica. 2018;31(1):32-35. Available at: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=81336

xx. Awoke N, Arota A. Profiles of hematological parameters in *Plasmodium falciparum* and *Plasmodium vivax* malaria patients attending Tercha General Hospital, Dawuro Zone, South Ethiopia. Infect. Drug Resist. 2019;Volume 12:521-527. DOI: 10.2147/IDR.S184489

Case report

Lhermitte-Duclos Disease and Cowden Syndrome. A Case Report

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Abstract
Case presentation. The report is of a 45-year-old female patient with a history of high blood pressure and multiple surgeries for cancer, including thyroid cancer, parotid carcinoma, breast cancer, and endometrial cancer. Incidentally, a lesion in the right cerebellar hemisphere was identified in a tomography of the paranasal sinuses, which was later confirmed in a brain magnetic resonance. The lesion had a striated appearance, characteristic of dysplastic gangliocytoma of the cerebellum or Lhermitte-Duclos disease. Considering the history of various types of cancer and the diagnostic criteria proposed by the International Cowden Consortium and the National Comprehensive Cancer Network, the diagnosis of Cowden syndrome, which had gone unnoticed until now, was established. **Treatment.** Subsequently, the patient was hospitalized due to the growth of a metastatic mass in the right hemicollar with involvement of the brachial plexus, cervical, infraclavicular, and right axillary lymph nodes. **Outcome.** She is receiving palliative treatment to control the symptoms and improve her quality of life, since she expressed her refusal to undergo tumor resection surgery.

Keywords
Lhermitte Duclos Disease, Incidental Findings, Diagnostic Imaging.

Resumen
Presentación del caso. Se trata de una paciente femenina de 45 años con antecedentes de hipertensión arterial y múltiples cirugías por cáncer, entre ellas, cáncer de tiroides, carcinoma de parótida, cáncer de mama y cáncer endometrial. De manera incidental se identificó una lesión en el hemisferio cerebeloso derecho en una tomografía de senos paranasales, que fue confirmada a través de una resonancia magnética cerebral. La lesión presentaba una apariencia estriada, característica de gangliocitoma displásico del cerebelo o enfermedad de Lhermitte-Duclos. Considerando los antecedentes de diversos tipos de cáncer y los criterios de diagnóstico propuestos por el Consorcio Internacional Cowden y la Red Nacional Integral del Cáncer, se estableció el diagnóstico de síndrome de Cowden que había pasado desapercibido hasta el momento. **Intervención terapéutica.** Posteriormente, la paciente fue hospitalizada debido al crecimiento de una masa metastásica en el hemicuello derecho con afectación del plexo braquial, adenopatías cervicales, infraclaviculares y axilares derechas. **Evolución clínica.** En la actualidad, se encuentra recibiendo tratamiento paliativo con el objetivo de controlar los síntomas y mejorar su calidad de vida, ya que expresó su negativa a someterse a una intervención quirúrgica de resección tumoral.

Palabras clave
Enfermedad de Lhermitte-Duclos, Hallazgos Incidentales, Diagnóstico por Imagen.

Lhermitte-Duclos disease and Cowden syndrome. A case report

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There are no conflicts of interest.

Introduction

Lhermitte-Duclos disease (LDD), also known as dysplastic gangliocytoma of the cerebellum, is a rare condition first described by Lhermitte and Duclos in 1920. Since then, about 300 cases have been documented in the literature.[i] It is a slow-growing benign tumor composed of atypical ganglion cells. According to the 2021 World Health Organization classification for the central nervous system, it is a grade I mixed glioneuronal tumor.[ii] It usually occurs in patients between 30 and 50 years of age, both sexes. Clinical symptoms are related to its location in the posterior fossa and may include headache, nausea, and visual problems.[i-iii]

It is worth mentioning that this type of gangliocytoma can emerge in isolation or association with Cowden syndrome (CS), in up to 35 % of cases.[iii] This syndrome is a rare multisystem disease characterized by multiple hamartomas in various tissues, particularly in the skin and mucous membranes, as well as in the gastrointestinal tract, breast, thyroid, and brain, resulting in a high risk of malignant neoplasms, especially in the breast, thyroid, and endometrium.[iv] Cowden syndrome results from loss-of-function mutations in the phosphatase and tensin homologous tumor suppressor gene (PTEN), located on chromosome 10q23.[v] It affects approximately one in 200 000 births, considered underestimated due to its variable penetrance.[vi] As of 2018, only 44 patients had been identified in the literature.[vii]

The diagnosis of Cowden syndrome is eminently clinical, based on the diagnostic criteria proposed by the International Cowden Consortium and the National Comprehensive Cancer Network (NCCN), which include mucocutaneous lesions and the presence of Lhermitte-Duclos disease, which is the primary established diagnostic criterion.[viii,ix]

Case presentation

The case is of a 45-year-old female patient, who was treated for the past two years in endocrinology service at a tertiary public hospital in San Salvador, El Salvador. The patient had a history of previous interventions in private clinics and a peripheral public hospital for diagnoses of arterial hypertension and a history of several types of metachronous neoplasms without genetic evaluation, including thyroid cancer, with thyroidectomy 14 years ago, developing hypothyroidism and secondary hypoparathyroidism; epidermoid carcinoma of the right parotid gland with complete resection 12 years ago; invasive micropapillary carcinoma of the right breast, with right mastectomy seven years ago, and endometrial cancer, with a hysterectomy five years ago. The patient received daily treatment with levothyroxine sodium 50 µ, calcium carbonate 1800 mg, vitamin D3 0.25 µ, irbesartan 150 mg, and propranolol 40 mg, all administered orally.

During a routine follow up, the patient reported nasal obstruction and occasional headache, with no other relevant symptoms. On physical examination, the patient presented good general condition, vital signs were within normal parameters, with a blood pressure of 120/70 mmHg, heart rate of 85 beats per minute, respiratory rate of 16 breaths per minute, body temperature of 36.4 °C, and blood oxygen saturation of 98 %. No pathological secretions were found inside the nasal cavities, neither pain on facial palpation, nor neurological alterations.

Laboratory test results (Table 1) showed low thyroid-stimulating hormone levels and elevated free thyroxine levels therefore, the dose of levothyroxine sodium was adjusted, decreasing it to 25 µ compared to the previous dose of 50 µ. In addition, the usual medications to control the associated pathologies were maintained.

The tomographic study of the paranasal sinuses showed signs of adequate pneumatization of the paranasal sinuses and nasal cavities, with no evidence of mucosal thickening or pathologic occupation of the sinuses. Incidentally, an ill-defined hypodense lesion was identified in the right cerebellar hemisphere, without specific features, which did not cause a significant mass effect on the surrounding structures

Table 1. Laboratory exams

Exams	Routine evaluation results	Results at the six-month evaluation	Reference values
Thyroid stimulating hormone	0.21 UI/mL	0.81 UI/mL	0.34 - 5.60 UI/mL
Free thyroxine	1.33 ng/dL	1.59 ng/dL	0.61 - 1.12 ng/dL
Antithyroglobulin	0.00 UI/mL	-	0.00 - 115.00 UI/mL
Thyroglobulin	5.11 ng/mL	-	3 - 42 ng/mL
Calcium	8.44 mg/dL	5.39 mg/dL	8.5 - 10.2 mg/dL
Hemoglobin	-	10.00 g/dL	12 - 16 g/dL
White blood cells	-	11.20×10^3/µL	5 - 10×10^3/µL
Platelets	-	328×10^3/µL	150 - 400×10^3/µL

Source: Data obtained from clinical records.

(Figure 1). Due to this finding, the Radiology Service recommended complementing with brain magnetic resonance imaging (MRI). Brain MRI (Figure 2 and 3) confirmed the presence of an intraaxial lesion in the right cerebellar hemisphere, with ovoid morphology, regular contours, and striated configuration with alternating hypo- and hyperintense bands in T2-weighted sequences. There was no perilesional edema or mass effect over the fourth ventricle. In addition, it showed a T2 pattern in diffusion sequences, and following intravenous contrast administration, there was a slight peripheral enhancement and punctate areas of intratumoral enhancement with dimensions of 22.3 x 38.8 x 21.8 mm in its dorsoventral, laterolateral, and rostrocaudal axes. Multivoxel spectroscopy showed reduced N-acetyl aspartate and the presence of an inverse lactate peak. These findings were compatible with right cerebellar dysplastic gangliocytoma or Lhermitte-Duclos disease diagnosis.

This finding, assessed in combination with the patient's history, and based on the NCCN guidelines for the diagnosis of Cowden syndrome, allowed the identification of and compliance with the main criteria, such as breast cancer, thyroid tumor, uterine cancer, and Lhermitte-Duclos disease. In addition, the presence of multiple forehead papules compatible with trichilemmomas, intentionally identified, corresponds to another relevant criterion in the patient.

Therapeutic intervention

The patient remained asymptomatic; though, six months after diagnosis, she consulted for a right hemicollar mass of progressive growth, accompanied by edema, paresthesias, and progressive paralysis in the right upper limb. The patient denied any other symptoms. On physical examination, the mass showed a solid consistency, firm to the touch with adherence to deep planes, measuring approximately 4 × 3 cm. In addition, the right upper limb showed a loss of muscle strength. Hospital admission was indicate.

Laboratory tests showed normal thyroid stimulating hormone and free thyroxine values, low calcium, hemoglobin levels as well as mild leukocytosis (Table 1).

During the hospitalization, an ultrasound was performed, which reported a heterogeneous mass in the right supra-clavicular region, as well as multiple cervical, infraclavicular, and right axillary lymphadenopathies. As a result, an MRI of the neck and brachial plexus was ordered (Figure 4), which

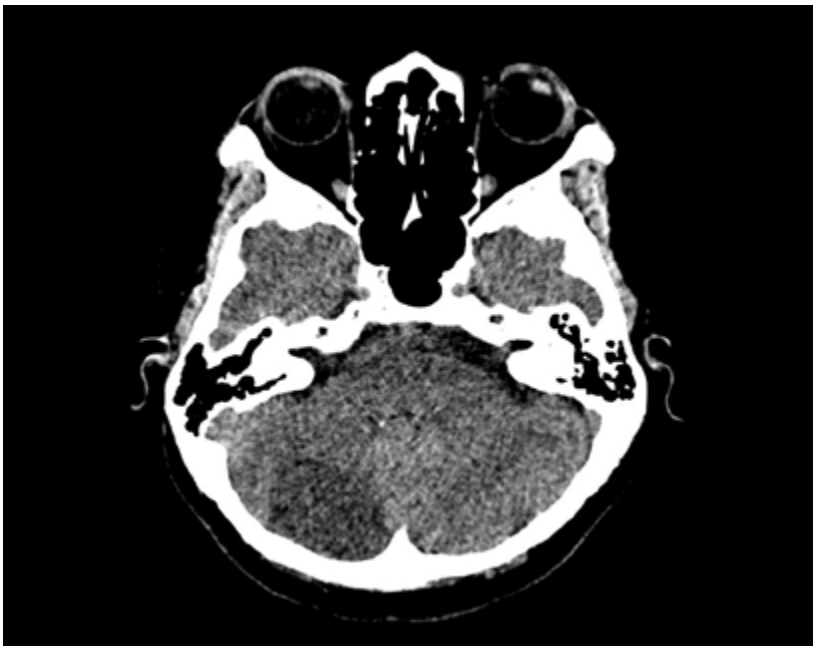

Figure 1. Single phase computed tomography study. Axial section of the posterior fossa in brain tomographic window. There is evidence of hypodense lesion in the right cerebellar hemisphere, with ovoid morphology, non-homogeneous appearance. There is no significant mass effect on the fourth ventricle, nor calcifications inside it

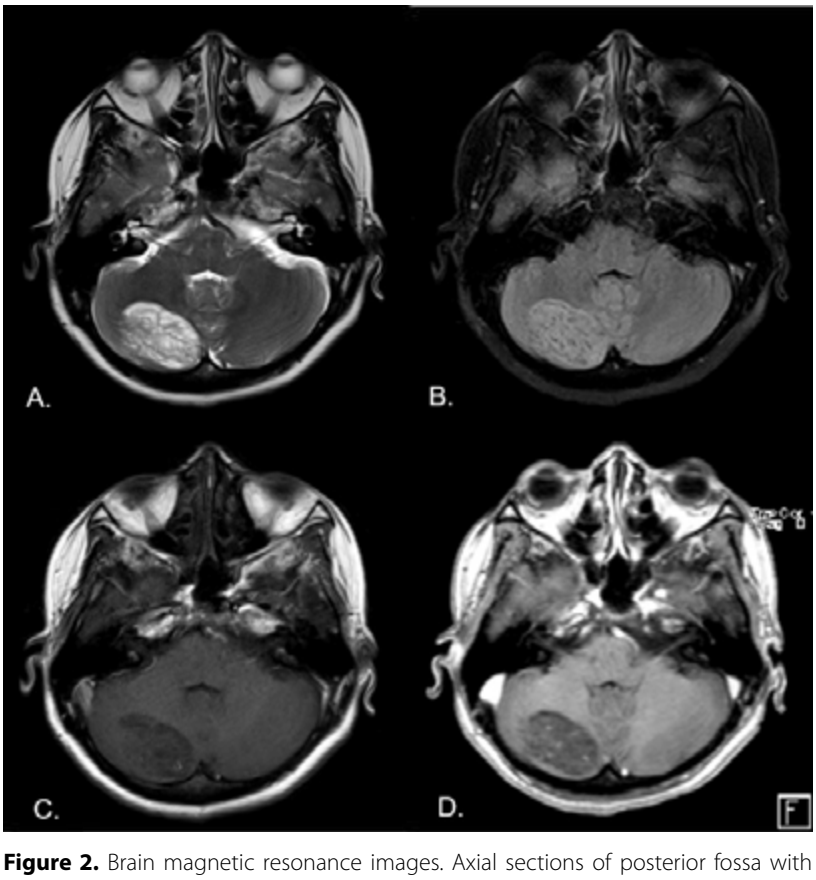

Figure 2. Brain magnetic resonance images. Axial sections of posterior fossa with T2-weighted sequences (A), FLAIR (B) T1 in single phase (C) and T1 postcontrast. Well-defined intraaxial lesion in the right cerebellar hemisphere. The lesion is mainly hyperintense on T2-weighted and FLAIR sequences (A and B), with a striated appearance, with alternating hyperintense and hypointense bands in relation to the adjacent gray matter. On T1-weighted images (C) it presents hypointense to isointense striations in the gray matter. After intravenous contrast administration (D), there is a slight peripheral enhancement and punctate areas of intratumoral enhancement. There is no evidence of vasogenic edema or local mass effect associated with the lesion

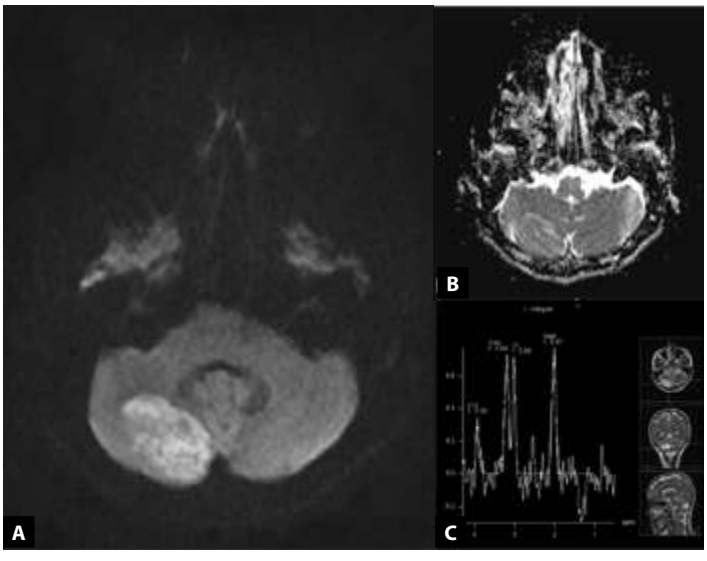

Figure 3. Brain magnetic resonance images. Diffusion sequences (A), ADC mapping (B) and long TE multivoxel spectroscopy, 135 ms (C). The cerebellar lesion shows a T2 effect in the diffusion sequences and ADC mapping (A and B), without areas of restrictive pattern. Multivoxel spectroscopy shows a reduction of N-acetylaspartate and the presence of an inverted lactate peak

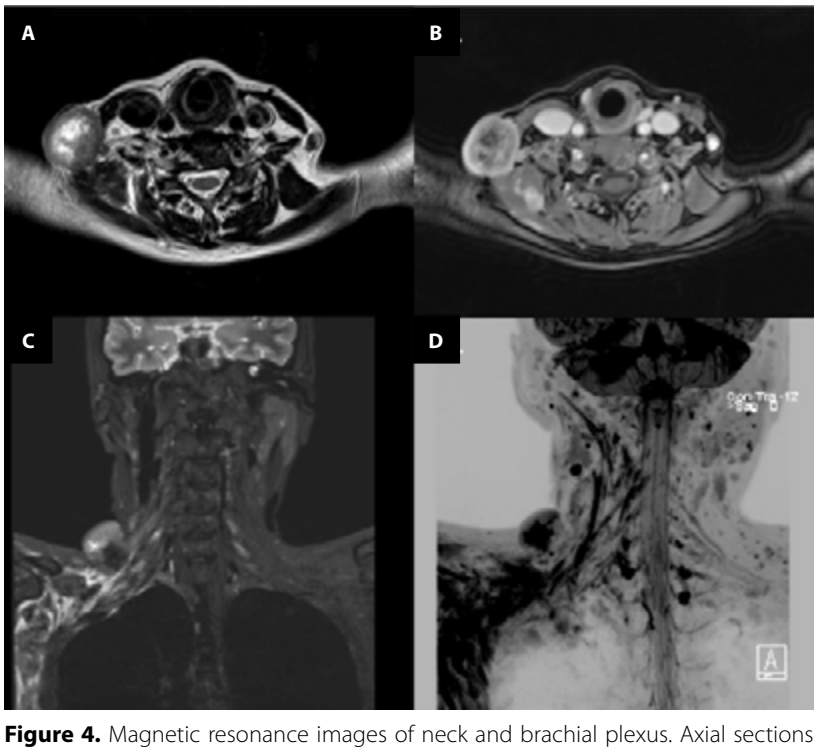

Figure 4. Magnetic resonance images of neck and brachial plexus. Axial sections of T2-weighted sequences (A), post-contrast T1 (B), oblique coronal section T2 SPACE / STIR sequence, coronal section of T2 SPACE / STIR 3D-MIP inverted grayscale sequence (C). A right supraclavicular solid mass is identified with irregular borders and heterogeneity in the T2-weighted sequence, showing a hyperintense center and heterogeneous enhancement after intravenous contrast administration, with central necrosis area. It infiltrates the deep tissues and roots of the brachial plexus. Brachial plexus trunks and fascicles show nodular thickening and alterations in signal intensity on T2/STIR sequence, and show enhancement after intravenous contrast administration. In addition, multiple cervical, infraclavicular and axillary adenopathies are observed on the right side (A-D). These findings are associated with atrophy and diffuse hyperintensity of the trapezius, scalene, as well as supraspinatus and infraspinatus muscles on the right side, with enhancement in relation to denervation (not shown)

confirmed the presence of the mass in the right supraclavicular region, infiltrating the brachial plexus and the ipsilateral scalene, trapezius, and shoulder girdle muscles, with muscle atrophy and the presence of cervical and right axillary lymphadenopathy. The mass biopsy confirmed the presence of a malignant epithelial neoplasm arranged in nests and cords infiltrating the stroma. Immunohistochemistry analysis with breast panel reported estrogen receptor-positive in 90 % of screened cells, progesterone receptor positive in 60 % of cells, HER2: negative (+/+++), and P53: positive in 1 % of cells. Ki67: negative. The findings could correspond to metastasis from breast cancer.

Clinical evolution

The patient was discharged from the hospital 11 days after admission, since she expressed her refusal to undergo surgery for tumor resection. At her last medical follow-up, palliative treatment was prescribed to control her symptoms and improve her quality of life. The patient continued with medications for the underlying chronic conditions and tramadol 50 mg orally indicated every eight hours for pain management.

Due to the autosomal dominant inheritance pattern of this disease, genetic counseling was provided to family members, informing them about Cowden syndrome, its clinical features, and the different associated tumors. The relevance of regular medical follow-up was emphasized, including periodic evaluations and specific screening tests according to established guidelines.

Clinical diagnosis

Lhermitte-Duclos disease in association with Cowden's syndrome (COLD syndrome).

Discussion

Lhermitte-Duclos disease is a rare, slow-growing hamartomatous lesion of the cerebellar cortex. Its main characteristic is the presence of dysplastic rather than neoplastic cells in the cerebellum.[i] It occurs most frequently in the third and fourth decades of life. However, it can manifest at any time from birth to the sixth decade.[i,x]

The nature and pathogenesis of LDD are still a matter of debate. Histologically, it is characterized by abnormal thickening and myelination of the molecular layer in the cerebellum, attenuation or absence of Purkinje cells, infiltration of the granular cell layer by abnormal dysplastic ganglion cells, and variability in white matter vacuoliza-

tion. These histological findings are hallmarks of the disease.[vii]

Characteristic symptoms include cranial nerve palsy, gait instability, ataxia, and sudden neurological deterioration due to acute or chronic hydrocephalus.[x] The severity of symptoms can vary depending on the volume of the lesion.[iii] As the tumor grows, signs of increased intracranial pressure may occur, such as headaches, nausea, vomiting, papilledema, mental disorders, and loss of consciousness. The duration of symptoms varies from a few months to more than ten years. Moreover, the tumor may present asymptomatically and be discovered incidentally during imaging studies.[xi]

Radiology plays an essential role in the diagnosis of ELD.[iii,x-xiv] MR is preferred over computerized tomography for evaluating the posterior fossa because of its ability to provide detailed soft-tissue imaging and perform specialized sequences that provide additional information on the structure and function of the cerebellum and brainstem. On computerized tomography, it is seen as a hypo-attenuated or iso-attenuated cerebellar mass adjacent to the normal cerebellum, without contrast uptake, and calcifications may be present.[x,xi]

On MR images, it is observed that in T1-weighted sequences there is a hypointense signal, while in T2-weighted sequences there is an alternating pattern of high and low signal with a classic striated appearance similar to "tiger stripes."[xi-xiv] These radiological findings correlate with pathological changes where the central core of the T1 hypointensity and T2 hyper-intensity corresponds to thinned white matter, widening of the granular cell layer and the inner portions of the dysplastic molecular layer. The outer layer (T1 isointense, T2 iso to hypointense) is attributed to the outer molecular layer and leptomeninges. On susceptibility sequences, abnormal vessels and areas of calcification can be observed.[x]

In special MR sequences, specifically in diffusion sequences, a T2 effect is evident in the abnormally thickened leaflets. In spectroscopy, a decrease in N-acetylaspartate and an increase in lactate are detected, which are characteristic features.[x-xii] Finally, on perfusion imaging, elevated local perfusion is usually observed.[viii]

In this case, the cerebellar lesion identified on MR showed the typical appearance described in the medical literature, which was relevant to reach the diagnosis.

LDD and CS are related since approximately 35 % of patients with CS characteristically present cerebellar dysplastic gangliocytoma.[iii] This connection has led it to be known as Cowden-Lhermitte-Duclos syndrome (COLD syndrome).[i,iii] Detection of one of these disorders may require further evaluation and follow-up.

Cowden syndrome (also known as Cowden disease or multiple hamartoma syndrome, OMIM 158350) is a rare genetic disorder with a highly variable autosomal dominant pattern of inheritance. It was first described in 1963 by Lloyd and Dennis in a patient named Rachel Cowden.[vi,xv] Its characteristics are the presence of multiple hamartomas of ectodermal, mesodermal, and endodermal origin.[vii] Loss of PTEN gene function contributes to benign hamartomatous tissue overgrowth, especially in the skin and mucous membranes, as well as in the gastrointestinal tract, breast, thyroid, and brain, thus increasing the risk of malignant neoplasms, especially breast cancer, thyroid cancer, and uterine cancer.[iv] It is a typical young adult disease, presenting in the second or third decade of life, with an average age at diagnosis of 39 years (between 40 to 75 years). It is slightly more common in women.[xv]

In 1997, it was discovered that CS is related to mutations in the PTEN gene, present on chromosome 10q23.[xv] Approximately 80 % of patients have an identifiable mutation in this gene. PTEN is a tumor suppressor gene that encodes a phosphatase and negatively regulates the PI3K/AKT and mTOR signaling pathways. It controls cell proliferation, cell cycle progression, and apoptosis. Loss of PTEN function contributes to cellular transformation and increases the risk of developing cancer in multiple organs.[iv,xv]

Benign manifestations include multiple gastrointestinal polyps (93 %, with 44 % as hamartomas), dermatological features (98 %), macrocephaly (93 %), benign breast lesions (74 %), thyroid lesions (71 %) and vascular malformations (18 to 35 %).[xvi] Patients have a lifetime risk of breast cancer (85 %), thyroid cancer (38 %), endometrial cancer (28 %), colorectal cancer (9 %), and melanoma (6 %).[vi,xv]

The updated diagnostic criteria for CS were developed by Pilarski *et al.* in 2013,[viii] and recognized by the National Comprehensive Cancer Network. According to the NCCN guidelines (Table 1),[viii,ix] the diagnosis is based on the presence of a pathogenic/likely pathogenic variant in the PTEN gene and, or specific clinical criteria: three or more major criteria (one of which must be macrocephaly, ELD or gastrointestinal hamartomas) or two major and three minor criteria.

These guidelines recommend imaging surveillance in patients with CS for early detection of possible cancers, allowing timely

resection of neoplasms.[ix] This intentional screening approach aims to identify and treat any malignancy early, thus improving prognosis and clinical outcomes in patients.[xv]

The recommended treatment for LDD is observation with symptom control unless mass effect symptoms are sufficiently problematic to warrant surgery. Complete surgical resection is associated with low recurrence rates.[iii] However, during surgery, the main technical challenge is the lack of a clear margin between the tumor and normal brain tissue. Complete resection of the lesion is difficult due to the slow growth of the tumor and diffuse boundaries with the adjacent cerebellum.[x] Intraoperative ultrasound has been described as a useful tool for real-time evaluation during neurosurgical operations.[xiv]

Ethical aspects

In the case presented, the patient's confidentiality was respected and the informed consent of the person responsible for the patient was obtained.

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References

i. Ideta MML, Paschoalino MCO, Oliveira LM, Santos NBD, Sanz MRV, Amorim RLOD. Lhermitte-Duclos Disease and Cowden Syndrome: A Case Report and Literature Review. Arq Bras Neurocir. 2019;38(04):319-323. DOI: 10.1055/s-0039-1693682

ii. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, *et al.* The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-1251. DOI: 10.1093/neuonc/noab106

iii. Joo GJ, Doumanian J. Radiographic Findings of Dysplastic Cerebellar Gangliocytoma (Lhermitte-Duclos Disease) in a Woman with Cowden Syndrome: A Case Study and Literature Review. Radiology Case. 2020;14(3):1-6. DOI: 10.3941/jrcr.v14i3.3814

iv. Morisaki T, Kashiwagi S, Kouhashi R, Yabumoto A, Asano Y, Takashima T, *et al.* Cowden Syndrome Diagnosed by Bilateral Breast Cancer with Lhermitte-Duclos Disease: A Case Report. Case Rep Oncol. 2020;13(1):419-423. DOI: 10.1159/000506979

v. Nelen M. Germline mutations in the PTEN/MMAC1 gene in patients with Cowden disease. Human Molecular Genetics. 1997;6(8):1383-1387. DOI: 10.1093/hmg/6.8.1383

vi. Montagne W, Wang RC. Cowden Syndrome Case Report: Use of an Ultrasonic Surgical Aspirator for Cosmetic Removal of Lip Hamartomas. Cureus. 2022 Oct 2. DOI: 10.7759/cureus.29839

vii. Dhamija R, Weindling SM, Porter AB, Hu LS, Wood CP, Hoxworth JM. Neuroimaging abnormalities in patients with Cowden syndrome: Retrospective single-center study. Neur Clin Pract. 2018;8(3):207-213. DOI: 10.1212/CPJ.0000000000000463

viii. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden Syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic Review and Revised Diagnostic Criteria. JNCI Journal of the National Cancer Institute. 2013;105(21):1607-1616. DOI: 10.1093/jnci/djt277

ix. Daly RM, Iuliano S, Fyfe JJ, Scott D, Kirk B, Thompson MQ, *et al.* Screening, Diagnosis and Management of Sarcopenia and Frailty in Hospitalized Older Adults: Recommendations from the Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR) Expert Working Group. J Nutr Health Aging. 2022;26(6):637-651. DOI: 10.1007/s12603-022-1801-0

x. Cheng CS, Ou CH, Chen JS, Lui CC, Yeh LR. Lhermitte-Duclos disease: A case report with radiologic-pathologic correlation. Radiol Case Rep. 2019;14(6):734-739. DOI: 10.1016/j.radcr.2019.03.020

xi. Beniwal HK, Satish T, Rao GP, Reddy MS, Manne S. Lhermitte-Duclos Disease: Incidental Finding in Traumatic Cerebral Hemorrhage. Indian Journal of Neurotrauma. 2022;19(01):044-046. DOI: 10.1055/s-0041-1729136

xii. Zhang H-W, Zhang Y-Q, Liu X-L, Mo Y-Q, Lei Y, Lin F, *et al.* MR imaging features of Lhermitte-Duclos disease: Case reports and literature review. Medicine (Baltimore). 2022;101(4):e28667. DOI: 10.1097/MD.0000000000028667

xiii. Khandpur U, Huntoon K, Smith-Cohn M, Shaw A, Elder JB. Bilateral Recurrent Dysplastic Cerebellar Gangliocytoma (Lhermitte-Duclos Disease) in Cowden Syndrome: A Case Report and Literature Review. World Neurosurg. 2019;127:319-325. DOI: 10.1016/j.wneu.2019.03.131

xiv. Li Y, Guo J, Wei H, Sun C, Chai Y, Fu X, *et al.* The surgical resection of

dysplastic cerebellar gangliocytoma assisted by intraoperative sonography: illustrative case. Journal of Neurosurgery: Case Lessons. 2021;2(14):CASE21451. DOI: 10.3171/CASE21451

xv. Dragoo DD, Taher A, Wong VK, Elsaiey A, Consul N, Mahmoud HS, *et al.* PTEN Hamartoma Tumor Syndrome/Cowden Syndrome: Genomics, Oncogenesis, and Imaging Review for Associated Lesions and Malignancy. Cancers. 2021;13(13):3120. DOI: 10.3390/cancers13133120

xvi. Bubien V, Bonnet F, Brouste V, Hoppe S, Barouk-Simonet E, David A, *et al.* High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet. 2013;50(4):255-263. DOI: 10.1136/jmedgenet-2012-101339

Case report

Solid Pseudopapillary Tumor of the Pancreas, an Unusual Neoplasm

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Tumor pseudopapilar sólido de páncreas, una neoplasia inusual

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Abstract
Case presentation. A 26-year-old woman who presented with pain in the epigastrium and left hypochondrium, with increased abdominal perimeter and loss of 5 kg of body weight. Physical examination revealed a large mass in the epigastrium, with regular borders, slightly painful to the touch and non-mobile. Imaging studies revealed a mixed neoplasm in the pancreatic body and tail. **Treatment.** A corpo-caudal splenopancreatectomy was performed, with complete removal of the tumor. **Outcome.** The patient received specialized care and close postoperative surveillance in the intensive care unit, with no relevant complications. After hospital discharge, the patient reported a good general condition in the follow-up controls, which included a computed tomography scan performed after 12 months, where no tumor remnants or recurrences were evidenced.

Keywords
Pancreatic Neoplasms, Splenectomy, Pancreatectomy, Helical Computed Tomography.

Resumen
Presentación del caso. Se trata de una mujer de 26 años que presentó dolor en epigastrio e hipocondrio izquierdo, con aumento del perímetro abdominal y pérdida de 5 kg de peso corporal. En el examen físico se detectó una masa de gran tamaño en el epigastrio, con bordes regulares, ligeramente dolorosa al tacto y no móvil. Los estudios de imagen revelaron una neoplasia mixta en el cuerpo y cola pancreática. **Intervención terapéutica.** Se practicó una esplenopancreatectomía corpo-caudal, con extirpación completa del tumor. **Evolución clínica.** La paciente recibió cuidados especializados y vigilancia estrecha posquirúrgica en la unidad de cuidados intensivos, sin presentar complicaciones relevantes. Tras el alta hospitalaria, la paciente refirió un buen estado general en los controles de seguimiento, que incluyeron una tomografía realizada a los 12 meses, donde no se evidenciaron restos o recidivas tumorales.

Palabras clave
Neoplasia Pancreática, Esplenectomía, Pancreatectomía, Tomografía Computarizada Helicoidal.

Introduction

Solid pseudopapillary tumor of the pancreas (SPPT) is a rare exocrine pancreatic neoplasm, which represents approximately 2 % of all pancreatic tumors.[i] It was first described by Frantz in 1959[ii] and later characterized by Hamoudi in 1970, due to this, it received names such as "Frantz" or "Hamoudi" tumor, in addition to other terms related to its histological appearance.[iii] In 1996, the World Health Organization established its current designation as "solid pseudopapillary tumor" of the pancreas.[iv]

SPPT has a tenfold higher incidence in women,[i,v] mainly in the second and third decade of life, with an average age of 22 years[v,vi] and can develop in any part of the pancreas, however, it occurs more frequently in the distal part of the body and tail.

It is asymptomatic, although in some cases it may present with a gradually growing abdominal mass and nonspecific abdominal pain or discomfort.[v]

The mass is usually large, with a well-defined capsule and variable presence of necrosis, hemorrhage and cystic changes. Histologically, it is distinguished by tumor cells, characterized by areas of oriented cells surrounding delicate fibrovascular nuclei, resulting in the pseudopapillary structure.[vi]

Different imaging modalities, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), are essential for diagnosis and differentiation from other pancreatic lesions.[vii] Complete resection of the tumor is curative in most cases.[v]

This case report presents the clinical, radiological, and pathological findings of a patient with PSPT diagnosed at the Rosales National Hospital, El Salvador.

The main objective is to highlight the importance of recognizing and correctly diagnosing this clinical entity to ensure adequate treatment. Additionally, it makes it possible to determine the optimal therapeutic strategy and achieve successful results in this disease management.

Case presentation

A 26-year-old woman with a history of mild, cramping, intermittent, non-radiating pain located in the epigastrium and left hypochondrium of one year of evolution. She was relieved with oral analgesics and accompanied by a progressive increase in the abdominal perimeter in the left flank and epigastrium and a loss of approximately 5 kg of body weight. She denied the presence of vomiting, fever, acholia, and choluria. Furthermore, she had no personal medical or surgical pathological history, and there was no family history of cancer.

The patient initially sought the assistance of a private physician, who subsequently requested abdominal ultrasonography, which revealed the presence of a mixed neoplasm in the retroperitoneum of the left hypochondrium; afterward, she was referred to the hospital.

During the physical examination, she presented without pallor or jaundice, with blood pressure of 120/70 mmHg, heart rate of 82 beats/minute, respiratory rate 18 breaths per minute, temperature of 37° and weight of 63 kilograms. The abdomen was globose, with moderate adipose panniculus, soft and depressible with a large mass, with regular edges, slightly painful to the touch and not mobile, located in the epigastrium, with no signs of peritoneal irritation.

Laboratory tests were performed (Table 1) and showed values within normal limits in the hemogram and liver tests. Special tests revealed normal levels of carcinoembryonic antigen, alpha-fetoprotein, and carbohydrate antigen 19-9.

A computed tomography (CT) scan showed a mass of 14.2 x 12.2 x 13.5 cm in its transverse, anteroposterior, and longitudinal axes occupying the pancreatic body and tail, with defined borders, polylobulated, and some capsular calcifications. The heterogeneous internal composition presented peripheral solid areas that performed with intravenous contrast material and the hypodense liquid component in its more central portions. No signs of infiltration to other organs or adenopathies were found (Figure 1). A solid pseudopapillary tumor of the pancreas was suggested as a preliminary possibility based on the imaging characteristics and the patient's age and gender.

Table 1. Laboratory values

Laboratory Tests	Result	Unit	Normal value	Laboratory Tests	Result	Unit	Normal value
Carcinoembryonic antigen	1.36	ng/mL	Smokers: 0-4.3 Non smokers: 0-3.4	Creatinine	0.60	mg/dL	0.4-1.5
Alphafetoprotein	6.37	ng/mL	0-7	Glucose	95	mg/dL	70-100
CA - 19-9	3.5	U/mL	0-39	Urea nitrogen	12	mg/dL	5-18
Hemoglobin	13.7	g/dL	12-16	Aspartate aminotransferase	26	UI/L	10-42
Hematocrit	41.1	%	36-48	Alanine aminotransferase	34	UI/L	10-40
Leukocytes	8.17	x 10^3/µL	5-10	Total Bilirubin	0.48	mg/dL	0.2-1.0
Neutrophils	66	%	55-65	Direct Bilirubin	0.11	mg/dL	0-0.4
Lymphocytes	20.9	%	20-40	Indirect Bilirubin	0.37	mg/dL	0.2-0.8
Platelets	312	x 10^3/µL	150-400	Alkaline phosphatase	55	UI/L	30-125

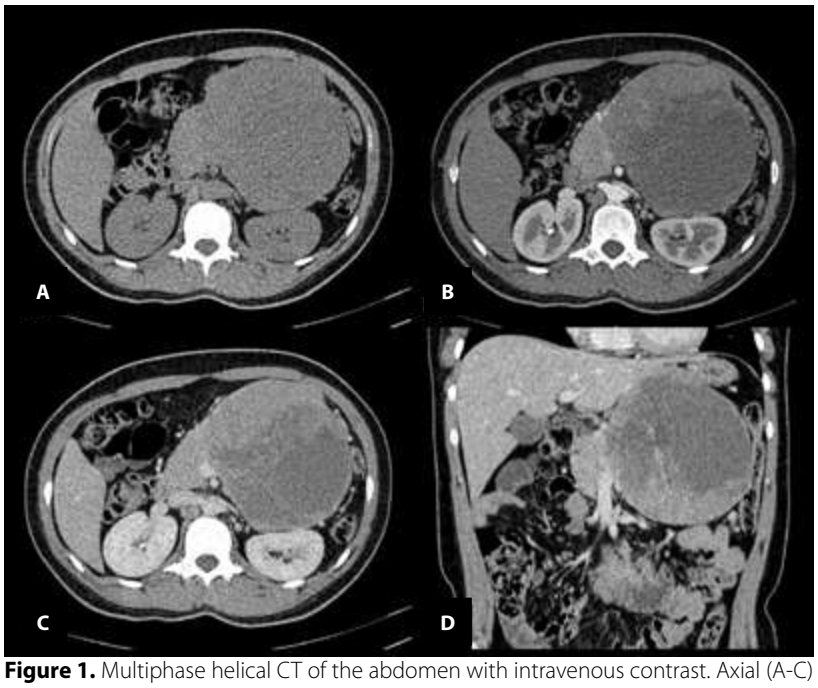

Figure 1. Multiphase helical CT of the abdomen with intravenous contrast. Axial (A-C) and coronal (D) slices in simple (A), arterial (B) and portal venous (C,D) phases

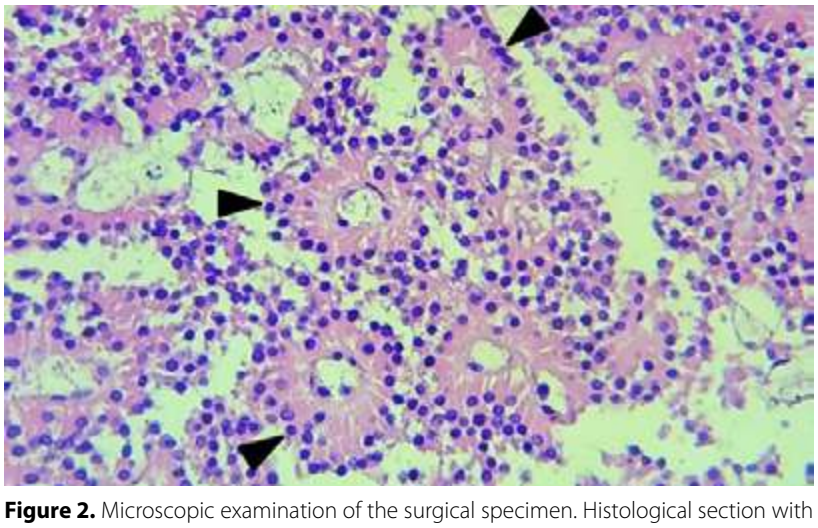

Figure 2. Microscopic examination of the surgical specimen. Histological section with hematoxylin and eosin stain (40x), showing monomorphic cells, poorly cohesive, with round, uniform, basophilic nuclei and eosinophilic cytoplasm, with intra- and extracytoplasmic hyaline globules that adhere to hyalinized fibrovascular cords in a pseudopapillary pattern with perivascular arrangement (black arrowheads). No vascular or perivascular invasion is evident in the capsule. Findings are consistent with a solid pseudopapillary tumor of the pancreas

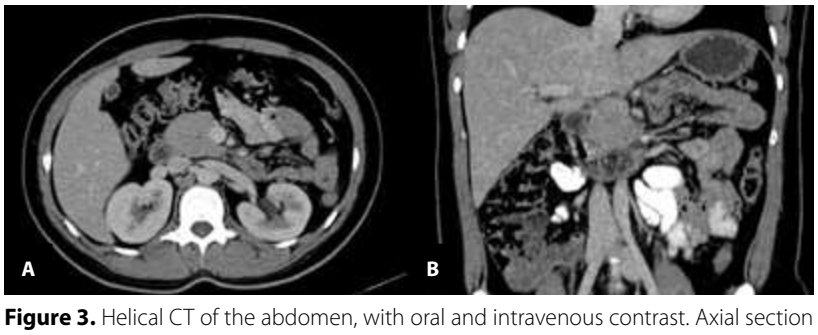

Figure 3. Helical CT of the abdomen, with oral and intravenous contrast. Axial section (A) and coronal section (B) in venous portal phase. Post-surgical changes consistent with a corpo-caudal splenopancreatectomy are evidenced. The pancreatic head is preserved. There is no evidence of tumor remnants or recurrences, nor intra-abdominal metastatic lesions or adenopathies

Tomographic sections of the upper abdomen showed a large encapsulated mass extending from the body to the tail of the pancreas, with lobulated borders that were well-defined and a heterogeneous internal structure with solid areas in the periphery showing enhancement with intravenous contrast material, together with a central liquid component of lower density. A mass effect was observed in the surrounding organs with a displacement of the same without finding signs of infiltration. (Figure 1)

Treatment

It was decided that surgical intervention was necessary, so five days after his admission, an open corpo-caudal splenopancreatectomy was performed. The tumor was removed from the body and tail of the pancreas, as well as the spleen, five days after admission.

During surgery, a tumor with mixed appearance and consistency was found in the body and tail of the pancreas, which exerted pressure on the portal vein and superior mesenteric vein but did not invade or compromise them, without invasion to neighboring organs. There were no complications during the procedure. The histologic report (Figure 2) showed an encapsulated pancreatic neoplasm consisting of a solid pseudopapillary tumor of the pancreas. Immunohistochemistry and hormone receptor test for progesterone was not performed due to lack of availability.

Outcome

Post-surgical recovery was performed in the Intensive Care Unit for three days, and the following ten days in the general surgery hospitalization area; finally, she was discharged without complications.

Three subsequent check-ups with specialists in general surgery and endocrinology were performed, in which she presented with good general health and no additional symptoms. After 12 months post-surgery, a body weight of 55 kg was recorded, and the follow-up tomographic study (Figure 3) showed no evidence of tumor residues, recurrences or intra-abdominal metastatic lesions.

Clinical diagnosis

Solid pseudopapillary tumor of pancreas.

Discussion

TPSP is a rare epithelial neoplasm of unknown origin that mainly affects women

in the second and third decades of life.[v] Unlike other pancreatic neoplasms, it occurs in young people and even children, with a predilection for Asian and African-American women.[iii] Its detection has increased thanks to the widespread use of imaging techniques such as CT and MRI, which allow the detection of smaller TPSP since many tumors are asymptomatic and found incidentally.[viii,ix]

It generally develops in the body and tail of the pancreas (55 to 60 %), can also affect the head and neck (35 to 40 %)[v,ix] and less frequently, extrapancreatic sites (1 to 1.8 %) such as the colon, mesentery, testis or retroperitoneum.[ix]

Most have a benign clinical course, but 10 to 20 % have been reported to present malignant degeneration with metastasis and adjacent invasion.[v-vii]

Five-year survival is excellent, ranging from 93.6 to 98.8 %. Tumors in the pancreatic head have a slightly less favorable prognosis, probably due to the surgical complexity of their anatomical location.[x]

Most patients are asymptomatic at the time of diagnosis. When symptoms are present, abdominal pain is the most common[v,xi], in addition to other nonspecific symptoms such as nausea, vomiting, weight loss, and the presence of a mass in the right or left upper quadrant of the abdomen.[vii,x-xii]

Laboratory tests are generally unaltered[xiii], and ACE, CA 19-9, and AFP tumor markers are rarely altered.[xi,xii]

Imaging reveals an encapsulated tumor with solid and cystic components, and sometimes with capsular and intraparenchymal calcifications.[iii,v,viii] Abdominal ultrasound is the initial method due to its easy access and non-invasive nature, showing solid lesions containing cystic areas or cystic lesions.[v] In the presence of diagnostic suspicion, it is recommended to complement CT and MRI, which provide a better characterization of the lesions.

CT shows an encapsulated mass with cystic and solid components due to necrohemorrhagic degeneration and calcifications in its periphery.[xii] On the other hand, MRI provides further characterization of the lesion. The body appears weaker on T1-weighted pictures but more intense due to internal bleeding on T2-weighted images. Typically, the solid component enhances poorly, and minimal thickening with capsular enhancement is seen.[iii,v,viii] Larger lesions enhance heterogeneously, while smaller lesions enhance homogeneously.[vii,viii] Internal hemorrhage is a characteristic finding, reported in a range of 29 to 88.9 % of cases. In most tumors larger than 3 cm in size, a peripheral capsule is observed.[viii]

Lanke *et al.* propose a management algorithm after detection by transabdominal ultrasound; CT and MRI are recommended; and in cases of low suspicion of TPSP, a fine needle puncture by endoscopic ultrasound with immunohistochemistry is suggested, which can be useful for preoperative diagnosis, even in patients with high suspicion.[xiv]

From the macroscopic point of view, they are large tumors with a diameter between 2 and 16 cm and an average size of 5 cm.[iii] They usually have a heterogeneous macroscopic appearance and are characterized by being round, well-defined, encapsulated, and having a mixed composition, both cystic and solid, in variable proportions.[viii,xi]

Histologically, it is characterized by a neoplasm with cells arranged in several layers around fibrovascular stalks, resulting in the formation of a pseudopapillary structure.[x-xv] The pseudopapillary architecture composed of hyaline globules, cholesterol clefts, foamy macrophages and nuclear grooves with absence of neuroendocrine chromatin (salt and pepper) are characteristic.[iii]

There are molecular alterations, such as karyotypic changes on chromosomes 2, 4, or X, with loss of heterozygosity in the HRAS gene and differential expression of genes, including those associated with tumors. In addition, up-regulation of p27 and p21 is observed, but no mutations in p53 or K-ras are observed, and additionally, ErbB and GnRH signaling pathways are affected.[ix,x,xv] They also have β-catenin mutations and overexpress cyclin D1 without becoming malignant, and there is evidence of FLI-1, CD56, and progesterone receptor expression, whose genes are on chromosome 11q.[xvi]

The differential diagnosis of TPSPs includes pancreatic adenocarcinomas, which are the most common cancers in the pancreas. These cancers exhibit a high level of aggressiveness and possess the potential for local invasion and metastasis. Furthermore, cystoadenomas and cystoadenocarcinomas must be in the differential diagnosis.[viii] Although the papillary features of these cystic lesions may resemble those of solid pseudopapillary tumors, their biological behavior and prognosis differ.[v,vii,viii]

Complete surgical resection is the treatment of choice, and the approach depends on the location of the tumor.[iii,v,vi,x,xiii,xvii] In tumors located in the head of the pancreas, pancreatoduodenectomy is an option associated with an overall good prognosis, although recurrence can occur[xii] and related complications have been reported, including pancreatic fistula, postoperative bleeding, delayed gastric emptying and infection.[viii] A laparoscopic approach can be used to treat

tumors located within the body and/or tail, allowing splenic preservation. Laparoscopic surgery has been shown to cause less blood loss, better postoperative recovery, shorter hospital stay, and lower risk of complications than laparoscopic surgery.[xii,xiii,xvii]

Two percent of patients experience recurrence after resection.[xviii] The risk may be increased by factors such as tumor size >5 cm, lymphovascular invasion, lymph node metastases, synchronous metastases, and positive margins.[xix]

This case includes the clinical, imaging and histologic features of a TPSP, with complete surgical resection, which generated a recovery without recurrence or malignancy.

In conclusion, the presence of a large pancreatic mass with large size mixed solid and cystic nature, encapsulation, and presence of hemorrhage in a young woman must generate suspicion of a TPSP.

Ethical aspects

This case reflects information obtained from clinical records respecting patient confidentiality. Informed consent was obtained from the patient together with a family witness. Data in the publication have been used for academic purposes.

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References

i. Mujtahedi SS, Shetty SK, Lobo FD. Solid pseudopapillary epithelial neoplasm (SPEN) of the pancreas involving the distal body and proximal tail: A case report. Int. J. Surg. Case Rep. 2021;80:105519. DOI: 10.1016/j.ijscr.2021.01.013

ii. Frantz V. Papillary tumors of the páncreas: benign or malignant? Tumors of the pancreas. In: Atlas of Tumor Pathology. 1st ed. Washington, DC: US Armed Forces Institute of Pathology; 1959. pp. 32-33.

iii. Hansen CP, Kristensen TS, Storkholm JH, Federspiel BH. Solid pseudopapillary neoplasm of the pancreas: Clinical-pathological features and management, a single-center experience. Rare Tumors. 2019;11:203636131987851. DOI: 10.1177/2036361319878513

iv. Klöppel G, Klöppel G, Weltgesundheitsorganisation, editors. Histological typing of tumours of the exocrine pancreas. 2nd ed., corrected print. Berlin Heidelberg: Springer; 1996. (International histological classification of tumours).

v. Papavramidis T, Papavramidis S. Solid Pseudopapillary Tumors of the Pancreas: Review of 718 Patients Reported in English Literature. J. Am. Coll. Surg. 2005;200(6):965-972. DOI: 10.1016/j.jamcollsurg.2005.02.011

vi. Kloppel G, Basturk O, Klimstra D, Lam A, Notohara K. Tumors of Pancreas. In: Digestive System Tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2019. pp. 283-360.

vii. De Robertis R, Marchegiani G, Catania M, Ambrosetti MC, Capelli P, Salvia R, *et al.* Solid Pseudopapillary Neoplasms of the Pancreas: Clinicopathologic and Radiologic Features According to Size. Am. J. Roentgenol. 2019;213(5):1073-1080. DOI: 10.2214/AJR.18.20715

viii. Kovac JD, Djikic-Rom A, Bogdanovic A, Jankovic A, Grubor N, Djuricic G, *et al.* The Role of MRI in the Diagnosis of Solid Pseudopapillary Neoplasm of the Pancreas and Its Mimickers: A Case-Based Review with Emphasis on Differential Diagnosis. Diagnostics. 2023;13(6):1074. DOI: 10.3390/diagnostics13061074

ix. Gurzu S, Bara T, Sincu M, Gabos S, Vlad DM, Bara T, *et al.* Solid pseudopapillary neoplasm of pancreas: Two case reports. Medicine (Baltimore). 2019;98(29):e16455. DOI: 10.1097/MD.0000000000016455

x. Zalatnai A, Kis-Orha V. Solid-pseudopapillary Neoplasms of the Pancreas is still an Enigma: a Clinicopathological Review. Pathol. Oncol. Res. POR. 2020;26(2):641-649. DOI: 10.1007/s12253-019-00671-8

xi. Miranda-Castillo F, Auria-Aspiazu D, Plaza-Vélez J, Villacís-Muñoz M, Benites-Ordinola C. Tumor de Frantz-Gruber, un tumor sólido quístico pseudopapilar del páncreas infrecuente. Cir. Gen. 2020;42(3):223-227. DOI: 10.35366/99964

xii. Torres OJM, Rezende MBD, Waechter FL, Neiva RF, Moraes-Junior JMA, Torres CCS, *et al*. Pancreatoduodenectomy for Solid Pseudopapillary Tumor of the Pancreas: A Multi-Institution Study. ABCD Arq. Bras. Cir. Dig. São Paulo. 2019;32(2):e1442. DOI: 10.1590/0102-672020190001e1442

xiii. Salinas W, Marani M, Reimondez S, Alcaraz A, Signorini F, Maraschio M, *et al.* Tumor sólido pseudopapilar de páncreas. Cir. Cir. 2021;89(2):3450. DOI: 10.24875/CIRU.19001163

xiv. Lanke G, Ali FS, Lee JH. Clinical update on the management of pseudopapillary tumor of pancreas. World J. Gastrointest. Endosc. 2018;10(9):145-155. DOI: 10.4253/wjge.v10.i9.145

xv. Din NU, Rahim S, Abdul-Ghafar J, Ahmed A, Ahmad Z. Clinicopathological and immunohistochemical study of 29 cases of solid-pseudopapillary neoplasms of the pancreas in patients under 20 years of age along with detailed review of literature. Diagn. Pathol. 2020;15(1):139. DOI: 10.1186/s13000-020-01058-z

xvi. Tiemann K, Heitling U, Kosmahl M, Klöppel G. Solid pseudopapillary neoplasms of the pancreas show an interruption of the Wnt-signaling pathway and express gene products of 11q. Mod. Pathol. 2007;20(9):955-960. DOI: 10.1038/modpathol.3800902

xvii. McCluney S, Wijesuriya N, Sheshappanavar V, Chin-Aleong J, Feakins R, Hutchins R, *et al.* Solid pseudopapillary tumour of the pancreas: clinicopathological analysis. ANZ J. Surg. 2018;88(9):891-895. DOI: 10.1111/ans.14362

xviii. Yepuri N, Naous R, Meier AH, Cooney RN, Kittur D, Are C, *et al.* Systematic review and meta-analysis of predictors of recurrence in patients with Solid Pseudopapillary Tumors of the Pancreas. HPB. 2020;22(1):12-19. DOI: 10.1016/j.hpb.2019.06.005

xix. Gao H, Gao Y, Yin L, Wang G, Wei J, Jiang K, *et al.* Risk Factors of the Recurrences of Pancreatic Solid Pseudopapillary Tumors: A Systematic Review and Meta-analysis. J. Cancer. 2018;9(11):1905-1914. DOI: 10.7150/jca.24491

Original article

Clinical Evolution in Patients with Carpal Tunnel Syndrome Treated with Ultrasound or Corticosteroid Infiltration

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Evolución clínica en pacientes con síndrome del túnel carpiano tratados con ultrasonido o infiltración con corticoesteroides

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Abstract

Introduction. Carpal tunnel syndrome is the most common compressive peripheral neuropathy of the upper extremity, which is caused by compression of the median nerve. Mild and moderate cases can be treated with conservative methods such as therapeutic ultrasound or corticosteroid infiltration. **Objective.** To describe the clinical evolution of patients with carpal tunnel syndrome treated with ultrasound therapy and corticosteroid infiltration. **Methodology.** A prospective open clinical trial was conducted in patients with mild and moderate carpal tunnel syndrome who consulted from October 1, 2021 to May 30, 2022. Two groups were formed: the group that received ultrasound treatment with 12 cases and the group treated with corticosteroid infiltration with six cases. Both groups were treated at the initial consultation and then at four and eight weeks after the start of treatment. **Results.** The descriptive results related to the intensity of pain, evaluated with the Visual Numeric Scale, are shown. Infiltration obtained two cases without pain and four with moderate pain, contrary to ultrasound which was maintained with four mild, three moderate and five intense cases. In symptoms, infiltration reduced the number of cases in four of the symptoms studied, while ultrasound reduced the number of cases in only two. In severity, assessed with the Boston carpal tunnel questionnaire, with infiltration, there were two asymptomatic cases and none with ultrasound. Regarding clinical signs, Tinel's sign disappeared in four cases in both groups, while Phalen's sign disappeared in four cases in ultrasound and two in infiltration. **Conclusion.** Infiltration produced asymptomatic patients and reduced more symptoms than ultrasonography in terms of pain intensity and severity. Clinical symptoms were less common with both treatments.

Keywords
Carpal Tunnel Syndrome, Ultrasonic Therapy, Pain, Adrenal Cortex Hormones, Conservative Treatment.

Resumen

Introducción. El Síndrome del túnel carpiano es la neuropatía periférica compresiva más común de la extremidad superior, que se produce por la compresión del nervio mediano. Los casos leves y moderados pueden tratarse con métodos conservadores como ultrasonido terapéutico o infiltración con corticoesteroides. **Objetivo.** Describir la evolución clínica de pacientes con síndrome de túnel carpiano tratados con terapia por ultrasonido e infiltración de corticoesteroides. **Metodología.** Ensayo clínico abierto, en pacientes con síndrome del túnel carpiano leve y moderado, que consultaron del 1 de octubre 2021 al 30 de mayo 2022. Se formaron dos grupos; el que recibió tratamiento con ultrasonido con 12 casos y el grupo tratado con infiltración con corticoesteroides con seis casos. Ambos grupos fueron intervenidos en la consulta inicial, y luego, en las cuatro y ocho semanas posteriores al inicio del tratamiento. **Resultados.** Se muestran los resultados descriptivos relacionados con la intensidad de dolor, valorada con la Escala Visual Numérica, la infiltración obtuvo dos casos sin dolor y cuatro con dolor moderado, contrario a ultrasonido que se mantuvo con cuatro casos leves, tres moderados y cinco intensos. En los síntomas, la infiltración redujo el número de casos en cuatro de los síntomas estudiados, en cambio el ultrasonido únicamente en dos. En severidad, valorada con el cuestionario de Boston para túnel carpal, con infiltración se obtuvieron dos casos asintomáticos y ninguno con ultrasonido. Respecto a los signos clínicos, el signo de Tinel desapareció en cuatro casos en ambos grupos, mientras que signo de Phalen desapareció en cuatro casos en ultrasonido y dos en infiltración. **Conclusión.** En intensidad de dolor y grado de severidad, la infiltración generó casos asintomáticos y redujo mayor cantidad de síntomas que el ultrasonido. Ambos tratamientos disminuyeron la presencia de signos clínicos.

Palabras clave
Síndrome del Túnel Carpiano, Terapia por Ultrasonido, Corticoesteroides, Tratamiento Conservador.

Introduction

Carpal Tunnel Syndrome (CTS) is the most common compressive peripheral neuropathy of the upper extremity. It is a condition resulting from the compression of the median nerve, varying between 32 and 110 mmHg compared to the normal 2 to 31 mmHg.[i] This condition may result in pain in the wrist area and middle, index, and thumb fingers, accompanied by paresthesia and loss of strength.[ii-iv]

The exact cause of CTS is not yet known; however, multiple risk factors have been found, including pregnancy, obesity, diabetes *mellitus*, rheumatoid diseases, and other local factors such as trauma and repetitive activities of the wrist joint, mainly related to occupational activities, and currently represents one of the health problems affecting the working capacity of the population.[i,iii,v,vi]

Women between the ages of 40 and 50 are four times more likely to suffer from CTS than men.[iii] The prevalence of CTS in the United States is 5 % per year. In the United States, CTS has an annual prevalence of 5 %.[vi] It has been observed that there is an association between age and sex because it occurs more frequently in the female population.[i] In the United Kingdom, a prevalence of 88 per 100 000 was recorded in men, in contrast to women, in whom an incidence of 193 per 100 000 was recorded.[iii]

According to the morbidemographic profile system of the outpatient medical consultation of the Salvadoran Social Security Institute in El Salvador, CTS is one of the top ten causes of outpatient consultation at the Physical Medicine and Rehabilitation Unit of the Salvadoran Social Security Institute.

The neurophysiological scale of carpal tunnel syndrome compromise takes into account the clinical criteria of the disease, such as the duration of symptoms, the present symptomatology, and the electrodiagnostic findings to determine the degree of nerve compromise; CTS is classified as mild when the symptoms have less than one year of evolution, there are no symptoms, the sensory conduction is abnormal, and the motor conduction is normal; moderate CTS is classified as moderate when the time of evolution is less than or more than one year, there are minimal symptoms, and there are alterations in sensory and motor conduction; Severe CTS is lasting longer than a year, having noticeable symptoms, alterations in sensory and motor conduction, and denervation.[ii,vii,viii]

There are multiple treatment options; surgery is recommended in severe cases and when there has not been a satisfactory evolution with conservative treatment.[iv] The initial management consists of non-surgical or conservative management, such as the use of wrist splints, which due to the effect of limiting the flexion and extension movements of the wrist, reduce the pressure of the median nerve inside the carpal tunnel; corticosteroid infiltration produces the deflation of the tenosynovial tissue that passes through the carpal tunnel, with the consequent decrease in local pressure; ultrasound therapy, the local application of high-frequency waves decreases inflammation and stimulates nerve regeneration through increased blood flow; the use of oral non-steroidal anti-inflammatory drugs has not shown a clear benefit; and acupuncture, which aims to stimulate trigger points, to optimize the energy pathway that generates symptom relief without acting on the pressure inside the carpal tunnel.[i,ii]

Previous comparative studies refer to the effectiveness of different types of treatment, but there are no significant differences between them to establish a suitable treatment. The effectiveness of ultrasound is not proven to be superior to other treatments. Infiltration is more effective than some physical methods.[ii,vii,ix,xi]

In El Salvador, according to the Salvadoran Social Security Institute's (ISSS) "Physiatry Management Guidelines, 2004"[xii] and the "Manual of Physical Therapy Procedures, 2006",[iv] the conservative treatments are therapeutic ultrasound[ii,xiii-xv] and infiltration with corticosteroids, such as triamcinolone acetonide,[ix,x,xii,xvi-xviii] which is registered in the Official List of Medications of the ISSS.[xix]

Patient follow-up and clinical evolution of patients with mild or moderate CTS could be performed according to the application of the Boston Carpal Tunnel Questionnaire[xx-xxii] (BCTQ) and the Numerical Rating Scale (NRS) for pain.[xxiii]

Since it refers to a health problem that most frequently affects the economically active population, their quality of life due to the severity of their symptoms, limiting their daily activities, and their work performance,[xxiv] it is important to establish an adequate and effective treatment that allows the patient's recovery in a shorter time, with a decrease in treatment costs and periods of incapacity. This study aimed to describe the clinical evolution of mild or moderate CTS in patients treated with two conservative treatment methods: triamcinolone acetonide infiltration and ultrasound therapy.

Methodology

Open clinical trial was conducted to evaluate the clinical evolution of patients with

mild or moderate CTS after conservative treatment with therapeutic ultrasound and corticosteroid infiltration.

The population consisted of patients with mild or moderate CTS who consulted for the first time at the Physical Medicine and Rehabilitation Unit of the ISSS in San Salvador over eight months, from October 1, 2021, to May 30, 2022, and who voluntarily agreed to participate in the study (Figure 1).

There were trained health personnel accessible for this study. A certified physiatrist performed triamcinolone infiltration in the locations selected for each treatment, while a certified physical therapist performed ultrasound therapy.

Adults who agreed to participate in the study and who had a diagnosis of mild or moderate CTS, symptomatic, i.e., presenting at least two symptoms or one symptom accompanied by a clinical sign present and who had not received treatment with infiltrations or previous surgical management for CTS and with a time of evolution greater than three months were included.

Patients who presented contraindications for the use of corticosteroids (sensitivity, infection, or skin lesion at the injection site) or contraindications for the use of therapeutic ultrasound (history of cancer in organs or structures close to the treatment area, bleeding tissues, or that could present bleeding) were excluded, as well as patients who presented conditions that could simulate symptoms of CTS, such as the diagnosis of polyneuropathies, cervical radiculopathy, among others.

The study began with 24 patients eligible to participate; 20 patients were selected to participate in the study. Initially, informed consent was requested; then, demographic and clinical data were obtained, the EVN and BCTQ questionnaires were applied, and they were distributed, using convenience sampling, in two treatment groups: the first one received continuous therapeutic ultrasound at a frequency of 3 MHz and intensity of 1 W /cm^2, with a transducer with a 5 cm^2 head, for 5 min, distributed twice a week, for five weeks, for a total of ten treatment sessions. The second group received one dose of infiltration in the palmar area of the wrist with 10 mg of triamcinolone acetonide and 1 mL of 2 % lidocaine in a 3 mL disposable syringe. Of this group, two patients decided to withdraw from the study.

Three evaluations were performed, the first one at the beginning of the treatment and two subsequent follow-ups at four and eight weeks.

The study included as independent variable, the type of treatment selected; therapeutic ultrasound or corticosteroid infiltration, and as dependent variable, the clinical evolution of carpal tunnel syndrome. Other variables taken into account were

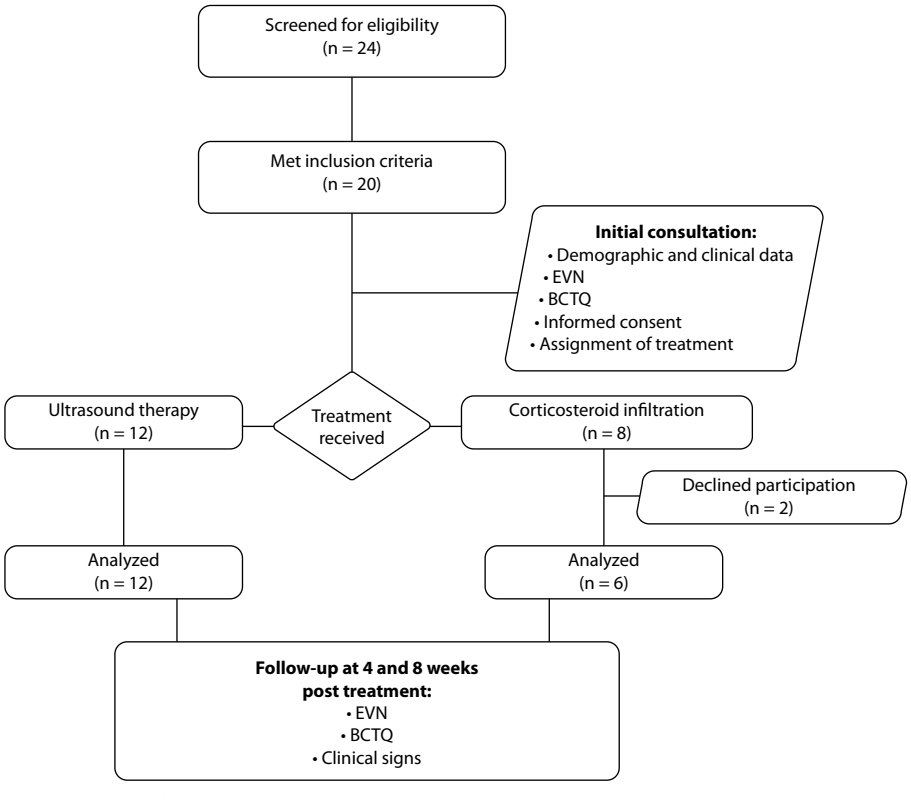

Figura 1. Patient flow

the patient's personal and clinical data, including age, time of evolution of CTS, affected hand, risk factors, including occupational risk and obesity, which was measured by calculating the body mass index;[xx] pain intensity, according to the NBS and symptom intensity according to the BCTQ; and the evaluation of the clinical signs present. (Tinel and/or Phalen)[vii,xx]

The checklist for this study was elaborated according to the variables identified in Microsoft Word. Then, the data were analyzed using Microsoft Excel.

The research complied with internationally established ethical principles to guarantee participant confidentiality. Personal and clinical data were kept confidential by the research team; neither the identity of the patients nor any other data that could identify them were disclosed. The informed consent used for this study was prepared based on the format proposed by the World Health Organization's Committee for the Ethical Evaluation of Research. This study was approved by the Ethics Committee for Health Research ISSS 2020-2023, dated 20/07/2021, and identified CEIS ISSS 2021-041 version 2.

Results

This study shows only descriptive data. Regarding the demographic data of the patients evaluated, the 18 cases corresponded to the female sex, with a higher frequency in those over 60 years of age (Table 1).

The time of evolution between 2 and 3 years was the most frequent, with seven cases reported. The most frequent risk factor was occupational hazards related to repetitive movements of the wrist joint, and obesity was identified in three of the 18 cases (Table 1).

The frequency of CTS was the same in both hands based on the affected hand's laterality. According to the findings of the electrophysiological study before therapy began, slight or moderate involvement was in 16 CTS patients, and one patient had a normal study.

Concerning pain intensity using the EVN scale, the group managed with ultrasound began with five cases of moderate intensity and seven cases of intense pain and ended the eight weeks of follow-up with four mild, three moderate and five intense cases. The infiltration group started with one case of mild intensity and five cases of moderate intensity, and ended the follow-up with two cases without pain and four cases of moderate intensity.

Table 1. Demographic and clinical data of patients with carpal tunnel syndrome

Variable	n
Age	
18 to 29 years old	2
30 to 39 years old	3
40 to 49 years old	4
50 to 59 years old	2
> 60 years old	7
Total	18
Treatment method	
Infiltration	6
Ultrasound	12
Total	18
Time of evolution	
< 1 year	4
1 to 2 years	5
2 to 3 years	7
3 or more years	2
Total	18
Risk factors	
Occupational factors	11
Obesity	3
Other	4
Total	18
Hand evaluated	
Right	9
Left	9
Total	18
Result of previous electrophysiological study	
No study presented	1
Normal	1
Mild	9
Moderate	7
Total	18

Regarding the presence of CTS symptoms checked in the BCTQ questionnaire, the group treated with ultrasound presented a reduction of two specific symptoms after eight weeks of treatment, in the symptom of loss of sensitivity in one case and in the symptom of functional difficulty in three cases. In the infiltrated group, hand/wrist pain, dysesthesias/paraesthesias, loss of sensation and functional difficulty at eight weeks post-treatment showed a decrease of one case each.

The severity of CTS, evaluated using the BCTQ questionnaire, presented eight mild cases and four moderate cases in the ultrasound group at the beginning of the

study and ended with nine mild cases, two moderate cases, and one severe case. Contrary to the infiltrated group, which had two asymptomatic cases, there were three mild and one moderate cases in the infiltrated group. (Table 2)

The clinical sign of Tinel was found to be present in six of the ten patients who presented it at the beginning of the study and were treated with ultrasound; similarly, in the infiltrated group, it was found to be present in two of the six cases that presented it before treatment.

On the other hand, Phalen's sign was identified in 12 cases at the beginning of treatment, and it was present in eight cases after treatment in the ultrasound therapy group. Finally, it was recorded in six with a reduction to four at the end of treatment in the group that received corticosteroid infiltration. (Table 3)

Discussion

Some conservative treatment modalities for mild and moderate CTS have evidence of their effectiveness in reducing symptoms, mainly the use of splints and corticosteroid infiltration, which have led to a decrease in pressure in the carpal tunnel area.[i,vi,xxv] The efficacy of manual therapy based on neurodynamic techniques in the conservative treatment of carpal tunnel syndrome has shown significant differences regarding pain

Table 2. Results of the EVN scale and the BCTQ questionnaire in the different stages of follow-up of patients with CTS treated with ultrasound or infiltration

Follow-up stage	First appointment		4 weeks		8 weeks	
Treatment	Ultrasound	Infiltration	Ultrasound	Infiltration	Ultrasound	Infiltration
	n	n	n	n	n	n
EVN Intensity						
No pain (0)	0	0	0	1	0	2
Mild (1-3)	0	1	2	1	4	0
Moderate (4-6)	5	5	8	4	3	4
Severe (7-9)	7	0	2	0	5	0
Severe (10)	0	0	0	0	0	0
BCTQ symptoms						
Asymptomatic	0	0	0	0	0	0
Hand/wrist pain	12	6	12	6	12	5
Dysesthesias/Paresthesias	12	6	12	6	12	5
Loss of sensation	11	3	10	3	10	2
Loss of strength	11	5	10	5	11	5
Functional difficulty	9	4	7	3	6	3
BCTQ severity						
Asymptomatic (1)	0	0	0	0	0	2
Mild (2)	8	3	8	5	9	3
Moderate (3)	4	3	4	1	2	1
Severe (4)	0	0	0	0	1	0
Severe (5)	0	0	0	0	0	0

( ): score.

Table 3. Clinical signs present in the different stages of follow-up of patients with Carpal Tunnel Syndrome treated with ultrasound or infiltration

Follow-up stage	First appointment		8 weeks	
Treatment	Ultrasound	Infiltration	Ultrasound	Infiltration
Clinical sign	n	n	n	n
Tinel	10	6	6	2
Phalen	12	6	8	4

and symptom severity;[xxvi] in this study, it was observed that patients treated with corticosteroids presented complete pain relief.[xxiv]

Therefore, as in other studies, there is insufficient evidence to support the greater benefit and efficacy of therapeutic ultrasound compared to other non-surgical interventions for CTS.[ii,xiii] In contrast, the evidence suggests that injection with a corticosteroid has better outcomes.[ii]

Concerning severity, both groups presented a reduction at the end of follow-up; however, the infiltrated group presented asymptomatic cases, which was not observed in the group treated with ultrasound.

The EVN scale and the BCTQ questionnaire are valid and reliable tools, established and internationally recognized for use in the evaluation of this type of health condition since they are reproducible methods.[xxi-xxiii] Efficacy studies of corticosteroid therapy have shown to reduce the symptoms of CTS.[ii,xvi] One study reported that 53 % of patients treated with corticosteroids had no symptom recurrence at six months; 31 % were symptom-free after 12 months. Furthermore, they found that patients who received a single injection had significantly better scores on the BCTQ.[ii]

The Phalen and Tinel signs are characterized by having a moderate diagnostic value in the diagnosis of CTS. The Tinel sign has a sensitivity between 23 and 67 % and a specificity of 55 to 100 %; the Phalen sign reports a sensitivity of 10 to 91 % and a specificity between 33 to 100 %.[xx] In this study, it was observed at the end of follow-up that there was a reduction in both signs, with greater reduction in Tinel´s sign in the group treated with corticosteroids, unlike Phalen's sign, which showed a similar reduction in both groups.

Previous studies have found that CTS affects women more than men and that this aspect, together with repeated dynamic movements of the wrist or fingers, constitute basic risk factors for this pathology[ii,xx]. Consequently, the results show that the total number of cases corresponded to the female sex, this being, together with occupational factors (related to repetitive movements), the most important risk factors.

In previous research, the highest percentage of these cases was found in people aged 45 to 64 years.[xiii] Some studies indicate that CTS is bilateral in 65 % to 84 % of the cases.[ii,vii]

It is suggested that further studies continue to evaluate the results obtained in the management of CTS with methods such as infiltration with corticosteroids and the use of therapeutic ultrasound, either separately or in comparison with other treatment methods.[ii,ix,xvii,xx,xxvii]

Conclusion

A reduction in the presence of symptomatology and clinical signs is achieved with both treatment methods. However, in terms of pain intensity and degree of severity of CTS, more asymptomatic cases were observed, and a greater reduction in the number of symptoms in the management with infiltration than in the management with ultrasound. However, a reduction in functional symptoms was observed.

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References

i. Schwartz RH, Urits I, Viswanath O. Carpal Tunnel Injection. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. Available at: https://pubmed.ncbi.nlm.nih.gov/32491760/

ii. Ostergaard PJ, Meyer MA, Earp BE. Non-operative Treatment of Carpal Tunnel Syndrome. Curr. Rev. Musculoskelet. Med. 2020;13(2):141-147. DOI: 10.1007/s12178-020-09616-0

iii. Genova A, Dix O, Saefan A, Thakur M, Hassan A. Carpal Tunnel Syndrome: A Review of Literature. Cureus. 2020. DOI: 10.7759/cureus.7333

iv. Pace V, Marzano F, Placella G. Update on surgical procedures for carpal tunnel syndrome: What is the current evidence and practice? What are the future research directions? World J. Orthop. 2023;14(1):6-12. DOI: 10.5312/wjo.v14.i1.6

v. Sánchez KMA, Sánchez RRR, Ortiz MJR, Bourne CXV. Síndrome de túnel carpiano. RECIAMUC. 2019;3(2):827-853. DOI: 10.26820/reciamuc/3.(2).abril.2019.827-853

vi. Wright AR, Atkinson RE. Carpal Tunnel Syndrome: An Update for the Primary

Care Physician. Hawaii J. Health Soc. Welf. 2019;11(2):6-10. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6874691/

vii. García FG, Silva FWD, Reis DR. Síndrome del túnel carpiano. Rev. Habanera Cienc. Médicas. 2014;13(5). Available at: https://revhabanera.sld.cu/index.php/rhab/article/view/512/367

viii. Hernández-Secorún M, Montaña-Cortés R, Hidalgo-García C, Rodríguez-Sanz J, Corral-de-Toro J, Monti-Ballano S, *et al.* Effectiveness of Conservative Treatment According to Severity and Systemic Disease in Carpal Tunnel Syndrome: A Systematic Review. Int. J. Environ. Res. Public. Health. 2021;18(5):2365. DOI: 10.3390/ijerph18052365

ix. Chesterton LS, Dziedzic KS, van der Windt DA, Davenport G, Myers HL, Rathod T, *et al.* The clinical and cost effectiveness of steroid injection compared with night splints for carpal tunnel syndrome: the INSTINCTS randomised clinical trial study protocol. BMC Musculoskelet. Disord. 2016;7:1-11. DOI: 10.1186/s12891-016-1264-8

x. Atthakomol P, Manosroi W, Phanphaisarn A, Phrompaet S, Iammatavee S, Tongprasert S. Comparison of single-dose radial extracorporeal shock wave and local corticosteroid injection for treatment of carpal tunnel syndrome including mid-term efficacy: a prospective randomized controlled trial. BMC Musculoskelet. Disord. 2018;19(1):32. DOI: 10.1186/s12891-018-1948-3

xi. Sim SE, Gunasagaran J, Goh K-J, Ahmad TS. Short-term clinical outcome of orthosis alone vs combination of orthosis, nerve, and tendon gliding exercises and ultrasound therapy for treatment of carpal tunnel syndrome. J. Hand Ther. Off. J. Am. Soc. Hand Ther. 2019;32(4):411-416. DOI: 10.1016/j.jht.2018.01.004

xii. Unidad de Medicina Física y Rehabilitación. Guias de Manejo de Fisiatría. San Salvador: Instituto Salvadoreño del Seguro Social; 2006. 46 p. Available at: https://aps.isss.gob.sv/Documents/Gu%C3%ADas,%20normas,%20manuales,%20pol%C3%ADticas/Lineamientos/LINEAMIENTOS%20ATENCION%20INTEGRAL%20EN%20LOS%20SERVICIOS%20DE%20MEDICINA%20FISICA%20Y%20REHABILITACION.pdf

xiii. Page MJ, O'Connor D, Pitt V, Massy-Westropp N. Therapeutic ultrasound for carpal tunnel syndrome. Cochrane Database Syst. Rev. 2013;2013(3):CD009601. DOI: 10.1002/14651858.CD009601.pub2

xiv. Wipperman J. Carpal Tunnel Syndrome. Am Fami Physician. 2016;94(12): 993-999. Available at: https://www.aafp.org/pubs/afp/issues/2016/1215/p993.html

xv. Unidad de Medicina Física y Rehabilitación. Manual de procedimientos de terapia física. San Salvador: Instituto Salvadoreño del Seguro Social; 2006. 95 p.

xvi. Babaei-Ghazani A, Nikbakht N, Forogh B, Raissi GR, Ahadi T, Ebadi S, *et al.* Comparison Between Effectiveness of Ultrasound-Guided Corticosteroid Injection Above Versus Below the Median Nerve in Mild to Moderate Carpal Tunnel Syndrome: A Randomized Controlled Trial. Am. J. Phys. Med. Rehabil. 2018;97(6):407-413. DOI: 10.1097/PHM.0000000000000877

xvii. Zhang S, Wang F, Ke S, Lin C, Liu C, Xin W, *et al.* The Effectiveness of Ultrasound-Guided Steroid Injection Combined with Miniscalpel-Needle Release in the Treatment of Carpal Tunnel Syndrome vs. Steroid Injection Alone: a Randomized Controlled Study | Cochrane Library. Biomed Res Int. 2019:9498656. DOI: 10.1155/2019/9498656

xviii. Salman Roghani R, Holisaz MT, Tarkashvand M, Delbari A, Gohari F, Boon AJ, *et al.* Different doses of steroid injection in elderly patients with carpal tunnel syndrome: a triple-blind, randomized, controlled trial. Clin. Interv. Aging. 2018;13:117-124. DOI: 10.2147/CIA.S151290

xix. Regulación de medicamentos. Listado oficial de medicamentos. San Salvador: Instituto Salvadoreño del Seguro Social; 2020. 84 p. Available at: https://aps.isss.gob.sv/Documents/Regulación%20de%20Medicamentos/LISTADO%20OFICIAL%20DE%20MEDICAMENTOS%20ISSS%20Junio%202021.pdf

xx. Herrera Castelblanco O, Romero Barajas A. Evaluación de la respuesta al tratamiento médico o quirúrgico en pacientes con Síndrome de Túnel del Carpo moderado bilateral en el Hospital Militar Central. Tesis de grado. Bogotá: Universidad Militar Nueva Granada; 2012.

xxi. Oteo-Álvaro Á, Marín MT, Matas JA, Vaquero J. Validación al castellano de la escala Boston Carpal Tunnel Questionnaire. Med. Clínica. 2016;146(6):247-253. DOI: 10.1016/j.medcli.2015.10.013

xxii. Andani Cervera J, Balbastre Tejedor M, Gómez Pajares F, Garrido Lahiguera R, López Ferreres A. Valoración del cuestionario de Boston como screening en patología laboral por síndrome del túnel carpiano. Rev Asoc Esp Espec Med Trab. 2017:31-38. Available at: https://scielo.isciii.es/pdf/medtra/v26n1/1132-6255-medtra-26-01-00031.pdf

xxiii. Vicente Herrero MT, Delgado Bueno S, Bandrés Moyá F, Ramírez Iñiguez De La Torre MV, Capdevila García L. Valoración del dolor. Revisión Comparativa de Escalas

y Cuestionarios. Rev. Soc. Esp. Dolor. 2018. DOI: 10.20986/resed.2018.3632/2017

xxiv. Martins RS, Siqueira MG. Conservative therapeutic management of carpal tunnel syndrome. Arq. Neuropsiquiatr. 2017;75:819-824. DOI: 10.1590/0004-282X20170152

xxv. Currie KB, Tadisina KK, Mackinnon SE. Common Hand Conditions: A Review. JAMA. 2022;327(24):2434. DOI: 10.1001/jama.2022.8481

xxvi. Wolny T, Linek P. Is manual therapy based on neurodynamic techniques effective in the treatment of carpal tunnel syndrome? A randomized controlled trial. Clin. Rehabil. 2019;33(3):408-417. DOI: 10.1177/0269215518805213

xxvii. Rayegani SM, Moradi-Joo M, Raeissadat SA, Bahrami MH, Seyed-Nezhad M, *et al.* Effectiveness of Low-Level Laser Therapy compared to Ultrasound in Patients With Carpal Tunnel Syndrome: A Systematic Review and Meta-analysis. J. Lasers Med. Sci. 2019;10(1):S82-S89. DOI: 10.15171/jlms.2019.S15

Original article

Adolescents and Young People's Perception of Care in Health Services in El Salvador

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Abstract
Introduction. Friendly Health Services are spaces of comprehensive and differential care for adolescents and young people, which start from their biological, social and emotional. **Objective.** Evaluate the perceptions of youth about the quality of care they received and their experience in the Community Family Health Units. **Methodology.** A mixed study was carried out that collected the perceptions of the participants in two successive stages. First with a questionnaire that evaluated the quality of care and experience of users, then through group and individual interviews that estimated the level of satisfaction. **Results.** Youth consult health establishments, although 68.2 % are unaware of the exclusive programs for them (Friendly Health Services). The most used service was general medicine (76.6 %). Regarding the care received, the respect, trust and privacy provided by health professionals was rated as excellent or very good (76 %). 39.7 % reported that the waiting time was 30 to 60 minutes, 17.6 % reported waiting more than two hours. **Conclusion.** Currently, there is a need to improve access to services for adolescents and young people by socializing the offer to encourage their use, increase attention in preventive areas and implement their evaluation with methods different from current ones.

Keywords
Adolescent Health Services, Quality of Health Care, Comprehensive Health Care, Evaluation of Health Services.

Resumen
Introducción. Los Servicios de Salud Amigables son espacios de atención integral y diferencial para personas adolescentes y jóvenes, que parten de sus necesidades biológicas, sociales y afectivas. **Objetivo.** Evaluar las percepciones de las juventudes sobre la calidad de atención que recibieron y su experiencia en las Unidades de Salud. **Metodología.** Se realizó un estudio mixto que recogió las percepciones de los participantes en dos etapas sucesivas. Primero, con un cuestionario se evaluó la calidad de atención y experiencia de los usuarios; luego, mediante entrevistas grupales e individuales se estimó el nivel de satisfacción. **Resultados.** El 68,2 % de los jóvenes y adolescentes desconocen los programas exclusivos para ellos. El servicio más utilizado es el de medicina general (76,6 %). En cuanto a la atención recibida, el respeto, la confianza y la privacidad brindada por los profesionales de salud fue calificada como excelente o muy buena (76 %). El 39,7 % reportó que el tiempo de espera fue de 30 a 60 minutos; el 17,6 % refirió esperar más de dos horas. **Conclusión.** Aunque la percepción de las unidades de salud por parte de los adolescentes y jóvenes en general es buena, los Servicios de Salud Amigables cuentan con barreras que interfieren en el acceso, oportunidad y aceptabilidad.

Palabras clave
Servicios de Salud del Adolescente, Calidad de la Atención, Atención Integralde Salud, Evaluación de Servicios de Salud.

Introduction

Friendly Health Services (FHS) are spaces for comprehensive and differential care for adolescents (10 to 19 years)[i] and young people (20 to 24 years)1 based on their biological, social, and affective needs,[ii] since the social environment determines the appearance of risk behaviors that represent an important public health problem.[iii]

Data from the World Health Organization (WHO) reported that worldwide, more than 1.1 million people between ten and 19 years of age died due to injuries, trauma (including those caused by traffic), violence, self-injurious behavior, infectious diseases (such as respiratory infections), and childbearing. Also, during this period, 42 out of every 1000 adolescents aged 15 to 19 gave birth.[iv]

In El Salvador, from January to September 2021, injuries affecting multiple regions of the body were reported as the main causes of death in 10 to 19 year-old males (31 %), and females (26 %).[v] Moreover, in 2022, 133 853 adolescent pregnancies occurred; of these, 6130 were in children aged under 14 years.[vi]

Therefore, based on international recommendations, the National Integrated Health System of El Salvador (SNIS) has implemented since 2018 the FHS model, located in primary care centers and hospitals in the central, paracentral, and western areas of the country, which offer preventive and curative care related to teenage pregnancy, mental health, violence, addictions, sexual health education, nutrition. This study has as its central axis the constant evaluation of the quality of care by adolescents and young people as social comptrollers.[vii] This motivated the realization of this study, which evaluated the perceptions of the quality of care of young people and adolescents in the health units to have inputs to update human resources and generate empirical evidence for health managers and implementers.[viii]

Methodology

Study design

Study with a mixed approach in successive stages. The quantitative phase was conducted with a descriptive cross-sectional design and the qualitative phase through a phenomenological design, in the period from June to September 2020, with data resulting from a consultancy process implemented by Doctors of the World Spain (Figure 1).

Sample

Quantitative phase

The sample was calculated from a population of 11 167, using the finite population formula, taking into account a prevalence of 50 % and a confidence interval of 95 %, obtaining a sample of 372 participants. The 10 % of non-response was added to this number, obtaining a sample of 409 participants. However, at the time of data collection, a larger population was captured, so the final sample studied was 478.

Qualitative phase

Thirteen participants from the quantitative phase who met the following inclusion criteria were considered for the qualitative phase.

Inclusion criteria

Quantitative phase

Users who consulted any healthcare area of the health units in the municipalities of Colón, Izalco, Jiquilisco, San Martín, San Martín, San Miguel, Soyapango, and Usulután, aged between 10 and 24 years, of male, female, and non-binary gender were required for their selection.

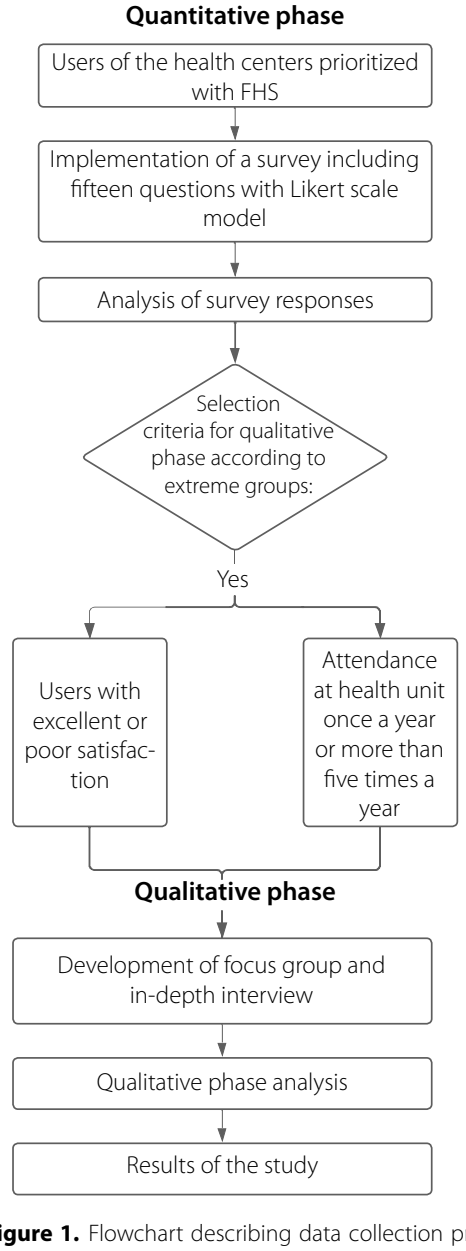

Figure 1. Flowchart describing data collection process

Qualitative phase

Participants who stated that they visited health centers one or more than five times a year and that their degree of satisfaction with health services was "excellent" or "bad".

Variables

1. Quality of care, i.e., ensuring that each adolescent and young person receives optimal healthcare, taking into account all factors and knowledge of the user and the healthcare professional to achieve maximum satisfaction with the process. (Table 1)[viii]
2. User experience, i.e. the interaction of adolescents and young people with the healthcare system. (Tabla 1)[viii]

Data Collection

Quantitative phase

It was carried out using a virtual questionnaire on the Google Forms platform adapted from the SERVQUAL model[ix,x] and the Colombian Friendly Health Services for Adolescents and Young People survey,[xi] which assessed the quality of care and user experience. The questionnaire was distributed through a link

Table 1. Study variables and dimensions in the quantitative and qualitative phase of the study

Quantitative phase		
Variables	Dimensions	Indicator
Socio-demographic characterization	General data	Sex
		Age
		Current activity
		Educational level
Quality of care	Use of health services (Opportunity)	Frequency of visits to the health facility in a year
		Service of the health unit you (the participant) use
	Ease of service identification (Accessibility)	Signposting of FHS in health units
		Knows there are FHS in health units
		Perception of the signage in each of the services.
		Perception of health services hours
		Delivery of educational material of your interest
	Care received (Acceptability)	Area of the health unit where the best treatment is received
		Perception of how the health professional performs the physical examination
		Perception of the respect, trust and privacy given by the health personnel.
		Perception of the way in which health personnel communicate at the time of consultation care
		Guidance as a complement to the reason for consultation
		Waiting time for medical, nutrition, psychology and dentistry professional care
		Waiting time for attention in the archive, radiology or laboratory
		You consider that they give you time to answer questions during care
		The indications you receive from the health personnel before or after the consultation are made clear to you
User experience	Experience in the areas of healthcare services	Perception of the care received in healthcare services
		Counseling on sexual and reproductive health
		Vaccination
		Pregnancy test
		Prenatal checkups and childbirth care
		Contraceptives
		Sexually Transmitted Infection/HIV counseling
		Dentistry
		Psychology
		Nutrition
		Alcohol or drug care
	Opinion space	Preferred means of expressing opinions or suggestions about the health services you receive

Qualitative phase	
Variable	Dimensions
User experience	Reasons why friendly services should exist
	Programs they consider important for adolescents
Quality of care	Attention received
	Reasons to not visit healthcare services
	Healthcare services expectations

via WhatsApp and was filled out self-administered or by the researcher via telephone in case of inconvenience.

This form included 28 questions: 15 with closed-ended Likert scale responses and 13 multiple-choice questions. The response options for the Likert scale questions were: 1. poor, 2. fair, 3. good, 4. very good, 5. excellent.

Qualitative phase

The information was collected through group interviews applied in person to 11 participants: six men and five women, between ten and 24 years old, from the urban and rural areas of Usulután and Jiquilisco. Also, individual in-depth interviews were conducted in person with two participants aged 15 and 20 years old, females from Soyapango and Colón, due to problems of access due to violence in other cities.

For this phase, an interview guide was used based on a guideline prepared with 11 open questions concerning the perceptions of young people on the level of satisfaction with the quality of care received and their experience. It ended at theoretical saturation with 13 participants between group and individual interviews (six men and seven women). All interviews were recorded with the consent of the participants.

Data analysis

Quantitative phase

The data were analyzed with descriptive statistics through frequencies and percentages; subsequently, the results of the analysis were represented in tables and figures with the support of the Excel program.

Qualitative phase

The data were transcribed, categorized, and analyzed with the support of the Atlas ti program. For identification purposes, codes of male participant (MP) and female participant (FP) were used followed by age in years, divided by hyphen; for example, male participant aged 21 years (MP-21) and female participant aged 14 years (FP-14). At the conclusion, the data were presented in prose and tables.

Ethical considerations

This study did not use human samples and only collected data verbally from the participants, who did not receive any remuneration and previously completed an informed consent or assent form. This study was reviewed and approved by the National Health Research Ethics Committee. The information provided by the participants was treated confidentially.

Results

Quantitative phase

A total of 478 questionnaires were completed by participants from the cities of Colón, Izalco, Jiquilisco, San Martín, San Miguel, Soyapango, and Usulután.

A. Characterization of adolescents and young people using health services.

The total number of participants consisted of 58.8 % females, 40.4 % males, and 0.8 % non-binary individuals. Regarding the age groups, 17.8 % of the respondents were between the ages of 10 and 14, while 58.8 % were between the ages of 15 and 19. The predominant level of schooling was high school (47.3 %) and junior high school (26.6 %).

B. Frequency of use of health services.

The highest percentage of people surveyed from once to twice a year was 48.1 % across all three genders. It is worth mentioning that the female gender, aged 15-19 years, are those who consulted more than five times a year (60 %), and of the three genders, the male gender rarely consults (25.9 %).

Regarding the health services or programs consulted, the most requested was general medicine (76.6 %), with a predominance of males. Prevention services such as nutrition, prenatal checkup, contraception, psychology, sex education, treatment of sexually transmitted infections (STIs), care for violence, as well as alcohol and drug prevention were requested by 5 %.

Likewise, 68 % of the participants reported that they were unaware of the Friendly Health Services or the spaces

exclusively for them. Of these, 60.1 % of the female gender is the least aware.

C. Care provided by the health personnel in the health unit's services.

The perception of the experience of accessibility to the services/programs evaluated was mostly categorized as "excellent" or "very good" with a predominance of respect, trust, and privacy with which the health professional attends. However, at least five instances rated them as "bad" particularly concerning the signage of the services. (Figure 2)

When asked which areas they liked the most, 38.1 % said they were treated well in all areas. The professionals who gave care were the best evaluated, with 32.4 %. Using the same criteria, 11.9 % said they didn't like how they were treated in any area, especially when giving data for the file (25.5 %).

Regarding the duration of waiting for consultation with a medical, dental, nutrition, or psychology professional, 39.7 % of respondents reported that the wait was between 30 and 60 minutes, while 17.6 % reported that the wait was longer than two hours. For care in support areas, such as file preparation, laboratory, or radiology, 48.7 % of respondents reported a waiting time of 30 to 60 minutes, while 6.3 % reported a waiting time exceeding two hours.

Figure 3 describes the perception of the young people about their experience in the areas of care. It was observed that the vaccination area is the most requested. Vaccination, dentistry, sexual and reproductive health, nutrition, psychology, and prenatal checkup services were evaluated in the highest percentage as "good" and STI/HIV, contraceptives, pregnancy tests, and alcohol drugs as "regular."

Qualitative phase

Participants were interviewed: six men and seven women (one of them at ten weeks' gestation). (Table 2)

Among the participants, nine are studying and four are seeking employment (neither studying nor working), who stated that they know that there is a referent person from the adolescent and youth program. However, they are not aware of the programs that are exclusive to them, nor under the term Friendly Health Services.

Discussion

This study revealed that the perceptions of adolescents and young people about the quality of care and their experience at the health unit were generally good, although the aspects perceived as bad became barriers to accessing health services.

It was evident that adolescents and young people perceive health services/programs with a curative vision, since the majority requested care with general medicine, dentistry or nutrition, and preventive services such as sexual and reproductive health care, alcohol and drug prevention, violence, STI/HIV treatment and contraception, to a lesser extent.

Brochado *et al.* attribute this finding to the fact that they use these programs as access to contraceptive methods and not to receive sexual health support, although they point out that a large percentage of this population does not even use these methods.[xii] Other studies attribute this to the environment and the restrictions that the adult world imposes on the mobility of

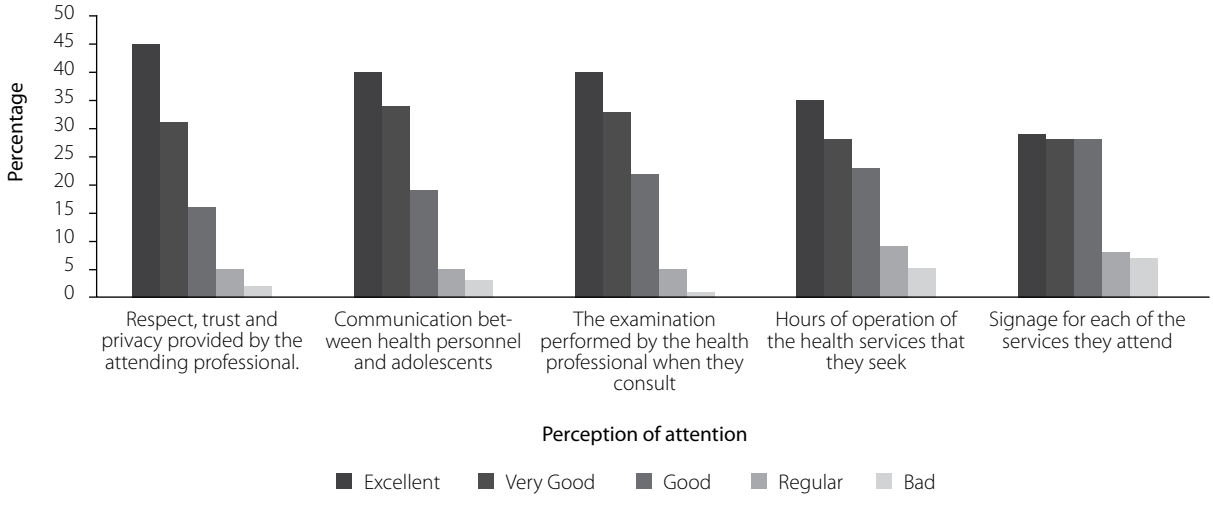

Figura 2. Youth evaluation of user experience according to the accessibility of services/programs in the health unit, 2020

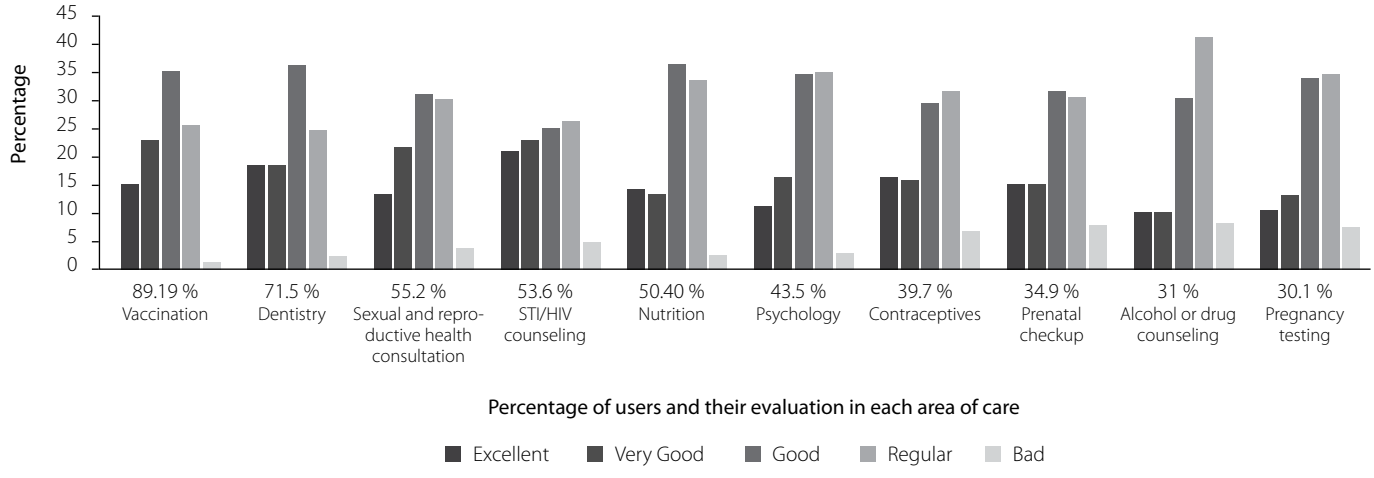

Figure 3. Evaluation of youth to user experience in the healthcare areas of the health units of Colón, Izalco, Jiquilisco, San Martin, San Miguel, Soyapango, and Usulután 2020

Table 2. Perception of adolescents and young people on the health services they receive

Variable	Dimension	Sub/descriptors	Narratives
User experience	Reasons for friendly services	Greater exclusivity. Timely advice. To have health information. Avoid mistakes that may affect future health. More frequent consultations.	"Yes, I want it because there would be more information for young people with these services" (FP-15 years old). "We would have more consultations" (FP-14 years old).
	Programs they consider important for adolescents	Child abuse. Drugs. Sexuality. Sexually transmitted diseases. Teenage pregnancy. Social inclusion.	"In my neighborhood, there are girls who have become pregnant at a very young age; most of them are 14 or 13 years old and already have a baby" (FP-21 years old). "There are friends who mock or discriminate (us) for normal changes according to their sex and these are things that are not their decision" (PM-15 years old). "Child abuse because there are many parents who put their children to work since they are young and that is not right" (FP-17 years old). "The children in my neighborhood are all lost; they have been smoking since they were very young " (FP-21 years old).
Quality of attention	Care provided	Favorable perception: They are helped when seeking care for illness. There is kindness. They are heard.	"So far so good. But it could be better" (FP-18 years old). “Pretty good, they are kind and can listen to us without interrupting" (PM-20 years old). "They have treated me well so far; they have been kind. I asked things I didn't know, and they have been kind and answered me" (FP-21 years old).
		Unfavorable perception: Lack of friendliness and courtesy. They inspire fear. Lack of additional tests and more in-depth analysis.	"I'm a little scared because they don't treat us well and they look kind of bitter. I wish they were friendlier" (PM-12 years old). "Sometimes they don't get to you quickly. You think they will see you, but sometimes they don't pay attention to you" (PM-15 years old).
		Perception of the physical space and supplies with which care is provided.	"What I don't really like about the clinic is the hygiene. I don't like the stretchers, when you are being examined. The doctor is nice, but there is a lack of hygiene with the things that are used. There is a lack of new things. I would also like it to be more private for the exams, not where all the other patients are. And where they check you, you are almost falling off of it. There should be someone to do the ultra pregnancy test because they send me somewhere else" (FP-21 years old).
	Reasons for not attending health services	If you’re not sick, you’re not attended to. Long wait times. Attention for preferences.	"I only go when I am sick. I don't like to go for other reasons because they say: "if you feel well, why do you come?" (FP-15 years old). "Sometimes you don’t get quick attention. You think they will, but sometimes they don't" (PM-15 years old). "I come sick, but another comes later and they pass first because of preference. I think there should be an order so that there is no difference" (15 years old).

Expectations of health services	Attention with more kindness, impartiality, trust, respect. Improve waiting time. Perform complementary tests as routine. Better evaluate to provide specific and varied treatments. Decentralize health services, go out into the community or schools. Long lasting youth-oriented programs.	"They should do a general check-up. That it doesn't come from you, but also from the doctor" (PM-24 years old). "They should be more polite, more respectful" (PM-12 years old). "Analyze the problem, do more examinations in order to reach a diagnosis. Don't just give acetaminophen for fever or headache to everyone, but analyze the problem well" (FP-15 years old). "They should implement more services in the dental area; where I go there is only cleaning and extraction of teeth. There should be fillings and more" (FP-20 years old). "I would like to feel confident because sometimes they offend or don't even want to attend" (PM-14 years old). "It would be good if they listened more to the youth, because right now, the way they are, they need to be listened to more and sometimes there is no time for the youth. They only go to the health unit when they are sick, but when they are not sick is when they need attention the most" (FP-21 years old). "It would be good if they taught something useful so we could do something" (PM-21 years old).

FP= female participant, PM= male participant.

young people.[xiii,xiv] This finding suggests that prevention training programs require greater awareness and socialization, both in the population aged 10 to 19 years and in their family and community environment.

The inadequacy of signage at health centers to promote programs exclusively for adolescents and young people, commonly referred to as Friendly Health Services, is a cause for concern, as it not only indicates deficiencies in the quality of care but also poses obstacles to access. The study conducted by Ibáez *et al.* attributes the low acceptance of FHS diverse programs and community outreach to the lack of awareness regarding these services.[xv,xvi]

Another parameter for evaluating the acceptability of the FHS was the health professional's attention, which was perceived as very good, as there were no reported failures in the respect, trust, and privacy they provide. However, a minority experienced discrimination and mistreatment, perceiving it as bad. These extreme perceptions could be based on the socio-cultural characteristics of adolescents and young people and reflect an inequitable quality of care.[xvii-xix]

Different studies highlight this perception as a barrier to access[xx-xxii] that is not only the responsibility of those who directly provide medical care but of all those involved in the process of obtaining it, from the consultation request, followed by waiting times, direct interaction with health personnel, to the receipt of the medication.

Concerning the perception of the experience, long waiting times were found to be one of the reasons for not attending health centers. Pastrana *et al.* reported in their study that waiting times are not established as a barrier for most adolescents; however, on certain occasions, they may have influenced them to refrain from consulting the FHS.[xxiii-xxv]

One of the limitations of the study was the lack of depth in the needs and particularities of the different genders due to the predominance of the female gender and the minority of the non-binary gender because although they have in common the biopsychosocial changes characteristic of age, each gender has different needs and behaviors that need to be exposed.

Another limitation was that the focus groups and individual interviews were only conducted in three cities due to the post-pandemic scenario of COVID-19 and social violence at the time of the study.

There is a need for future studies that equitably include all genders to assess differences or similarities in perceptions of quality of care and their experiences.

Conclusion

Although the perception of US by adolescents and youth is generally good, the FHS have flaws in the quality of care and user experience that may constitute barriers that interfere with access, timeliness, and acceptability of services.

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References

i. Jesús-Reyes DD, González Almontes E. Acceso, trato y atención en los servicios de salud amigables para adolescentes de Monterrey, Nuevo León, México. Papeles Poblac. Junio de 2022; 28(112):199-223. DOI: 10.22185/24487147.2022.112.16
ii. González-Quiñones JC, Hernández-Pardo AM, Salamanca-Preciado JP, Guzmán-Castillo KA, Quiroz-Rivera RM. Cambios en prevalencias de conocimientos, actitudes y prácticas de sexualidad en adolescentes escolarizados, Bogotá, 2011-2015. Rev Salud Pública. 2019; 21(2):202-8. DOI: 10.15446/rsap.v21n2.73371
iii. Dayal R, Gundi M. Assessment of the quality of sexual and reproductive health services delivered to adolescents at Ujala clinics: A qualitative study in Rajasthan, India. PLoS One. 2022; 17(1):e0261757. DOI: 10.1371/journal.pone.0261757
iv. Temas de salud, La Salud del adolescente. Organización Mundial de la Salud. 2022. 4p. Available at: https://www.who.int/es/health-topics/adolescent-health#tab=tab_1
v. Organización Mundial de la Salud. Salud del adolescente. 2024. Date of citation: January 15, 2024. Available at: https://www.who.int/es/health-topics/adolescent-health#tab=tab_2
vi. Fondo de Población de las Naciones Unidas de El Salvador Mapa de Embarazo en Adolescentes. 2023. 94p. Available at: https://elsalvador.unfpa.org/sites/default/files/pub-pdf/mapa_embarazos_2023_web.pdf
vii. Ministerio de Salud de El Salvador. Lineamientos técnicos para la atención integral en salud de adolescentes y jóvenes en las RIIS. 2018. Available at: https://asp.salud.gob.sv/regulacion/pdf/lineamientos/lineamientos_tecnicos_atencion_adolescentes_y_jovenes_riis.pdf
viii. Moreno Rangel, Y. Los servicios amigables para adolescentes y jóvenes. Una estrategia pendiente en promoción de la salud sexual y reproductiva. Universalud. Rev. Ciencias salud. 2018; 8(1): 4-12. Available at: https://dialnet.unirioja.es/servlet/articulo?codigo=8996302
ix. Ganga Contreras F, Alarcón Henríquez N, Pedraja Rejas L. Medición de calidad de servicio mediante el modelo SERVQUAL: el caso del Juzgado de Garantía de la ciudad de Puerto Montt - Chile. Ingeniare Rev Chil Ing. diciembre de 2019; 27(4):668-81. DOI: 10.4067/S0718-33052019000400668
x. Salvador Silverman M, Moreno Altamirano L, Hernández-Montoya D, Martinez González A, Ochoa Diaz-López H. Construcción y validación de un instrumento para medir la satisfacción de los pacientes del primer nivel de atención médica en la Ciudad de México. Gac Med Mex. 22 Enero de 2016; 152:43-50. Available at: https://www.anmm.org.mx/GMM/2016/n1/GMM_152_2016_1_043-050.pdf
xi. Ministerio de la Protección Social de Colombia, Fondo de las Naciones Unidas para la Infancia. Servicios de salud amigables para adolescentes y jóvenes. Un modelo para adecuar las respuestas de los servicios de salud a las necesidades de adolescentes y jóvenes de Colombia. 2008. Available at: https://colombia.unfpa.org/sites/default/files/pub-pdf/ssaja2.pdf
xii. Brochado Ariza KP, Duran Ravelo J, Hernández-Palma HG. Realidad de los jóvenes con relación a la salud sexual y su percepción del programa servicios amigables del municipio de Santa Lucía. Cienc E Innov En Salud 2020; e94: 410-420. DOI: 10.17081/innosa.94
xiii. Bhatta BR, Kiriya J, Shibanuma A, Jimba M. Parent-adolescent communication on sexual and reproductive health and the utilization of adolescent-friendly health services in Kailali, Nepal. PLoS One. 19 de febrero de 2021;16(2):e0246917. DOI: 10.1371/journal.pone.0246917
xiv. Decker MJ, Atyam TV, Zarate CG, Bayer AM, Bautista C, Saphir M. Adolescents' perceived barriers to accessing sexual and reproductive health services in California: a cross-sectional survey. BMC Health Serv Res. 2021; 21:1263. DOI: 10.1186/s12913-021-07278-3
xv. Ibáñez-Cuevas M, Torres-Pereda P, Olvera M, Pastrana-Sámano R, Heredia-Pi IB. Calidad de la atención en los servicios de salud amigables para adolescentes en Morelos, México: Perspectiva de usuarios y prestadores. 2021 DOI: 10.33064/iycuaa2021833750
xvi. García Vázquez J, Quintó Domech L, Nascimento M, Agulló-Tomás E. Evolución de la salud sexual de la población adolescente española y asturiana. Rev Esp Salud Pública. 2020; 93 (4): e1-14. Available at: https://scielosp.org/pdf/resp/2019.v93/e201909071/es
xvii. Belay HG, Arage G, Degu A, Getnet B, Necho W, Dagnew E, *et al.* Youth-friendly sexual and reproductive health services utilization and its determinants in Ethiopia:

A systematic review and meta-analysis. Heliyon. 2021.; 7(12):e08526. DOI: 10.1016/j.heliyon.2021.e08526

xviii. Arije O, Madan J, Hlungwani T. Quality of sexual and reproductive health services for adolescents and young people in public health facilities in Southwest Nigeria: a mystery client study. Glob Health Action. 2022. 15(1): 1-12. DOI: 10.1080/16549716.2022.2145690

xix. Bali S, Chatterjee A, Nagi RS, Gupta S, Singhal K. How to make services adolescent friendly? A cross-sectional study on awareness of adolescent friendly health clinics in Central India. J Family Med Prim Care. 2022; 11(10):6127-6134. DOI: 10.4103/jfmpc.jfmpc_365_22

xx. Pandey PL, Seale H, Razee H. Exploring the factors impacting on access and acceptance of sexual and reproductive health services provided by adolescent-friendly health services in Nepal. PLoS One. 2019; 14(8):e0220855. DOI: 10.1371/journal.pone.0220855

xxi. Obiezu-Umeh C, Nwaozuru U, Mason S, Gbaja-Biamila T, Oladele D, Ezechi O, *et al.* Implementation Strategies to Enhance Youth-Friendly Sexual and Reproductive Health Services in Sub-Saharan Africa: A Systematic Review. Front Reprod Health. 2021; 3(1): 1-13. DOI: 10.3389/frph.2021.684081

xxii. Torres-Ospina SM, Delgadillo-Morales ÁM, Orcasita-Pineda LT, Conocimientos, experiencias y actitudes sobre derechos sexuales y derechos reproductivos en adolescentes y jóvenes. Hacia Promoc Salud. Enero de 2021; 26(1):52-68. DOI: 10.17151/hpsal.2021.26.1.6

xxiii. Pastrana-Sámano R, Heredia-Pi IB, Olvera-García M, Ibáñez-Cuevas M, Castro FD, Hernández AV, *et al.* Servicios Amigables para Adolescentes: evaluación de la calidad con usuarios simulados. Rev Saúde Pública. 6 de abril de 2020; 54:36. DOI: 10.11606/s1518-8787.2020054001812

xxiv. Desmond C, Seeley J, Groenewald C, Ngwenya N, Rich K, Barnett T. Interpreting social determinants: Emergent properties and adolescent risk behavior. PLoS ONE. 2019; 14(12):e0226241. DOI: 10.1371/journal.pone.0226241

xxv. Groenewald C, Isaacs N, Qoza P. Hope, agency, and adolescents' sexual and reproductive health: A mini review. Front Reprod Health. 2023; 5 (1): 1-13. DOI: 10.3389/frph.2023.1007005

Original article

Influencing Factors in the Survival of Dialysis Patients in El Salvador

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Abstract
Introduction. The chronic kidney disease is responsible for approximately 2.4 million deaths worldwide, five year survival in patients after starting dialysis was between 39 and 60 % depending on the country. **Objective.** Analyze the factors that influence the five years survival in patients after starting renal replacement therapy in El Salvador. **Methodology.** It is a retrospective cohort study from patients included in dialysis and renal replacement therapy national registry from January 2016 to February 2023, the start point for the following was the initiation of dialysis, the event of interest was patient´s death, the Kaplan-Meier method was used to determine one year and five year survival; and Cox regression with Royston-Parmar model was used to analyze the factors that influence survival. **Results.** The study included 7088 patients, one and five-years survival was 79.5 % (CI 95 %: 78.6-80.5) and 50.6 % (CI 95 %: 49.1-52.1) respectively. The Cox regression for age of treatment initiation resulted in a hazard ratio of 1.02 (CI 95 %: 1.01-1.02), while for farmers, the hazard ratio was 1.09 (CI 95 %: 1.00-1.18), for hypertensive etiology the hazard ratio was 0.7 (CI 95 %: 0.64-0.78). **Conclusion.** Data suggest that age of treatment initiation, and jobs related to agriculture were associated with less five year survival in dialysis patients.

Keywords
Chronic Renal Insufficiency, Dialysis, Survival Analysis.

Resumen
Introducción. La enfermedad renal crónica es responsable de aproximadamente 2,4 millones de defunciones a nivel mundial. La supervivencia a los cinco años después de iniciar diálisis se encuentra entre un 39 a 60 % dependiendo del país. **Objetivo.** Describir la situación epidemiológica de los pacientes con diálisis y analizar los factores que influyen en la supervivencia de pacientes a cinco años de iniciar tratamiento sustitutivo renal en El Salvador. **Metodología.** Estudio de cohorte retrospectivo de los pacientes incluidos en el Registro Nacional de Diálisis y Trasplante Renal desde enero de 2016 hasta febrero de 2023. El seguimiento se comenzó al inicio de la diálisis, el evento de interés fue la muerte del paciente. Se utilizó el método de Kaplan-Meier para determinar la supervivencia al año y a los cinco años y la regresión de Cox con el modelo de Royston-Parmar para analizar los factores que influyen sobre la supervivencia a los cinco años. **Resultados.** El estudio incluyó 7088 pacientes, la supervivencia a uno y cinco años fue del 79,5 % (IC 95 %: 78,6-80,5) y 50,6 % (IC 95 %: 49,1-52,1) respectivamente. La regresión de Cox para la edad de inicio de tratamiento resultó en un hazard ratio de 1,02 (IC 95 %: 1,01-1,02), mientras que para el oficio de ser agricultor el hazard ratio fue 1,1 (IC 95 %: 1,01-1,18) y para la etiología hipertensiva el hazard ratio fue de 0,7 (IC 95 %: 0,64-0,78). **Conclusión.** La edad de inicio de tratamiento y el ser agricultor están asociados con una menor supervivencia a cinco años en pacientes con diálisis.

Palabras clave
Insuficiencia Renal Crónica, Diálisis, Análisis de Supervivencia.

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Factores que influyen en la supervivencia de pacientes con diálisis en El Salvador

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Introduction

Chronic kidney disease (CKD) is defined as permanent damage to renal structure and function, characterized mainly by a glomerular filtration rate of less than 60 mL/min per 1.73 m^2 or the presence of markers of renal damage that persist for at least three months. When the glomerular filtration rate falls below 15 mL/min per 1.73 m^2, it is considered renal failure, and when it falls between 5 to 10 mL/min, renal replacement therapy is recommended[i-iii].

The main causes of CKD worldwide are arterial hypertension and diabetes *mellitus*; however, in the Central American and Caribbean region, another important cause of kidney disease has also been identified, which generally affects male patients engaged in agriculture and has been called Mesoamerican nephropathy.[ii,iv]

Globally, CKD represents a major public health problem, with a progressive increase in prevalence in the general population and an increase in the use of renal function replacement therapy, such as hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation. This places a significant burden on healthcare systems. According to reports from 2022, it is estimated that more than 850 million people worldwide suffer from chronic kidney disease, with approximately 2.4 million deaths.[v]

In 2015, the prevalence of CKD was estimated at 12.6 % in El Salvador. In 2019, the CKD mortality rate in the country was 72.9 per 100 000 population, ranking as the second highest in the Americas, after Nicaragua (73.9).[vi] In the country, the rate of patients on renal replacement therapy for 2018 (RRT) was 677 per million inhabitants, exceeding the regional rate for Central America and the Caribbean (392 per million inhabitants).[vii]

Patients who started dialysis between 2004 and 2008 in the United States had a five-year survival rate of 39 %, in Europe 41 %, and in Japan 60 %.[viii] In El Salvador, five-year survival in patients who begin renal replacement therapy is unknown, nor has research been conducted on the factors that influence mortality in these patients.

Consequently, these findings highlight the importance of analyzing the mortality associated with CKD in El Salvador. Understanding the underlying causes of survival is crucial for implementing effective preventative and management strategies.

This study aimed to describe the epidemiological situation of dialysis patients and to analyze the factors that influence the five-year survival of patients who start renal replacement therapy in El Salvador.

Methodology

The study is a retrospective dynamic cohort of patients in the National Registry of Dialysis and Renal Transplantation of El Salvador. It was implemented in 2016 and is part of the Information System for Patients with Chronic Diseases (SIEC). It is aimed at keeping track of patients receiving RRT by the Ministry of Health of El Salvador and has national coverage.[ix] The start of follow-up was taken as the date of initiation of RRT up to five years of treatment; the event of interest was the death of the patient; patients who died less than 24 hours after initiation of treatment were excluded.

The initial database contained 7321 records. Of these, 72 duplicates, 51 cases of patients who died less than 24 hours from the start of treatment, 39 records corresponding to foreign patients, 24 cases of patients who had received renal transplants, 22 records with incomplete data, and 25 cases of patients who had not received initial treatment were excluded. As a result, the final database used for analysis consisted of 7088 records.

The database initially consisted of 56 variables, of which 30 related to identification, management characteristics, and medical procedures that were not of interest for the research were eliminated, ending with 26 variables for the study.

The variables used were date of birth, sex, municipality, occupation, initial treatment, date treatment started, etiology, current treatment, arterial hypertension, diabetes *mellitus*, cancer, hepatitis B, hepatitis C, HIV/AIDS, lithiasis, hyperuricemia, lupus erythematosus, other diseases, peritoneal access, type of PD management, hemodialysis access, discharge condition, cause of death, date of death, and place of death. In addition, the variable age at treatment initiation was constructed from the date of birth and treatment initiation.

Quantitative variables were tested for normality using the Anderson-Darling test, and frequencies, proportions, and crude rates were calculated. The median and interquartile range were used as measures of central tendency and dispersion, respectively. The national and municipal prevalence rate of dialysis patients was rated using the population projections in 2023 provided by the National Statistics and Census Office,[x] and a stratified choropleth map by quartiles was prepared from the calculated rates.

The Kaplan-Meier estimator was used to calculate the overall survival rate at one and five years, and the log-rank test was used to test statistical significance.

Cox regression was initially employed for the multivariate analysis. Furthermore, this model was evaluated using the likelihood ratio, and it was determined that the model constructed predicted survival better than a model without covariates.

The predictive capacity of the model was evaluated using the Harrel concordance index, and a cut-off point of 0.6 or higher was established to consider it a good concordance. The risk proportionality analysis was

used to verify sensitivity and compliance with the proportionality assumptions, and an overall value of $p < 0.01$ was obtained.

Since the concordance index was less than 0.6 and the assumption of proportionality of exposure was not met, a Cox multivariate analysis with Royston-Parmar random effects was performed because this model fits better to complex distributions.[xi,xii]

The evaluation of the fit of the second model was by the likelihood ratio test, Wald test, and log-rank test. A significance level of $p < 0.01$ was obtained for all of these tests. The Harrel concordance test yielded a value that exceeded the established cut-off point.

Microsoft Excel 365 and RStudio version 4.3.0 were used for data cleaning, processing and analysis, and QGIS version 3.30.1 for geospatial analysis.

This research was conducted according to the Helsinki principles for research on human subjects, using only the information contained in existing databases, which were anonymized and coded respecting the confidentiality of the individuals.

Results

The median age of the patients was 53 years (IR: 40 to 63 years), 69.5 % of the records corresponded to males, and in 56 % of the cases, the etiology of CKD could not be identified, with arterial hypertension and diabetes *mellitus* being the main known causes. Other etiologies, such as those of congenital, glomerular, or obstructive origin, collectively accounted for 5.8 % (Table 1).

A total of 45.6 % of the patients had some comorbidity, with arterial hypertension followed by diabetes *mellitus* being the most frequent. Among the other conditions identified, which totaled 3.5 % of the records, renal lithiasis (0.5 %), cancer (0.4 %), HIV infection (0.1 %), and systemic lupus erythematosus (0.1 %) stand out. The rest of the comorbidities identified have percentages of less than 0.1 %.

When the database was extracted from the system on February 28, 2023, a total of 3997 patients were actively receiving renal replacement therapy. A prevalence of 631 dialysis patients per million inhabitants was determined, with a prevalence of 62.4 % (N: 2493) on peritoneal dialysis and 37.6 % (N: 1504) on hemodialysis. The municipalities with the highest prevalence rates are situated in proximity to bodies of water and are associated with agricultural activities (Figure 1).

Of the patients with peritoneal dialysis, 64.1 % (N: 1599) had a soft catheter, 35.8 % (N: 891) had a rigid catheter, 39.1 % (N: 976) were receiving treatment on an outpatient basis and 60.8 % (N: 1514) in hospitals; there is no data on the type of catheter and treatment modality in 0.1 % (N: 3) of the PD patients. Of the hemodialysis patients, 77.8 % (N: 1177) receive treatment by catheter, 22.1 % (N: 332) by arteriovenous fistula, and no data is recorded in 0.1 % (N: 2).

A total of 2873 deaths were recorded in the database. Of these, 60.3 % (N: 1733) were in hospital. 39.3 % (N: 1128) of the patients died of unknown causes, 36.7 % (N: 1053) due to cardiovascular causes, 20.8 % (N: 597) due to infectious complications, 1.5 % (N: 43) due to complications related to renal disease, 0.7 % (N: 20) due to complications of the dialysis procedure, 0.5 % (N: 14) due to external cause injuries, 0.4 % (N: 12) due to discontinuation of treatment, 0.2 % (N: 5) due to neoplasms and in one patient anemia was recorded as the cause of death. 91.4 % (N: 2626) of the deaths occurred during the first five years of RRT.

The result of the Kaplan Meier analysis determined a survival of 79.5 % (CI 95 %: 78.6 - 80.5) after one year from the start of renal replacement therapy and a survival of 50.6 % (CI 95 %: 49.1 - 52.1) at five years (Figure 2).

When comparing survival by sex and initial treatment modality at five years from the start of treatment, no statistically significant difference was observed. Patients with agriculture-related trades had lower survival at five years (48.37 %; CI 95 %: 48.36 - 48.38 and 51.66 %; CI 95 %: 51.65 - 51.67) compared to those with other trades, patients with diabetic etiology also had lower survival compared to other etiologies (41.25 %; CI 95 %: 41.23 - 41.27 and 52.41 %; CI 95 %: 52.40 - 52.42), the results of the log Rank test for these variables were p value < 0.01 (Figure 3). Hypertensive etiology had higher survival compared to other etiologies (54.64 %; CI 95 %: 54.63 - 54.66 and 49.33 %; CI 95 %: 49.33 - 49.34), the difference was statistically significant ($p < 0.05$).

A hazard ratio (HR) of 1.02 ($p < 0.01$) was obtained for the variable age at treatment initiation; that is, a one-year increase in age increases the probability of death by 2 % five years after treatment initiation.

The HR for patients whose occupation was farming was 1.09, with a p-value of 0.049. It indicates that being a farmer increases the likelihood of death by 9 % five years after the commencement of treatment. The HR of patients with vascular etiology was 0.71, with a p-value < 0.01.

The exposure factor for the variable "sex" was male, resulting in an HR of 1.00. The variable "initial treatment" used hemodialysis as an exposure factor, with an HR of

Table 1. Characterization of patients in the National Registry of Dialysis and Renal Transplantation of El Salvador until February 2023.

Variable	Deceased (N:2873)			Living patients (N:4215)			Total (N 7088)	
	N	%	p-value	N	%	p-value	N	%
Gender and age								
Male	2009	69.9	0.3987	2916	69.2	0.3092	4925	69.5
Female	864	30.1	0.3987	1299	30.8	0.3092	2163	30.5
Median age	54 years (IR[a]: 42 - 63)			52 years (IR: 39 - 62)			53 years (IR: 40 - 62)	
Occupation								
Farmer	1073	37.3	<0.01	1280	30.4	<0.01	2353	33.2
Others occupations[b]	1800	62.7	<0.01	2935	69.6	<0.01	4735	66.8
Etiology								
Hypertensive	482	16.8	<0.01	1188	28.2	<0.01	1670	23.6
Diabetic	501	17.4	<0.01	538	12.8	<0.01	1039	14.7
Other causes	169	5.9	0.6733	241	5.7	0.6154	410	5.8
Not identified	1721	59.9	<0.01	2248	53.3	<0.01	3969	56.0
Comorbidities								
Arterial hypertension	1270	44.2	0.0016	1740	41.3	0.0001	3010	42.5
Diabetes *mellitus*	490	17.1	0.0904	671	15.9	0.04176	1161	16.4
Others	67	2.3	<0.01	183	4.3	<0.01	250	3.5
No comorbidities	1505	52.4	0.0011	2335	55.4	<0.01	3840	54.2
Initial treatment								
Peritoneal dialysis	2261	78.7	0.6046	3302	78.3	0.5673	5563	78.5
Hemodialysis	612	21.3	0.6046	913	21.7	0.5673	1525	21.5

a. Interquartile range, b. All other professions are classified in the database.

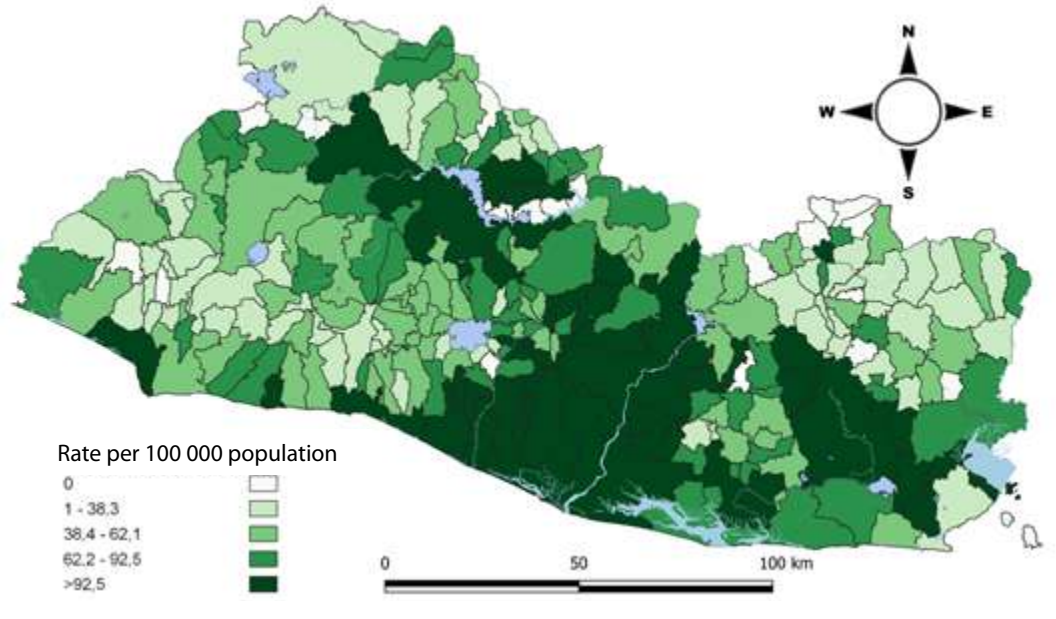

Figure 1. Prevalence of dialysis patients, El Salvador, February 2023.

0.94. The HR for diabetes etiology was 1.04. The p-values for all three variables exceeded 0.05. Figure 4 depicts the HR values and their confidence intervals.

Discussion

It was a survival study using the Kaplan Meier technique and the Royston Parmer model. Among the findings, the 5-year survival rate was higher than the unadjusted survival rate in the United States and Europe, 39 % and 41 %, respectively. However, it was lower than the 60 % survival rate in Japan. It is important to note that these mortality rates were calculated for patients who started dialysis between 2004 and 2008, so survival may vary if patients with later start dates are considered.[viii]

A study conducted in Colombia with a cohort of 12 508 patients over 18 years of age showed a survival rate similar to that found in this study, with a rate of 53 % after five years of treatment.[xiii] Another study conducted in Indonesia, although with a smaller cohort including only patients on peritoneal dialysis, found a five year survival of 52 %.[xiv] Due to the low survival rate among dialysis patients, the early detection of CKD and the implementation of measures to halt its progression are deemed the most effective measures to prolong the lives of renal patients.[ii]

Studies comparing treatment modalities do not suggest consistent findings. While

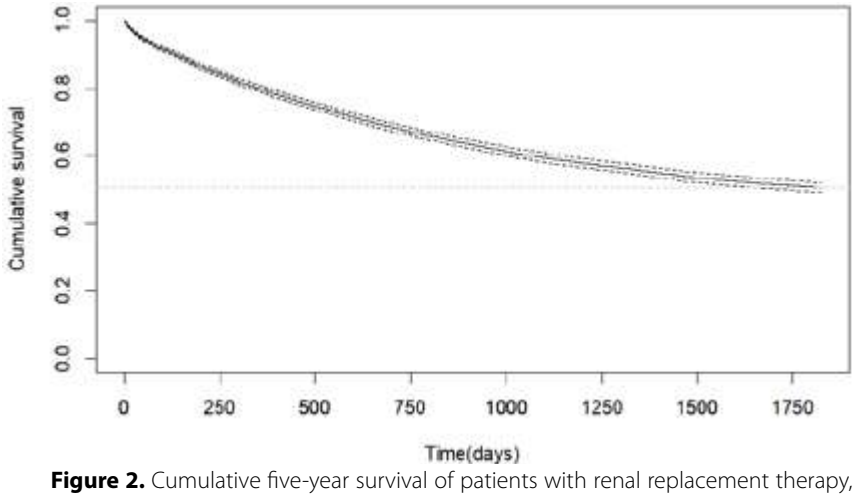

Figure 2. Cumulative five-year survival of patients with renal replacement therapy, El Salvador, February 2023.

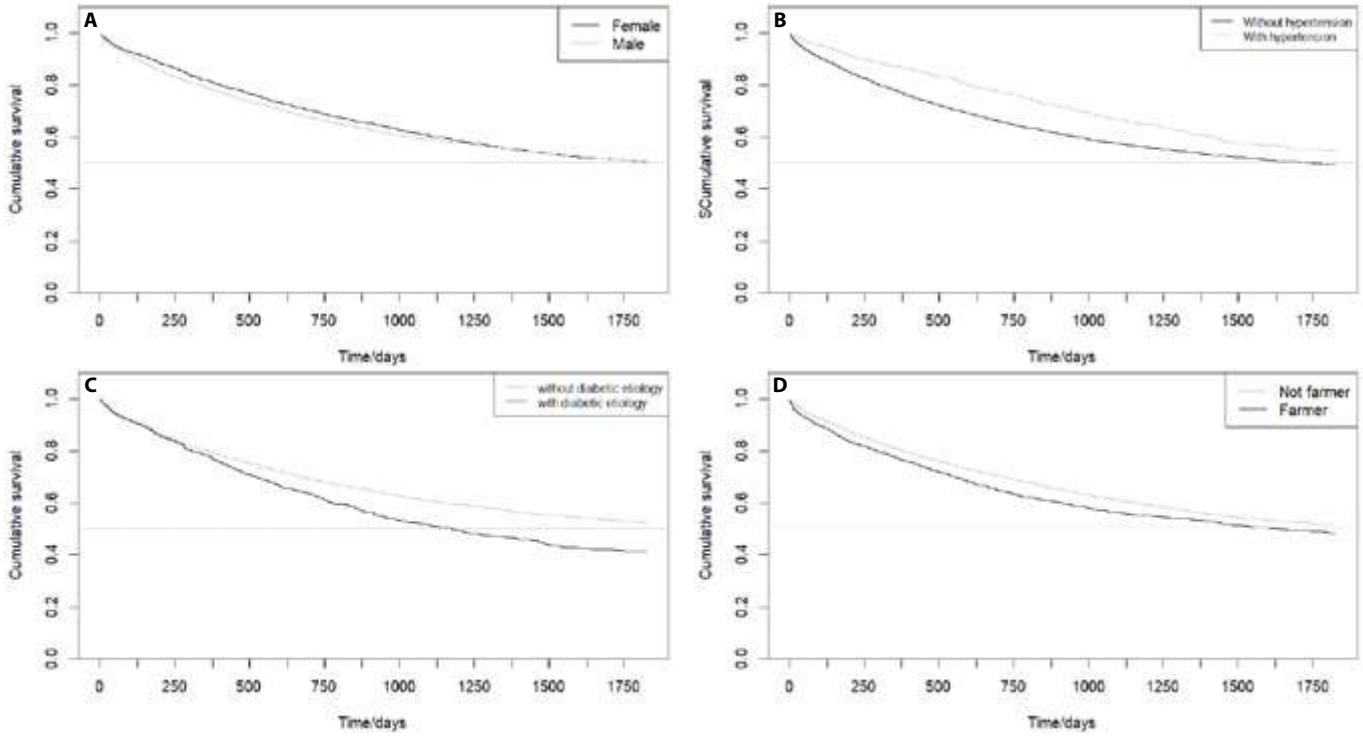

Figure 3. Cumulative five-year survival of patients with renal replacement therapy classified by sex, etiology, profession and initial treatment, El Salvador, February 2023.

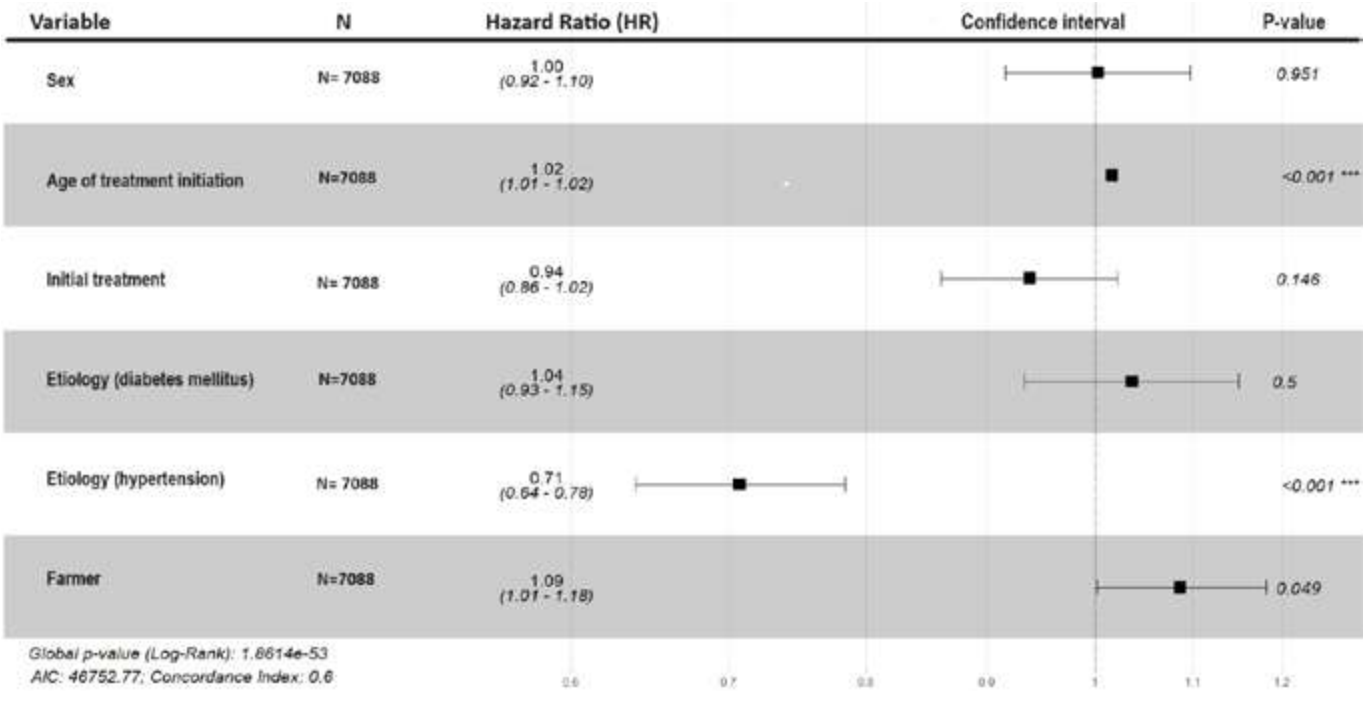

Figure 4. Cox multivariate model with Royston-Parmar random effects

some have found greater survival in patients undergoing hemodialysis, such as the Colombian cohort study mentioned above,[xiii] other studies have found no significant difference between treatment modalities,[xv,xvi] and others suggest that the differences may be related to a greater burden of comorbidities in one group or another.[xv,xvii] For this reason, some clinical guidelines recommend leaving the treatment modality to the patient's choice, according to their needs and clinical situation.[i,ii]

There were no significant differences in survival between sexes in this study; similar findings have been reported in research conducted in the United States and Europe. Even though men are at greater risk of kidney disease, there are no differences in prognosis after the onset of RRT.[xviii,xix] The causes of this phenomenon are not entirely clear, although some research has suggested that CKD increases cardiovascular risk in women, increasing their mortality.[xx]

Advanced age is an important risk factor that increases the probability of death in patients with RRT. A meta-analysis that included 12 studies comparing patients older than 65 years with those of younger age found that patients older than 65 years had a 2.80 times higher risk of death (CI 95 %: 2.45 - 3.09) and a p-value < 0.01.[xxi] In addition, a cohort in Brazil with 5081 hemodialysis patients found that the older the patient, the higher the risk of death.[xxii]

Research on the subject has linked increased mortality in this age group to a greater burden of comorbidities, physical and cognitive disability, and the decreased functional capacity of adulthood, which makes patients less resistant to the loss of amino acids and proteins that occurs during peritoneal dialysis, as well as to the insulin resistance, chronic inflammation, vascular calcification, and loss of musculoskeletal tissue that occur as a consequence of CKD.[xxiii-xxv]

According to results from a study conducted in the country in 2014, hypertension and diabetes *mellitus* were the main identifiable causes of CKD, and it was not possible to identify the etiology in 50 % of cases.[xxvi]

The Kaplan Meier analysis determined that patients with diabetic etiology had a lower survival rate; however, it was not statistically significant in the multivariate analysis, unlike other studies that have determined that CKD with diabetic etiology has a worse prognosis and a higher probability of death.[xvi,xxii] Hypertensive etiology resulted in a higher probability of survival in this study.

This result seems to indicate that there is another etiology that, in addition to causing an important proportion of CKD cases, could affect the prognosis of the patients; a possible explanation would be Mesoamerican nephropathy, a disease characterized by renal and tubulointerstitial damage that mainly affects male patients and farmers.[iv,xxvii,xxviii] This would be congruent with the fact that during this investigation an important percentage of patients were farmers,

and that a significant association was found between being a farmer and a higher risk of mortality, there is previous evidence that indicates that this can be considered as an important risk factor in mortality related to CKD.[xviii,xix]

Most of the patients undergoing dialysis in this study were men. This finding is consistent with other studies, such as those done in the country[xxvi,xxix] in which men have been shown to have a higher prevalence of CKD.[xxx]

Arterial hypertension has been identified as a common comorbidity in other studies of people with CKD.[xxxi] A study published in 2016 that analyzed ten years of data from patients with CKD in the Bajo Lempa area, El Salvador, found that 29.7 % of patients had arterial hypertension, a lower proportion than that found in this study.[xxix] It was expected due to the pathophysiology of chronic disease, as the kidney is one of the primary organs involved in blood pressure regulation.[i]

In 2014, the Ministry of Health of El Salvador provided care to 38.6 % of patients in RRT, resulting in a total of 1445 patients. During that time, this number has increased almost three times, becoming even higher than the SRR prevalence rate reported in that year. The Ministry of Health's rate of patients seen per million individuals is slightly lower than the prevalence of 677 patients per million individuals reported by the Central American and Caribbean Association of Nephrology and Hypertension in 2018. These findings indicate a significant increase in demand for renal care.[vii,xxvi]

In El Salvador, PD is the main method of renal replacement, unlike the world trend, where it is estimated that more than 90 % of patients are treated with HD. This data is because PD is considered the first choice in the guidelines for the care of renal patients in force in the country.[xxxii] In Guatemala and Costa Rica PD is also the main treatment modality, while in the rest of the countries of the Central American and Caribbean region HD predominates.[vii]

In a study that included databases from 20 Latin American countries and 49 European countries, the main causes of death identified were cardiovascular diseases, followed by infectious diseases and deaths of unknown causes.[xxxiii] In Colombia, a retrospective cohort of 9798 patients over 18 years of age in RRT was carried out, where the two leading causes of death were the same.[xxxiv] However, a higher percentage of deaths of unknown causes was observed.

The database used for the study was pre-built and contained only information from the Ministry of Health. It is crucial to remember that if patients receiving treatment at other facilities were included, the true prevalence of dialysis patients may be higher. Furthermore, the lack of comprehensive data or the absence of systematic data collection prevented the inclusion of certain variables in the evaluation.

It is necessary to take the findings related to the etiology of CKD with caution because this was not identified in more than 50 % of the patients. Therefore, a more comprehensive registry of the causes of CKD is necessary to yield more conclusive outcomes.

There may be other variables not collected in the database that could influence patient survival, such as nutritional status, socioeconomic status, and glomerular filtration rate at the start of renal treatment. These additional factors could have a significant impact on the results and it is important to consider them in future research to obtain a more complete understanding of the determinants of survival in patients with CKD on RRT.

Conclusions

Only half of the patients who start dialysis in El Salvador survive five years after starting treatment. Age at initiation of treatment and being a farmer are significant factors associated with a higher risk of mortality five years after initiation of renal replacement therapy, while the etiology of arterial hypertension was associated with a higher survival compared to other causes of CKD.

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References

i. Bargman JM, Skorecki K. Chronic Kidney Disease. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson JL, editors. Harrison's Principles of Internal Medicine. 21st ed. New York, NY: McGraw-Hill Education; 2022.

ii. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic

kidney disease. Lancet Lond. Engl. 2021;398(10302):786-802. DOI: 10.1016/s0140-6736(21)00519-5

iii. KDIGO CKD Evaluation and Management - KDIGO. Date of citation: 5 de noviembre de 2023. Available at: https://kdigo.org/guidelines/ckd-evaluation-and-management/

iv. Correa-Rotter R, García-Trabanino R. Nefropatía mesoamericana: una nueva enfermedad renal crónica de alta relevancia regional. Acta Médica. 2018;16:16-22. Available at: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=82350

v. Ingelheim B. 9 de cada 10 personas que padecen enfermedad renal crónica no saben que tienen esta enfermedad | Boehringer Ingelheim. Boehringer Ingelh. Spain. 2023. Date of citation: 5 de noviembre de 2023. Available at: https://www.boehringer-ingelheim.com/es/prensa/notas-de-prensa/9-de-cada-10-personas-que-padecen-enfermedad-renal-cronica-no-saben-que-tienen

vi. Instituto Nacional de Salud. Encuesta Nacional de Salud 2021. El Salvador: Instituto Nacional de Salud; 2021. Available at: https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1372915

vii. García-Trabanino R, Arroyo L, Courville K, Chica CI, Bohorques R, Rodríguez G, *et al.* La diálisis peritoneal en Centroamérica y el Caribe: estado actual, necesidades y propuestas. Rev. Nefrol. Latinoam. 2018;15(2):52-64. DOI: 10.24875/NEFRO.18000041

viii. Thurlow JS, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, Nee R. Global Epidemiology of End-Stage Kidney Disease and Disparities in Kidney Replacement Therapy. Am. J. Nephrol. 2021;52(2):98-107. DOI: 10.1159/000514550

ix. Ministerio de Salud de El Salvador. Lineamientos técnicos para el Registro Nacional de Diálisis y Trasplante Renal. San Salvador, El Salvador; 2022. Available at: https://asp.salud.gob.sv/regulacion/pdf/lineamientos/lineamientostecnicosparaelregsitronacionaldedialisisytrasplanterenal-Acuerdo-440-v1.pdf

x. Oficina Nacional de Estadística y Censos. Población y estadísticas demográficas Date of citation: 5 de noviembre de 2023. Available at: https://onec.bcr.gob.sv/poblacion-y-estadisticas-demograficas/

xi. Royston P. Flexible Parametric Alternatives to the Cox Model, and more. Stata J. Promot. Commun. Stat. Stata. 2001;1(1):1-28. DOI: 10.1177/1536867X0100100101

xii. Ng R, Kornas K, Sutradhar R, Wodchis WP, Rosella LC. The current application of the Royston-Parmar model for prognostic modeling in health research: a scoping review. Diagn. Progn. Res. 2018;2(1):4. DOI: 10.1186/s41512-018-0026-5

xiii. Herrera L, Gil F, Sanabria M. Hemodialysis vs Peritoneal Dialysis: Comparison of Net Survival in Incident Patients on Chronic Dialysis in Colombia. Can. J. Kidney Health Dis. 2021;8:2054358120987055. DOI: 10.1177/2054358120987055

xiv. Gunawan A, Sakti PT. Five-Year Survival Rate of Patients with End-Stage Renal Disease on Continuous Ambulatory Peritoneal Dialysis (CAPD) at Malang CAPD Center, Indonesia. Acta Medica Indones. 2023;55(1):4-9. Available at: https://www.actamedindones.org/index.php/ijim/article/view/2117/pdf

xv. Vicentini CA de A, Ponce D. Comparative analysis of patients' survival on hemodialysis vs. peritoneal dialysis and identification of factors associated with death. Braz. J. Nephrol. 2022 45(1):8-16. DOI: 10.1590/2175-8239-JBN-2021-0242en

xvi. Guzman-Ventura W, Caballero-Alvarado J. Sobrevida de pacientes en hemodiálisis crónica versus diálisis peritoneal crónica. Rev. Peru. Med. Exp. Salud Pública. 2022;39:161-169. DOI: 10.17843/rpmesp.2022.392.10853

xvii. de Arriba G, Gutiérrez Avila G, Torres Guinea M, Moreno Alia I, Herruzo JA, Rincón Ruiz B, *et al.* La mortalidad de los pacientes en hemodiálisis está asociada con su situación clínica al comienzo del tratamiento. Nefrología. 2021;41(4):461-466. DOI: 10.1016/j.nefro.2020.11.006

xviii. Hecking M, Bieber BA, Ethier J, Kautzky-Willer A, Sunder-Plassmann G, Säemann MD, *et al.* Sex-Specific Differences in Hemodialysis Prevalence and Practices and the Male-to-Female Mortality Rate: The Dialysis Outcomes and Practice Patterns Study (DOPPS). PLoS Med. 2014;11(10):e1001750. DOI: 10.1371/journal.pmed.1001750

xix. Carrero JJ, de Jager DJ, Verduijn M, Ravani P, De Meester J, Heaf JG, *et al.* Cardiovascular and Noncardiovascular Mortality among Men and Women Starting Dialysis. Clin. J. Am. Soc. Nephrol. 2011;6(7):1722. DOI: 10.2215/CJN.11331210

xx. Villar E, Remontet L, Labeeuw M, Ecochard R, Registry on behalf of the AR des N de RCA-A and the FRE and IN (REIN). Effect of Age, Gender, and Diabetes on Excess Death in End-Stage Renal Failure. J. Am. Soc. Nephrol. 2007;18(7):2125. DOI: 10.1681/ASN.2006091048

xxi. Jiang C, Zheng Q. Outcomes of peritoneal dialysis in elderly vs non-elderly patients: A systemic review and meta-analysis.

PLOS ONE. 2022;17(2):e0263534. DOI: 10.1371/journal.pone.0263534

xxii. Barra ABL, Roque-da-Silva AP, Canziani MEF, Lugon JR, Strogoff-de-Matos JP. Characteristics and predictors of mortality on haemodialysis in Brazil: a cohort of 5,081 incident patients. BMC Nephrol. 2022:77-77. DOI: 10.1186/s12882-022-02705-x

xxiii. Brown EA, Finkelstein FO, Iyasere OU, Kliger AS. Peritoneal or hemodialysis for the frail elderly patient, the choice of 2 evils? Kidney Int. 2017;91(2):294-303. DOI: 10.1016/j.kint.2016.08.026

xxiv. Roshanravan B, Khatri M, Robinson-Cohen C, Levin G, Patel KV, Boer IH de, *et al.* A Prospective Study of Frailty in Nephrology-Referred Patients With CKD. Am. J. Kidney Dis. 2012;60(6):912-921. DOI: 10.1053/j.ajkd.2012.05.017

xxv. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of Frailty among Dialysis Patients. J. Am. Soc. Nephrol. 2007;18(11):2960. DOI: 10.1681/ASN.2007020221

xxvi. García-Trabanino R, Trujillo Z, Colorado AV, Magaña Mercado S, Henríquez CA. Prevalencia de pacientes con tratamiento sustitutivo renal en El Salvador en 2014. Nefrología. 2016;36(6):631-636. DOI: 10.1016/j.nefro.2016.01.015

xxvii. Marín Trigueros D, Guadamuz Hernandez S, Suarez Brenes G, Salas Garita F, Marín Trigueros D, Guadamuz Hernandez S, *et al.* Nefropatía Mesoamericana. Med. Leg. Costa Rica. 2020;37(1):121-129. Available at: https://www.scielo.sa.cr/scielo.php?script=sci_arttext&pid=S1409-00152020000100121

xxviii. Wijkström J, Leiva R, Elinder C-G, Leiva S, Trujillo Z, Trujillo L, *et al.* Clinical and Pathological Characterization of Mesoamerican Nephropathy: A New Kidney Disease in Central America. Am. J. Kidney Dis. 2013;62(5):908-918. DOI: 10.1053/j.ajkd.2013.05.019

xxix. García-Trabanino R, Hernández C, Rosa A, Domínguez Alonso J. Incidencia, mortalidad y prevalencia de enfermedad renal crónica terminal en la región del Bajo Lempa, El Salvador: 10 años de registro comunitario. Nefrología. 2016;36(5):517-522. DOI: 10.1016/j.nefro.2016.03.018

xxx. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FDR. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS ONE. 2016;11(7):e0158765. DOI: 10.1371/journal.pone.0158765

xxxi. Murton M, Goff-Leggett D, Bobrowska A, Garcia Sanchez JJ, James G, Wittbrodt E, *et al.* Burden of Chronic Kidney Disease by KDIGO Categories of Glomerular Filtration Rate and Albuminuria: A Systematic Review. Adv. Ther. 2021;38(1):180-200. DOI: 10.1007/s12325-020-01568-8

xxxii. Ministerio de Salud de El Salvador. Lineamientos técnicos para la atención de pacientes con enfermedad renal crónica en terapia dialítica. San Salvador, El Salvador; 2018. Available at: https://www.transparencia.gob.sv/institutions/minsal/documents/276070/download

xxxiii. Luxardo R, Kramer A, González-Bedat MC, Massy ZA, Jager KJ, Rosa-Diez G, *et al.* The epidemiology of renal replacement therapy in two different parts of the world: the Latin American Dialysis and Transplant Registry versus the European Renal Association-European Dialysis and Transplant Association Registry. Rev. Panam. Salud Pública. 2018;42:e87. DOI: 10.26633/rpsp.2018.87

xxxiv. Sanabria M, Moreno J, Vesga J, Astudillo K, Bunch A, López P, *et al.* Mortalidad observada versus esperada en una red de unidades de diálisis en Colombia. Acta Medica Colomb. 2017;42(2):106-111. DOI: 10.36104/amc.2017.790

Original article

Somatoform Disorders and Personality Traits in Hospitalized Patients with Chronic Back Pain in El Salvador

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Abstract

Introduction. The somatoform symptoms disorder is characterized by multiple psychical symptoms that can't be attributed to another physical or mental health diagnosis or drug abuse, having personality disorders as the most common comorbidity. **Objective.** To determine the frequency of somatoform disorders, it's most important characteristics and different personality traits among patients with chronic back pain. **Methodology.** Cross-sectional descriptive study carried out with patients admitted to the neurosurgery department of the General Hospital of the Salvadoran Social Security Institute. Data collection was carried out using the Screening for Somatoform Symptoms 2 scale and the International Personality Disorder Examination scale. The qualitative variables were analyzed through absolute frequencies. The quantitative variables were analyzed through measures of central tendency and dispersion. The statistical analyzes were carried out using the Statistical Package for the Social Sciences version 26. **Results.** The study included 60 patients, 40 of them women, 31 between 41 and 60 years old. Twenty-eight patients presented eight or more symptoms, excluding low back pain. Forty-five patients reported symptoms for more than one year. Fifty-three patients presented somatoform disorder. The most frequent personality disorders were obsessive-compulsive (31), borderline (21) and paranoid (21). **Conclusion.** Patients with chronic lower back pain who require hospital admission have a high frequency of somatoform disorders, with the main symptom being pain in the legs or arms; furthermore, these patients are characterized by mostly presenting obsessive-compulsive personality traits.

Keywords

Somatoform Disorders, Personality Disorders, Low Back Pain, Borderline Personality Disorder.

Resumen

Introducción. El trastorno somatomorfo se caracteriza por la presentación de múltiples síntomas físicos que no pueden ser atribuidos a otra enfermedad física, mental o al uso de sustancias, teniendo como comorbilidad más prevalente a los trastornos de personalidad. **Objetivo.** Determinar la frecuencia de trastorno somatomorfo, sus características principales y diferentes rasgos de personalidad entre pacientes con lumbalgia crónica. **Metodología.** Estudio descriptivo transversal realizado con pacientes ingresados en el servicio de neurocirugía del Hospital General del Instituto Salvadoreño del Seguro Social. La recolección de datos se realizó a través de la escala *Screening for Somatoform Symptoms 2* y la escala *International Personality Disorder Examination*. Las variables cualitativas fueron analizadas a través de frecuencias absolutas. Las variables cuantitativas fueron analizadas a través de medidas de tendencia central y de dispersión. Los análisis estadísticos fueron realizados en el programa *Statistical Package for the Social Sicience*, versión 26. **Resultados.** Se incluyeron 60 pacientes, 40 de ellos mujeres, 31 entre los 41 y 60 años. Veintiocho pacientes presentaron ocho o más síntomas, excluyéndose dolor lumbar. Cuarenta y cinco pacientes reportaron sintomatología por más de un año. Cincuenta y tres pacientes presentaron trastorno somatomorfo. Los trastornos de personalidad más frecuentes fueron obsesivo-compulsivos (31), límites (21) y paranoides (21). **Conclusión.** Los pacientes con dolor lumbar crónico que requieren ingreso hospitalario presentan una alta frecuencia de trastornos somatomorfos, con dolor en piernas o brazos como síntoma principal; además, estos pacientes se caracterizan por presentar en su mayoría rasgos de personalidad obsesivo-compulsivos.

Palabras clave

Trastornos Somatomorfos, Trastornos de la Personalidad, Dolor de la Región Lumbar, Trastorno de Personalidad Limítrofe.

OPEN ACCESS

Trastornos somatomorfos y rasgos de personalidad en pacientes hospitalizados por lumbalgia crónica en El Salvador

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Introduction

Somatoform disorder is characterized by the persistence of physical symptoms that suggest the presence of a medical illness but are not fully explained by this condition or by the direct effects of another substance or mental illness.[i] It may begin at any stage of life and is seen more frequently in women, with an estimated female-to-male ratio of 10:1. This condition is accompanied by diminished quality of life, inability to perform basic functions, and an increase in associated expenses, primarily for unnecessary medical tests or treatments.[ii]

The comorbidity of somatoform pain disorders is up to six times greater in the population with pain disorders than in the general population, describing a significant relationship with personality disorders, defined as a set of characteristics that deviate from the pattern of normality and that cause dysfunction in one or more specific areas of life.[iii,iv] Up to 50.6 % of patients with somatoform disorder are diagnosed with personality disorders, with this comorbidity even being considered as the most severe of the somatoform disorders.5 Similarly, personality disorders are associated with chronic pain[vi,vii] with a prevalence between 31 and 81 %; when studying low back pain, prevalence is around 60 %, being higher than those observed in acute pain.[viii]

Among disorders most commonly associated with somatoform disorder, histrionic, narcissistic, paranoid, borderline, antisocial, and avoidant personality disorders have been described.[viii] On average, between 20 and 25 % of patients seen in primary care services develop a chronic illness due to somatic symptoms,[i] and only 45 % of them receive an accurate diagnosis and are referred to a specialist, generating a high rate of inter-consultations and a higher frequency of specialized consultations.[ix-xi]

In Europe, the prevalence of somatoform disorders in the general population is estimated to be between 12.9 % and 18.4 % depending on the country and area, and in the USA, between 5 % and 7 %,[xii] making it one of the most common categories of patient concern in the primary healthcare setting.[xiii] In Europe, the ratio of patients with medically unexplained physical symptoms to hospitalization costs is higher in neurology services (1.9 %) than in other services, with only 0.3 % in psychiatry services.[xiv]

At national level, there are still no published studies that determine the prevalence of somatoform disorders in the Salvadoran population. The number of patients with chronic low back pain that are affected by any of the different personality disorders or by a somatoform disorder is unknown. The objective of this study is to determine the frequency of somatoform disorder, its predominant characteristics, and different personality traits among patients with chronic low back pain.

Methodology

A cross-sectional descriptive study conducted between August and October 2021, with patients admitted to the neurosurgery service of the General Hospital of the Salvadoran Social Security Institute, which is a third-level hospital located in the capital of El Salvador; it serves contributors, pensioners, and beneficiaries from all over the country, it has three specialties and 18 subspecialties, has a capacity of 428 beds, and employs a staff of 2180 employees.

The sampling for the selection of the study population was non-probabilistic by convenience since all the patients admitted during the three-month window were included, making a total of 60 patients. To participate, patients had to meet the following criteria: to be 18 years old or older, male or female, and with a diagnosis of chronic low back pain. Patients who did not wish to participate or sign the informed consent form, patients whose disease was the result of a traumatic, infectious, metastatic, or inflammatory spinal lesion, patients whose lesion was the result of non-disc degenerative spinal disease, and patients who could not respond to the screening instruments used in the study because they were in a state of altered consciousness or intellectual deficit, either by filling out or verbally assisted, were excluded.

Data collection used the Screening for Somatoform Symptoms 2 (SOMS-2)[xv] scale and the International Personality Disorder Examination (IPDE)[xvi] scale to determine factors compatible with somatoform disorders and to determine personality traits. Both scales were placed in the same Word document to facilitate data collection. Originally, these scales were intended to be self-administered; however, in some cases, they were administered by the investigators due to the condition of the patients.

For data collection, interviews were conducted from Monday to Friday during the study period. A maximum of two interviews per day were conducted by the researchers and medical students specializing in psychiatry and mental health who were previously trained to apply the instrument. Each interview lasted an average of 45 minutes.

The SOMS-2 scale includes all symptoms of somatoform disorder. This scale consists of 53 items with dichotomous responses; the patient should respond positively only to those items present in the last two years. Items 1 to 35 assess the possible symptoms of somatization disorder; items 36 to 42, the symptoms that may occur during an anxiety crisis, low mood, or in undifferentiated somatoform disorder, and items 43 to 53 assess the inclusion and exclusion criteria of the different subgroups of somatoform disorders. At the end of the scale, 16 additional items are included (items 53 to 68) that inquire about the number of visits to the physician in the last year, the influence of the symptoms on the patient's quality of life, or whether the patient takes medication for his or her complaints.

The concept of somatoform disorder, contemplated in the Diagnostic and Statistical Manual of Mental Disorders version 4 (DSM-4), was used, despite a new conceptualization in the most recent version DSM-5, because the SOMS-2 scale was standardized with DSM-4 criteria and has not been revised or updated for its most recent version.

The symptom of back pain was excluded from the scale since it was taken as a selection criterion and not as a symptom of somatoform disorder. For the diagnosis of somatoform disorder, the cut-off point was taken as the report of four symptoms since this is a factor that increases sensitivity and specificity concerning seven or more symptoms; however, for the report of severity of somatoform disorder, the cut-off point was taken as having presented at least four symptoms, placing patients who reported less than four symptoms in the "not diagnosed" category.

The IPDE scale is an instrument consisting of 77 questions with two possible answers, true or false, which can be corrected using the template supplied with the scale, and allows one to visualize how many answers do not coincide with those expected and presented by the individual for each personality trait. The result is only categorical, as it does not intend to calculate dimensional scores. It is a screening instrument and, therefore, should not be used as a formal psychiatric diagnosis. This scale uses as a cut-off point for each trait, four or more unexpected responses, and assesses paranoid, schizotypal, schizoid, sociopathic, histrionic, borderline, narcissistic, obsessive-compulsive, avoidant, and dependent personality traits.

To quantify the pain level experienced by each patient, a Likert scale for pain was applied consisting of five negative points (0 - 4), one neutral (5), and five positive points (6 - 10), where the patient had to indicate his or her level of pain according to intensity, through an ordered and unidimensional scale.

When found with positive results, they were classified as predominant personality traits; given that the tool is not for diagnosis, a personality disorder diagnosis was not performed.

For the statistical analysis, each person was initially classified by personality trait, taking four or more unexpected responses as a cut-off point. To do this classification, a digital tool was created with C++ programming language, in which the data obtained from the questionnaire were entered, obtaining the classification for each patient. From this classification, 10 variables were created (one for each trait), with the results.

Subsequently, a matrix was created in the statistical analysis program Statistical Package for the Social Sciences version 26, where the data were digitized for analysis. Qualitative variables were analyzed by means of absolute frequencies and quantitative variables were analyzed through measures of central tendency and dispersion. The data were presented in tables and figures, as appropriate to the nature of the results.

Prior to data collection, permission was granted by the hospital management officials and each patient was invited to participate, information of the objective of the study was provided, and expressly clarified that participation was completely voluntary. Each participant read and signed the informed consent form. The data obtained were for the exclusive use of the researchers. The database was anonymized and safeguarded by the researchers. The research protocol was evaluated and approved by the Health Research Ethics Committee of the General Hospital of the Salvadoran Social Security Institute through approval letter 537P218MO21.

Results

Of the total number of patients (60), 40 were women. The average age is 46 years, with a minimum of 18 and a maximum of 78. The age group with the highest number of patients (17 patients) is 41 to 50 years, followed by 51 to 60 years with 14 patients. Figure 1 shows the age distribution according to the sex of the patient.

Table 1 details the symptoms of somatoform disorder distributed by sex. Women reported a higher number of symptoms than men. The most commonly reported symptoms were pain in the legs or arms (39), headaches (36), nausea (34) and dry

mouth (33). In the distribution by sex, the symptoms (excluding back pain) most frequently reported by men were pain in legs or arms (14), nausea (13), and joint pain (13), while by women, they were also pain in legs or arms (25), in addition to headaches (24) and stomach pain (22).

Table 2 shows the symptoms of anxiety crises distributed by sex. It was found that, for both men and women, the most frequently experienced symptoms were unpleasant sensations or numbness or tingling (35), loss of touch or sensation of pain (19), and double vision (15).

Table 3 shows the symptoms excluding somatoform disorder distributed by sex. It is evident that, for the common symptoms between sexes, 12 patients reported amnesia, while only three reported loss of consciousness, and one presented convulsive episodes (described in the instrument as "seizures"). Among menstrual symptoms, the most common were painful menstruation (12 women) and irregular menstruation (10 women). Only five men reported erectile or ejaculatory dysfunction.

Screening for Somatoform Symptoms 2

Within the classification by severity of the disorder, seven patients did not meet diagnostic criteria for the somatoform disorder, nine had mild disorder, 11 had moderate severity, and 33 described severity of the disorder.

According to the SOMS-2 scale, 28 patients had eight or more symptoms, five presented seven symptoms, 14 between four and six symptoms, and three patients had less than four symptoms.

Of the 28 patients with eight or more symptoms, 20 are female; of the patients with seven symptoms, eight are male; of the patients with between four and six symptoms, 11 are female; and of the patients with fewer than four symptoms, two are female and one is male.

The frequency of visits that patients made to the doctor due to their symptoms, data showed that 15 patients made one to two visits, 20 patients made between three and six visits, 15 patients made between six and 12 visits, and 10 patients made more than 12 visits.

According to the time of symptom evolution for somatoform disorder, the most frequent was greater than two years, in 33 patients; followed by the period between one and two years of symptom development which was recorded in 12 patients; nine patients reported symptoms between six months and one year, and finally, six patients reported a symptomatic evolution time of less than six months.

The diagnosis of somatoform disorder had previously been made in 12 patients, who reported four to six symptoms; 14 patients, seven symptoms, and 27 reported eight or more symptoms, while four patients who reported four or more symptoms did not meet enough criteria for the diagnosis of somatoform disorder. Three patients reported

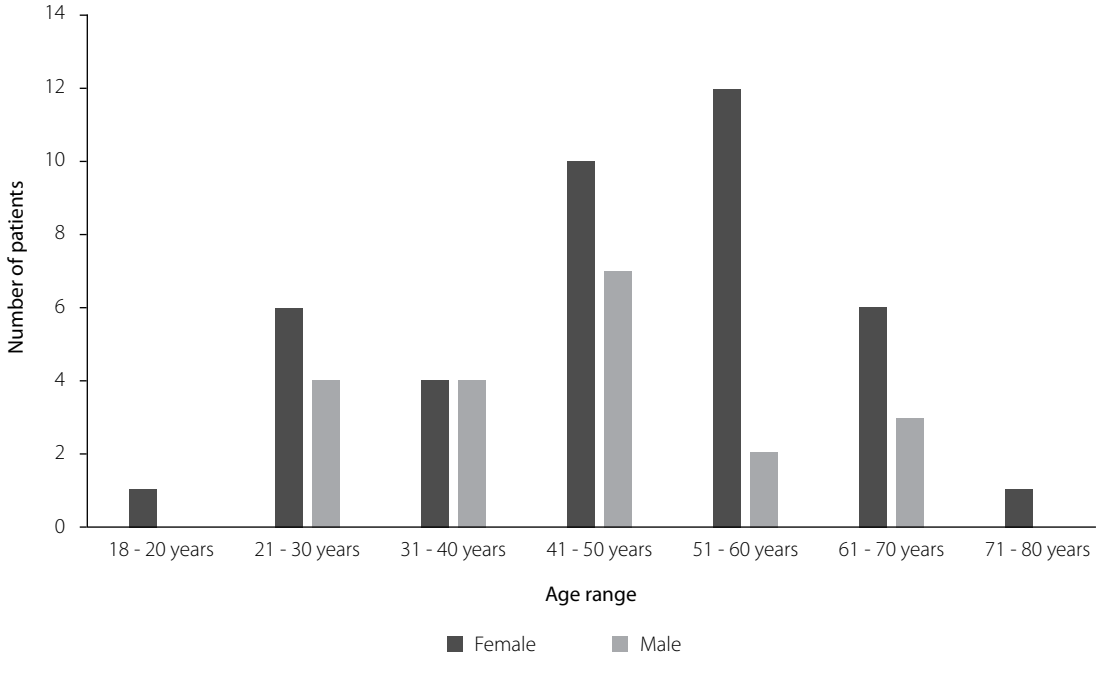

Figure 1. Distribution by age according to sex of patients with chronic low back pain admitted to the neurosurgery service of the General Hospital of the Salvadoran Social Security Institute. August-October 2021

Table 1. Somatoform disorder symptoms distributed by sex of patients with chronic low back pain admitted to the neurosurgery service of the General Hospital of the Salvadoran Social Security Institute, August-October 2021.

Somatoform disorder symptoms	Men	Women	Total
Headache	12	24	36
Stomach pain	6	22	28
Joing pain	13	17	30
Pain in legs or arms	14	25	39
Chest pain	7	11	18
Pain in the anus	4	4	8
Pain during sexual intercourse (coitus)	4	10	14
Pain during urination	4	9	13
Nausea	13	21	34
Swelling or bloating	10	20	30
Discomfort around the heart area	6	13	19
Vomiting	7	11	18
Gastric reflux	9	21	30
Hiccups or burning sensation in the chest or stomach	6	9	15
Food intolerance	2	9	11
Loss of appetite	7	13	20
Bad taste in the mouth, or pasty tongue	12	14	26
Dry mouth	12	21	33
Frequent diarrhea	2	9	11
Fluid discharge from the anus	1	1	2
Frequent urination	5	8	13
Frequent bowel movements	2	7	9
Severe palpitations	10	19	29
Upset stomach or feeling sick to the stomach	10	17	27
Sweating (hot or cold)	7	17	24
Flushing or redness	4	10	14
Shortness of breath (without prior exertion)	7	9	16
Painful breathing or hyperventilation	3	6	9
Excessive tiredness or mild exertion	5	15	20
Skin stains or discoloration	5	7	12
Sexual indifference (loss of libido)	4	12	16
Unpleasant sensations in or around the genitals	4	7	11
Difficulty with coordination or balance	9	13	22
Paralysis or localized weakness	7	11	18

Table 2. Anxiety crisis symptoms distributed by sex of patients with chronic low back pain admitted to the neurosurgery service of the General Hospital of the Salvadoran Social Security Institute, August-October 2021.

Anxiety crisis symptoms	Men	Women	Total
Difficulty swallowing	5	8	13
Aphonia (loss of voice)	4	9	13
Urinary retention	4	5	9
Hallucinations	2	1	3
Loss of touch or sensation of pain	9	10	19
Unpleasant sensation or numbness or tingling	12	23	35
Double vision	5	10	15

four or fewer symptoms, all of whom did not meet the diagnosis of somatoform disorder.

No patient reported mild pain; however, 12 patients had moderate pain, 14 had severe pain, 19 had very severe pain, and 15 patients reported the worst pain imaginable.

The International Personality Disorder Examination

The personality traits more prevalent in the study sample were obsessive-compulsive (31 patients), borderline (21 patients), paranoid (21 patients), avoidant (19 patients) and histrionic (17 patients). It was observed that, of the total number of patients with obsessive-compulsive traits, 20 matched with severe severity of somatoform disorder, 19 with borderline traits, 14 with paranoid traits, 11 with avoidant traits, and 10 with histrionic traits reported characteristics of severe severity of somatoform disorder.

Table 4 shows the number of patients according to pain intensity and personality traits. Ten patients with obsessive-compulsive personality traits presented the worst pain imaginable, and eight paranoid patients also exhibited the worst pain imaginable.

Discussion

The study aimed to establish the number of patients treated for chronic low back pain who suffer from somatoform disorder in the neurosurgery service of the ISSS General Hospital over a period of three months. In addition, the different personality traits that characterize them were also identified.

Table 3. Exclusionary symptoms distributed by sex of patients with chronic low back pain admitted to the neurosurgery service of the General Hospital of the Salvadoran Social Security Institute, August-October 2021.

Excluding symptoms	Men	Women	Total
Blindness	3	4	7
Deafness	3	2	5
Seizures	1	0	1
Amnesia (memory loss)	3	9	12
Loss of consciousness	1	2	3
Painful menstruation	Not applicable	12	12
Irregular menstruation	Not applicable	10	10
Excessive menstrual bleeding	Not applicable	7	7
Continued vomiting during pregnancy	Not applicable	1	1
Unusual or heavy vaginal discharge	Not applicable	1	1
Erectile or ejaculatory dysfunction	5	Not applicable	5

Table 4. Types of personality traits distributed according to the Likert scale score for pain in patients admitted to the neurosurgery service of the General Hospital of the Salvadoran Social Security Institute, August-October 2021

Personality traits	Likert scale score for pain				Total
	Moderate pain	Severe pain	Very severe pain	Worst pain imaginable	
Paranoid	3	3	7	8	21
Schizoid	5	4	2	0	11
Schizotype	3	0	0	1	4
Histrionic	4	3	8	2	17
Antisocial	3	1	0	0	4
Narcissistic	2	2	3	0	7
Borderline	0	4	8	9	21
Obsessive compulsive	4	8	9	10	31
Dependent	1	1	2	3	7
Avoidant	0	6	4	9	19

No patient reported Likert scale scores compatible with the "no pain" and "mild pain" categories, therefore they are not included in the table.

Also it was found that most patients with chronic low back pain presented somatoform disorders at different levels of severity. Similarly, half of them presented obsessive personality traits, while a smaller group presented borderline personality traits or paranoid traits. However, there is no study currently available to compare these results with.

The majority of patients were women and identifying a wide range concerning age distribution, it was found that a higher number of patients were between 41 and 60 years old. These results are comparable with the research carried out by Meucci *et al.*, through a systematic review, which reported up to a 50 % higher prevalence of chronic low back pain in women than in men and a higher prevalence in the age range of 20 to 59 years.[xvii] Similarly, Thomas *et al.* reported that, of a total of 162 participants in the study on chronic low back pain, 57 % were women.[xviii] As an explanation for this distribution by sex, Pak has shown that being a woman, together with other features, is a significant risk factor for chronic pain.[xix]

Similarly, Thompson *et al.* reported that women consult significantly more than men for both physical and mental health causes, concluding that women are more active in both prevention and treatment than men.[xx] Meints *et al.* similarly observed sex differences in more dynamic models of experimental pain, such as temporal summation, more pronounced in women, and diffuse noxious inhibitory controls (DNIC), a form of endogenous pain modulation in which the perception of a painful stimulus is attenuated by a pain stimulus applied at a remote site. Several studies indicate that the DNIC response is more pronounced in men than in women, suggesting better functioning of the endogenous pain inhibitory system among men.[xxi]

Moreover, the majority of patients exhibited personality traits consistent with the somatoform disorder diagnosis, regardless of severity. In addition, when pain intensity was quantified by scoring on a Likert pain scale, it reported that the most frequently described pain intensity by patients was severe pain.These findings are in agreement with Samuelly-Leichtag *et al.* and Henker *et al.*, who proposed that certain aspects of personality, such as catastrophizing, conditioned pain modulation, and gender, contribute to the increased perception of pain intensity in patients with chronic low back pain.[xxii,xxiii]

Regarding personality traits, among the patients in this study, obsessive-compulsive personality traits were found most frequently, followed by paranoid traits, borderline traits, avoidant traits, and histrionic traits. Poloni *et al.* report in their study of patients with somatoform disorder that this is associated with high prevalences of mental disorders, mainly anxiety and personality disorders.[xxiv] They also conclude that a personality disorder in patients with medically unexplained symptoms significantly increases the probability of also having a somatoform disorder.

In 2018, Herzog *et al.* identified that most patients with somatoform disorder reported between two and five medical visits for their symptoms, as well as a long evolution of symptoms, even up to 15 years before their diagnosis.[xiii] The results found in this study agree with the above, evidenced by the fact that one-third of the patients reported having consulted for their symptoms between three and six times, with a lower distribution among the other ranges. Also, it showed that approximately one-third of the patients have suffered from symptoms compatible with somatoform disorder for more than two years.

This study shows that more than half of the patients have at least one anxiety symptom; these results are higher than those obtained by Piontek *et al.*, who found 25 % of patients with anxious characteristics. It may be related to the fact that the study was conducted with hospitalized patients with acute pain.[xxv]

Poloni *et al.* propose that the total number of somatic symptoms reported by patients with somatoform disorder is a predictor of disability,[xxiv] even being considered one of the diseases that leads to the highest percentage of disability worldwide, as well as to increased hospital costs. These findings are consistent with this study, which showed that most patients reported seven or more symptoms of somatoform disorder, resulting in a high degree of physical and mental discomfort, as well as leading to significant disability.

The difficulty of the study was related to the quality of the information provided by the patients, given that it depended on the data they remembered at the time of filling out each scale, which could generate information bias, as well as selection bias, if the number of symptoms or characteristics reported as positive was higher or lower than the actual number.

Given the close relationship between mental pathology and spinal pathology, it would be of great benefit to implement general screening measures for mental health disorders in patients admitted with spinal pathology. Roon-Cassini *et al.* state that timely screening and treatment of post-

traumatic stress disorder and depression can improve institutional outcomes.[xxvi]

Similarly, it is crucial to implement an early psychological assessment evaluation and, if necessary, a psychiatric one in patients with low back pain with scales for depression, anxiety, and somatoform disorder such as those used in this study to be able to analyze patients with low back pain. It would enhance the detection of conditions that merit psychological or psychiatric management and improve the postoperative outcome of patients who undergo surgery.

Further research is recommended to study the somatoform syndrome combined with a specific assessment of personality, with the potential to perform tests with greater sensitivity and specificity, and adequate time for their evaluation and a larger population to identify the prevalence of somatoform and personality disorders, in addition to the factors that contribute to the increase of these health problems in the population.

Conclusions

Patients with chronic low back pain who require hospital admission present a high frequency of somatoform disorders, characterized mainly by leg or arm pain, headaches, and nausea; in addition, these patients present obsessive-compulsive, borderline, and paranoid personality traits. Timely detection of cases can help to take action according to their needs and well-being and to ensure that healthcare professionals are duly trained and equipped to respond.

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References

i. Kurlansik SL, Maffei MS. Somatic Symptom Disorder. Am Fam Physician. 2016;93(1). Available at: https://www.aafp.org/pubs/afp/issues/2016/0101/p49.pdf

ii. Löwe B, Levenson J, Depping M, Hüsing P, Kohlmann S, Lehmann M, *et al.* Somatic symptom disorder: a scoping review on the empirical evidence of a new diagnosis. Psychol Med. 2022 Mar;52(4):632-648. DOI: 10.1017/s0033291721004177

iii. Collinet A, Ntilikina Y, Romani A, Schuller S, Sauleau E-A, Charles YP. Psychopathological profile and sagittal alignment in low-back pain. Orthop Traumatol Surg Res. 2023;109(2):103474. DOI: 10.1016/j.otsr.2022.103474

iv. Bayon Perez C, Rodriguez-Cahil C, Cloninger C. Trastornos de la personalidad. In: Tratado de psiquiatria. Libreria editoriaL Marban; 2012. pp. 1390-1397.

v. Van Dijk SDM, Hanssen D, Naarding P, Lucassen P, Comijs H, Oude Voshaar R. Big Five personality traits and medically unexplained symptoms in later life. Eur. psychiatr. 2016;38:23-30. DOI: 10.1016/j.eurpsy.2016.05.002

vi. Taberner MMT, Perez Pareja J, Medinas Amorós MM, Palmer Pol A, Sesé Abad A. Aspectos psicológicos relevantes en el estudio y el tratamiento del dolor crónico. Clínica y Salud [online]. 2008;19(3):295-320. Available at: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1130-52742008000300003&lng=es

vii. Ackerman MD, Stevens MJ. Acute and chronic pain: Pain dimensions and psychological status. J. Clin. Psychol. 1989;45(2):223-228. Available at: https://doi.org/10.1002/1097-4679(198903)45:2<223::AID-JCLP2270450208>3.0.CO;2-Y

viii. Rodríguez Salgado B, Bolengevich Segal H. El paciente con dolor en la interconsulta psiquiátrica. In: Aspectos de interés en la Psiquiatria de enlace. 1ra ed. España: ERGON; 2010. pp. 285-302.

ix. Hüsing P, Löwe B, Piontek K, Shedden-Mora M. Somatoform disorder in primary care: T he influence of co-morbidity with anxiety and depression on health care utilization. Evaluation Clinical Practice. 2018;24(4):892-900. DOI: 10.1111/jep.12898

x. Barsky AJ, Orav EJ, Bates DW. Somatization Increases Medical Utilization and Costs Independent of Psychiatric and Medical Comorbidity. Arch Gen Psychiatry. 2005;62(8):903. DOI: 10.1001/archpsyc.62.8.903

xi. Grupp H, Kaufmann C, König H-H, Bleibler F, Wild B, Szecsenyi J, *et al.* Excess costs from functional somatic syndromes in Germany — An analysis using entropy balancing. Journal of Psychosomatic Research. 2017;97:52-57. DOI: 10.1016/j.jpsychores.2017.04.002

xii. Dunphy L, Penna M, EL-Kafsi J. Somatic symptom disorder: a diagnostic dilemma. BMJ Case Rep. 2019;12(11):e231550. DOI: 10.1136/bcr-2019-231550

xiii. Herzog A, Shedden-Mora MC, Jordan P, Löwe B. Duration of untreated illness in patients with somatoform disorders. Journal of Psychosomatic Research. 2018;107:1-6. DOI: 10.1016/j.jpsychores.2018.01.011

xiv. Henningsen P. Management of somatic symptom disorder. Dialogues in

Clinical Neuroscience. 2018;20(1):23-31. DOI: 10.31887/DCNS.2018.20.1/phenningsen

xv. Gili M, Bauzá N, Vives M, Moreno S, Magallón R, Roca M. Validación de la versión española de la escala Screening for Somatoform Symptoms-2 para la evaluación de síntomas somáticos en Atención Primaria. Atención Primaria. 2015;47(5):273-278. DOI: 10.1016/j.aprim.2014.07.001

xvi. World Health Organization. Assessment and diagnosis of personality disorders. The ICD-l0 international personality disorder examination (IPDE). 1997. 226 p.

xvii. Meucci RD, Fassa AG, Faria NMX. Prevalence of chronic low back pain: systematic review. Rev. Saúde Pública. 2015;49(1). DOI: 10.1590/S0034-8910.2015049005874

xviii. Thomas JS, Clark BC, Russ DW, France CR, Ploutz-Snyder R, Corcos DM, for the RELIEF Study Investigators. Effect of Spinal Manipulative and Mobilization Therapies in Young Adults With Mild to Moderate Chronic Low Back Pain: A Randomized Clinical Trial. JAMA Netw Open. 2020;3(8):e2012589. DOI: 10.1001/jamanetworkopen.2020.12589

xix. Pak DJ, Yong RJ, Kaye AD, Urman RD. Chronification of Pain: Mechanisms, Current Understanding, and Clinical Implications. Curr Pain Headache Rep. 2018;22(2):9. DOI: 10.1007/s11916-018-0666-8

xx. Thompson AE, Anisimowicz Y, Miedema B, Hogg W, Wodchis WP, Aubrey-Bassler K. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Fam Pract. 2016;17(1):38. DOI: 10.1186/s12875-016-0440-0

xxi. Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;87:168-182. DOI: 10.1016/j.pnpbp.2018.01.017

xxii. Samuelly-Leichtag G, Eisenberg E, Zohar Y, Andraous M, Eran A, Sviri GE, *et al.* Mechanism underlying painful radiculopathy in patients with lumbar disc herniation. European Journal of Pain. 2022;26(6):1269-1281. DOI: 10.1002/ejp.1947

xxiii. Henker J, Keller A, Reiss N, Siepmann M, Croy I, Weidner K. Early maladaptive schemas in patients with somatoform disorders and somatization. Clin Psychology and Psychoth. 2019;26(4):418-429. DOI: 10.1002/cpp.2363

xxiv. Poloni, Caselli, Ielmini, Mattia, De Leo, Di Sarno, *et al.* Hospitalized Patients with Medically Unexplained Physical Symptoms: Clinical Context and Economic Costs of Healthcare Management. Behavioral Sciences. 2019;9(7):80. DOI: 10.3390/bs9070080

xxv. Piontek K, Shedden-Mora MC, Gladigau M, Kuby A, Löwe B. Diagnosis of somatoform disorders in primary care: diagnostic agreement, predictors, and comaprisons with depression and anxiety. BMC Psychiatry. 2018;18(1):361. DOI: 10.1186/s12888-018-1940-3

xxvi. deRoon-Cassini TA, Hunt JC, Geier TJ, Warren AM, Ruggiero KJ, Scott K, *et al.* Screening and treating hospitalized trauma survivors for posttraumatic stress disorder and depression. J Trauma Acute Care Surg. 2019;87(2):440-450. DOI: 10.1097/TA.0000000000002370

Narrative review

Genetic Alterations Associated with Parkinson's and Alzheimer's Disease: Evolution and Response to Treatment

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Abstract
Parkinson's and Alzheimer's are the most frequent neurodegenerative diseases worldwide. They have a multifactorial etiology, including genetics, and are of interest in current scientific research. A narrative review was carried out with the aim of determining the genetic alterations associated with these pathologies, as well as their influence on their evolution and response to treatment. Original articles, literature reviews, systematic reviews, meta-analyses in English and Spanish, with publication date between January 1, 2018 and May 20, 2023, were consulted in databases such as PubMed and Medline. MeSH terms "Alzheimer Disease", "Parkinson Disease", "Drug Therapy" and "Mutation" were used. Hereditary risk for Parkinson's disease is usually polygenetic, however, there are genes related to monogenic mutations. Alterations in α-synuclein, glucocerebrosidase and leucine-rich kinase 2 genes have been identified that are related to an increased risk of developing Parkinson's disease, in addition to variations in the clinical picture and age of symptom onset. As for Alzheimer's disease, alterations in the genes of the amyloid precursor protein, presenilin 1 and 2 are related to the familial form of the disease; on the other hand, those of apolipoprotein E4 have been identified in the sporadic form, and are therefore considered to be the most important genetic risk factor for its development.

Keywords
Alzheimer Disease, Parkinson Disease, Drug Therapy, Mutation.

Resumen
La enfermedad de Parkinson y Alzheimer son las enfermedades neurodegenerativas más frecuentes a nivel mundial. Tienen etiología multifactorial, entre ellas, la genética; y son motivo de interés en la investigación científica actual. Se realizó una revisión narrativa con el objetivo de determinar las alteraciones genéticas asociadas a estas patologías, además su influencia en la evolución y respuesta al tratamiento de ellas. Se consultaron artículos originales, revisiones bibliográficas, sistemáticas, metaanálisis en inglés y español, con fecha de publicación entre el 1 enero de 2018 y el 20 de mayo de 2023, en bases como PubMed y Medline. Se utilizaron los términos MeSH «*Alzheimer Disease*», «*Parkinson Disease*», «*Drug Therapy*» y «*Mutations*». El riesgo hereditario para la enfermedad de Parkinson suele ser poligenético, sin embargo, existen genes relacionados con mutaciones monogénicas. Se identifican alteraciones en genes de α-sinucleína, glucocerebrosidasa y quinasa 2 rica en leucina que se relacionan con mayor riesgo de desarrollar Parkinson, además de variaciones en el cuadro clínico y edad de inicio de síntomas. En cuanto a la enfermedad de Alzheimer, las alteraciones en los genes de la proteína precursora amiloide, presenilina 1 y 2 se relacionan con la forma familiar de la enfermedad; por otra parte, las de apolipoproteína E4 se han identificado en la forma esporádica, por lo que se consideran como el factor de riesgo genético más importante para su desarrollo.

Palabras clave
Enfermedad de Alzheimer, Enfermedad de Parkinson, Tratamiento Farmacológico, Mutación.

OPEN ACCESS

Alteraciones genéticas asociadas a la enfermedad de Parkinson y Alzheimer: evolución y respuesta al tratamiento

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Introduction

Among the most frequent neurodegenerative diseases, Alzheimer's disease (AD) and Parkinson's disease (PD) stand out. AD is the most common cause of dementia, accounting for 60-80 % of cases worldwide. The World Health Organization reported a prevalence of 8.5 million cases of PD by 2019, doubling its prevalence in the last 25 years.[i,ii]

Neurogenetics is the field of science that studies the role of genes in the development and function of the nervous system.[iii] Interventions in neurogenetics are aimed at identifying the primary pathophysiological processes that begin years before symptoms appear.[iv]

Multiple variants have been described in the presentation of neurodegenerative diseases, depending on the age of onset, with early or late onset. The importance of characterizing these genotypic variants lies in the possibility of identifying the genetic predisposition of some patients, who may debut with atypical and aggressive symptoms, with a worse prognosis, in a more timely manner. This provides the opportunity to identify new biomarkers, therapeutic targets, and the development of risk scales for these pathologies.[v]

In this review, a literature search of original articles and literature reviews, systematic, meta-analysis in English and Spanish, in PubMed, Medline and SciELO databases, using the MeSH terms "Alzheimer disease", "Parkinson disease", "drug therapy", "Genetic mutations", published mainly between January 1, 2018 and May 20, 2023, while also including some articles from previous years that were considered relevant to the basis of this review, was performed. Therefore, this literature review aims to determine the genetic alterations associated with Parkinson's and Alzheimer's diseases; and their influence on the evolution and response to treatment of these pathologies.

Discussion

Genetic alterations related to Parkinson's disease

It is estimated that between 3 and 5 % of PD cases are linked to alterations in known genes with monogenic inherited risk, and between 16 and 6 % to non-monogenic inherited risk, with more than 90 variants described as being involved;[vi] Nalls *et al.* conducted a genome-wide association study, in which they compared 37 688 PD cases with 1.4 million controls, identifying 78 loci affecting PD risk. Their findings suggest that the most frequently identified variants present lower pathogenic risk, but when interacting with genetic and environmental factors contribute to the degree of PD risk. However, monogenic mutations in the α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), parkin (PRKN), PTEN-induced kinase 1 (PINK1), and glucocerebrosidase (GBA) genes generate elevated risk.[vii]

For the SNCA gene, on chromosome 4q, which encodes the α-synuclein protein, variants with undetermined significance in autosomal dominant PD have been identified by sequencing studies; Day *et al.* suggest that these mutations produce protein misfolding, subsequent accelerated aggregation and intracellular accumulation, increasing oxidative stress by interrupting proteasome function.[viii]

The LRRK2 gene, located on chromosome 12q, encodes the enzyme kinase, where its mutations are associated with autosomal dominant PD, being identified in approximately 1 to 2 % of all PD patients and in 5 % of the familial form.[ix] Jankovic *et al.* describe that the mutation hotspots are mainly located in the functional domains of the enzyme, generating dysregulation of the kinase and GTPase activities, with a toxic gain of function that could be the underlying mechanism.[x]

Mutations in the PRKN and PINK1 genes, located on chromosomes 6q and 1p respectively, have been identified in up to 77 % of juvenile PD cases and between 10 to 20 % of early-onset cases. They have autosomal recessive inheritance; generating dysfunctional mitochondria lysosomes by macroautophagy, which produces altered mitophagy. Simon *et al.* describe that PARKIN indirectly regulates PGC-1α levels, an important transcriptional regulator, involved in gene expression necessary for mitochondrial biogenesis and multiple antioxidant defenses.[vi,ix]

The GBA gene, located on chromosome 1q, encodes the lysosomal enzyme glucocerebrosidase, which breaks down glucocerebroside into glucose and ceramide, important in the degradation of sphingolipids. Variants of this occur in approximately 8.5 % of patients with PD and autosomal dominant inheritance pattern; carriers have an approximately four times higher risk of PD than the general population, associated with accumulation and aggregation of α-synuclein.[x]

Alzheimer's disease

For early-onset AD (before 65 years of age), more than 400 mutations have been identified in three genes: amyloid precursor protein (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2), which represent 5 % of cases of AD with an autosomal dominant inheritance pattern. Late-onset AD (after 65 years of age) is associated with polymorphisms of the apolipoprotein E (Apo E) gene, present in up to 65 % of cases, being the main susceptibility gene.[ii]

The APP gene, located on chromosome 21q, encodes a transmembrane protein from which amyloid β (Aβ) is derived by the action of gamma-secretases; Kamboh *et al.* describe that its mutation represents 10 % to 15 % of cases of autosomal dominant familial AD, affecting the function of gamma-secretase and increasing the production of Aβ.[xi]

The PSEN1 and PSEN2 genes, located on chromosomes 14q and 1q, respectively, encode the PSEN1 and PSEN2 proteins, part of the gamma-secretase complex that regulate the proteolytic activity of gamma-secretase on APP. Breijyeh *et al.* describe that their mutations are mostly of undetermined significance with an autosomal dominant inheritance pattern.[xii]

Qin *et al.* postulate that PSEN1 mutation is frequent in up to 75 % of cases of familial AD, with more than 200 variations in it; on the other hand, mutations in PSEN2 occur in about 12 % with more than 40 variations; with altered gamma-secretase function, producing Aβ; PSEN1 mutations alter neuronal function affecting GSK-3β activity and kinesin-I based motility, leading to neurodegeneration.[xiii]

On chromosome 19 is located the gene for Apo E, a glycoprotein expressed in astrocytes and microglia, in three isoforms: Apo E2, Apo E3 and Apo E4; this protein acts as a receptor-mediated endocytosis ligand for lipoproteins, including cholesterol, important for myelin production and normal brain function; on the other hand, carriers of the Apo E4 allele have a higher risk of developing AD, increasing three times for heterozygous carriers and 15 times in homozygotes; while the homozygosity of the Apo E2 allele has been identified as a protective factor for AD.[xiv]

Apo E4 binds competitively to Aβ receptors on the surface of astrocytes, preventing Aβ uptake, promotes the seeding and aggregation of Aβ into oligomers and fibrils, reducing its elimination from the interstitial fluid. These depositions of Aβ in the form of amyloid plaques cause cerebral amyloid angiopathy and cerebral vascular damage, important in the pathogenesis of AD.[xv]

Relationship of genetic alterations to the clinical course and prognosis of patients

Parkinson's disease

The clinical presentation of PD is characterized by motor and non-motor symptoms; classic symptoms being resting tremor, rigidity, bradykinesia and postural disturbances. The non-motor symptoms described are cognitive impairment, orthostatic autonomic dysfunction, hyperhidrosis, depression, anxiety, dementia, sleep disorders and sensory abnormalities such as anosmia, paresthesia and pain.[xvi]

Post *et al.* define early-onset PD as the onset of symptoms between 21 and 40 years of age, and describe that there are usually genetic alterations associated with differences to the clinical course of classic PD, with a higher frequency of dystonia and dyskinesias associated with the use of levodopa. The classic subtype of late-onset PD is characterized by onset of symptoms after the age of 60 years.[xvii]

As part of the UK Tracking Parkinson's Study, Malek *et al.* studied 1893 patients with PD and found that the L444P mutation was the most frequent pathogenic mutation of the GBA gene. Patients with this mutation were on average five years younger at the onset of PD than non-carriers, more likely to have gait difficulty, postural instability with no significant differences in cognitive function in early stages of the disease compared to non-carriers.[xviii]

A meta-analysis by Creese *et al.* found that PD patients carrying GBA mutations have a 2.4-fold increased risk of developing cognitive impairment, as well as a 1.8-fold and 2.2-fold increased risk of developing psychosis and depression, respectively, compared to patients with sporadic PD (non-mutation carriers).[xix]

Variants in LRRK2 have also been associated with changes in the clinical phenotype of PD patients. The presence of the G2019S mutation is associated with slower motor deterioration compared with PD patients not carrying the mutation. Yahalom *et al.* evaluated 225 Ashkenazi Jewish patients with PD and found that the G2019S mutation was associated with younger age of symptom onset compared to patients with N370S mutation or patients without mutations.[xx]

Omer *et al.* studied 10 090 PD patients and compared patients with mutations in LRRK2, GBA and LRRK2+GBA, identifying that carriers of LRRK2 alone or LRRK2+GBA have a milder clinical phenotype with better scores on the unified PD rating scale compared to those with mutations in GBA alone.[xxi]

Pang *et al.* describe that mutations in LRRK2 modify the effect of GBA mutations, resulting in PD with milder symptoms compared to patients with mutations in GBA alone. However, carriers of both mutations have much higher risk for developing PD and lower age of symptom onset than patients carrying only one mutation.[xxii]

Alterations in the SNCA gene also confer changes in the clinical phenotype of

PD patients. Magistrelli *et al.* found that mutations in SNCA have a lower age of symptom onset, more severe non-motor symptoms and earlier onset.[xxiii] A meta-analysis conducted by Shu *et al.* found that some variants in SNCA of the variants of the 271-bp allele confer a higher risk of presenting symptoms at a younger age, while variants of the 267-bp allele have the opposite effect.[xxiv]

PD with PRKN mutations is characterized by disease onset at younger ages, lower limb dystonia at presentation, absence of cognitive impairment, frequent motor fluctuations and dyskinesias[xxv]. On the other hand, the PD phenotype with PINK1 mutations is characterized by slower progression with typical symptoms of tremor, bradykinesia, rigidity, younger age of symptom onset. Cognitive impairment and psychiatric disturbances such as psychosis are rare in these patients.[xxvi]

Alzheimer's disease

AD is clinically characterized by progressive cognitive impairment with insidious onset and progressive alterations in episodic memory, visual/spatial and executive functions; the most frequent presentation is at advanced age (over 60 years). Subsequently, topographical disorientation and difficulties with multitasking emerge, in addition to behavioral changes, mobility problems, hallucinations and seizures.[xxvii]

The Apo E4 gene is considered the most important genetic risk factor for sporadic AD. Tellechea *et al.* found that the presence of Apo E4 is associated with younger age of onset of AD symptoms, more often of the amnesic type compared to the pattern of preservation in the hippocampus.[xxviii]

Baril *et al.* found an association between Apo E4 and greater severity of insomnia, which worsens cognitive function and memory in AD.[xxix] Frey *et al.* studied 144 patients with AD and found that those who do not carry the E4 allele of the Apo E gene have a non-amnestic AD phenotype, showing cognitive impairment in domains unrelated to memory (language, behavior, attention, executive and visuospatial functions).[xxx]

Alterations in PSEN1 are associated with a lower average age at symptom onset compared to alterations in the APP and PSEN genes2.[xxxi] Huang *et al.* found that the Asp678His mutation in the APP gene was associated with faster progression to severe dementia within 5 to 10 years of the age of symptom onset.[xxxii] Wang *et al.* found that patients with the Ile716Thr mutation in APP had marked impairment *in situ*ational memory, with an age of symptom onset between 35 and 40 years.[xiii]

In studying the V717I mutation of APP in five Chinese families, Zhang *et al.* found that the mean age of symptom onset was 54.7 years, the initial symptoms were executive dysfunction, disorientation and subtle memory loss; neurological symptoms were of late onset and were characterized by marked spastic paraparesis and cerebellar ataxia.[xxxiii]

Qiu *et al.* found a new genetic alteration (Gly111Val) in the PSEN1 gene; they found no differences in the clinical phenotype of carriers, with short-term memory loss being the most frequent symptom.[xxxiv] In contrast, Li *et al.* studied the Glu116Lys variant, and found that carriers presented disorientation and memory impairment from the age of 35 years and progressed rapidly with psychiatric symptoms; some patients died at the age of 40 years.[xxxv]

Another study conducted by Qiu *et al.* found the M139L alteration in PSEN1 and reports that the mean age of symptom onset was 45 years, the main symptoms experienced by carriers were progressive memory impairment, visuospatial disturbances and irritability.[xxxvi] Li *et al.* also found the Ile202Phe variant, whose carriers showed memory impairment from the age of 36 years and subsequently developed language difficulties and personality changes.[xxxvii]

Mutations in PSEN2 tend to be rarer. Qin *et al.* found that patients with these mutations have an older age of symptom onset than patients with mutations in APP or PSEN1, have a slower progression and symptoms similar to sporadic or idiopathic AD.[xiii]

Relationship of genetic alterations to response to treatment

Parkinson's disease

In PD, levodopa remains the gold standard in initial management, with greater benefit in control of motor manifestations compared to dopaminergic agonists. Two important pathways are involved in dopamine synthesis: the catechol o-methyltransferase pathway and amino oxidase B pathway.[xxxviii]

Initial descriptions of LRRK2 emphasized the clinical similarities between this condition and idiopathic PD, specifically that both are progressive forms of parkinsonism that respond well to levodopa (L-DOPA) therapy.[xxxix]

Lantin *et al.* conducted a study to explore the association between polymorphisms in dopaminergic pathway genes, finding that the rs921451 polymorphism in the dopa-decarboxylase gene had an effect on

response to L-DOPA treatment in Chinese PD patients. However, this could vary due to ethnic differences.[xl]

Likewise, mutations associated with dopaminergic pathways have an important effect on the adverse effects of drugs. Yin *et al.* evidenced in their meta-analysis that the AA genotype of the rs4680 polymorphism of catechol-O-methyltransferase potentially increases the risk of levodopa-induced dyskinesia in a recessive genetic model for PD patients.[xli]

Alzheimer's disease

The Food and Drug Administration has approved two pharmacological groups for the treatment of AD, acetylcholinesterase inhibitors (ACE inhibitors), including donepezil, rivastigmine and galantamine. Another group are the N-methyl-D-aspartate receptor modulators, in which only memantine has been approved.[xlii] It is important to note that they do not act at the level of the pathological processes involved in the development of the disease, and the different genetic variants are responsible for approximately 75 to 85 % of the variability in response to treatment.[xliii]

Cheng *et al.*, in a meta-analysis that included 30 studies, did not identify any significant influence on the response to treatment with ICS in patients carrying the Apo E4 allele compared to non-carriers.[xliv] Jia *et al.* carried out a prospective multicenter study with 241 patients in which they identified a better response to treatment by non-carriers, with an increase in the Mini-Mental State Examination score.[xlv]

Similarly, a better response to treatment with donepezil or rivastigmine has been identified in patients carrying the Apo E3 variant compared to Apo E4.[xlvi] In patients who also present the BCH K genotype, there is less response to rivastigmine and memantine, due to the synergy between the Apo E4 allele and this variant.[xlvii]

Wallin *et al.*, in a prospective multicenter study, identified a better response to treatment with galantamine in older patients with low cognitive and functional capacities at the start of the study, a faster rate of progression prior to treatment, and a lower incidence of the Apo E4 allele.[xlviii]

Drugs for AD patients with PSEN1-mutated AD are limited to symptomatic therapies and no specific treatments are available. Drug repurposing based on induced pluripotent stem cells identified bromocriptine as a therapeutic candidate for AD with PSEN1 mutation.[xlix] Table 1 summarizes the main genetic alterations studied in this review and some less frequent ones, but also of interest to the scientific community.

Currently, the evidence is still building. Studies are underway to evaluate the influence of genetics on the clinical and response to specific treatments in people with neurodegenerative diseases such as PD and AD.

Table 1. Summary of the main genetic alterations related to PD and AD. Own Authorship[xiii,xxvi,l]

Mutation	Inheritance pattern	Risk level	Frequency	Clinical presentation	Response to treatment	Evolution
Parkinson's Disease						
GBA	Dominant	Medium	Common	Younger age of symptom onset, greater severity of motor symptoms	There may be less response to treatment, but studies are inconclusive.	Motor phenotype similar to idiopathic PD. Non-motor symptoms are greater, with more cognitive, neuropsychiatric involvement and autonomic dysfunction.
LRRK2	Dominant	Very high	Common	More benign clinical course, symptoms similar to sporadic or idiopathic PD	There are no significant differences with respect to levodopa therapy.	Slower progression almost similar to the progression of idiopathic PD. There may be early olfactory disturbances.
SNCA	Dominant	Very high	Uncommon	Clinical course similar to sporadic or idiopathic PD. May present at an early age.	There is a good initial response to treatment.	Progression similar to idiopathic PD unless it occurs together with other alterations in GBA or LRRK2, being more accelerated. Dementia and cognitive impairment may develop.

Mutation	Inheritance pattern	Risk level	Frequency	Clinical presentation	Response to treatment	Evolution
PRKN	Recessive	Very high	Rare	Younger age of onset of symptoms, usually less cognitive impairment.	Good response to levodopa, motor fluctuations and dystonia are common.	Overall good prognosis for patients or similar to sporadic PD.
PARK1	Recessive	High	Rare	Younger age of onset of symptoms, typical PD symptoms predominate.	Good response to levodopa treatment.	Better or similar prognosis than patients with sporadic PD
DJ1	Recessive	High	Very rare	It is associated with juvenile onset.	Adequate response to levodopa treatment.	It usually progresses slowly
PINK1	Recessive	Very high	Very rare	It is associated with juvenile onset.	Adequate response to levodopa treatment.	Progresión lenta.
VPS35	Dominant	Very high	Very rare	Earlier age of onset.	Adequate response to levodopa treatment.	Earlier age of onset than idiopathic PD. Similar clinical course.
Alzheimer's disease						
APP	Dominante	High	Rare	Age of onset of symptoms similar to sporadic PD. Greater impairment in situational and visuospatial memory.	Similar response to sporadic AD.	Faster and more severe progression to dementia. Lower frequency of psychiatric alterations. In some publications it was identified in cases of early onset. May be associated with myoclonus and epileptic seizures..
PSEN1	Dominante	High	Rare	Age of onset of symptoms lower than sporadic AD and AD with alterations in APP or PSEN2. Episodic memory loss is the most frequent symptom.	Similar response to sporadic AD.	Faster progression or similar to sporadic AD. Faster and more severe progression to psychiatric disturbances and personality changes. Progression of dementia similar or faster than sporadic AD.
PSEN2	Dominante	High	Rare	Age of onset of symptoms similar to sporadic AD.	Similar or better response as sporadic AD.	Similar or slower progression to sporadic AE.
Apo E4	Dominante	Medium to high	Uncommon	Younger age of symptom onset, marked amnestic clinical phenotype similar to sporadic AD.	Lower response to treatment with AChEIs* vs. non-carriers	Progression similar to sporadic or idiopathic AD. There may be early sleep and circadian cycle disturbances. There is variability in clinical presentation.
Apo E4	Dominante	Medio a Alto	Poco común	Menor edad de aparecimiento de los síntomas, fenotipo clínico amnésico marcado similar a EA esporádica.	Menor respuesta al tratamiento con CEI contra no portadores.	Progresión similar a EA esporádica o idiopática. Puede haber alteraciones del sueño y del ciclo circadiano de manera temprana. Hay variabilidad en la presentación clínica.

Conclusion

Genetic variations have been described that influence the age of symptom presentation in neurodegenerative diseases, with ages of presentation lower than the usual evolution, in addition to more disabling neurocognitive and motor symptoms. In PD, earlier ages of symptom onset are observed in patients with mutations of the GBA, SNCA, PRKN and PARK1 genes.

In terms of response to treatment, in patients with GBA mutations, less response has been described with faster progression to cognitive deficit. In AD, dementia develops at a younger age in people with PSEN1 gene mutations. Less response to conventional treatments has been observed with APO E4 mutations. Progression is faster and more severe in APP and PSEN1 gene mutations.

References

i. Organización Mundial de la Salud. Enfermedad de Parkinson. 2023. Date of citation: August 9, 2023. Available at: https://www.who.int/es/news-room/fact-sheets/detail/parkinson-disease

ii. Andrade J, Santiago A, Aguilar J, Vargas I, Cadena A, Sánchez C, *et al.* Alzheimer's Disease: An Updated Overview of Its Genetics. IJMS. 2023;24(4):3754. DOI: 10.3390/ijms24043754

iii. Izquierdo A, Palomo M, Celi J. Neurogenética. Medicine - Programa de Formación Médica Continuada Acreditado. 2019;12(77):4559-4566. DOI: 10.1016/j.med.2019.05.004

iv. Smedinga M, Darweesh S, Bloem B, Post B, Richard E. Towards early disease modification of Parkinson's disease: a review of lessons learned in the Alzheimer field. J Neurol. 2021;268(2):724-733. DOI: 10.1007/s00415-020-10162-5

v. Mendez M. Early-onset Alzheimer Disease and Its Variants. CONTINUUM: Lifelong Learning in Neurology. 2019;25(1):34-51. DOI: 10.1212/CON.0000000000000687

vi. Bloem B, Okun M, Klein C. Parkinson's disease. The Lancet. 2021;397(10291):2284-2303. DOI: 10.1016/S0140-6736(21)00218-X

vii. Nalls M, Blauwendraat C, Vallerga CL, Heilbron K, Bandres S, Chang D, *et al.* Expanding Parkinson's disease genetics: novel risk loci, genomic context, causal insights and heritable risk. Genetics; 2018. DOI: 10.1101/388165

viii. Day J, Mullin S. The Genetics of Parkinson's Disease and Implications for Clinical Practice. Genes. 2021;12(7):1006. DOI: 10.3390/genes12071006

ix. Simon D, Tanner C, Brundin P. Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. Clinics in Geriatric Medicine. 2020;36(1):1-12. DOI: 10.1016/j.cger.2019.08.002

x. Jankovic J, Tan E. Parkinson's disease: etiopathogenesis and treatment. J Neurol Neurosurg Psychiatry. 2020;91(8):795-808. DOI: 10.1136/jnnp-2019-322338

xi. Kamboh M. Genomics and Functional Genomics of Alzheimer's Disease. Neurotherapeutics. 2022;19(1):152-172. DOI: 10.1007/s13311-021-01152-0

xii. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020;25(24):5789. DOI: 10.3390/molecules25245789

xiii. Qin Q, Yin Y, Wang Y, Lu Y, Tang Y, Jia J. Gene mutations associated with early onset familial Alzheimer's disease in China: An overview and current status. Molec Gen & Gen Med. 2020;8(10):e1443. DOI: 10.1002/mgg3.1443

xiv. Hoogmartens J, Cacace R, Van Broeckhoven C. Insight into the genetic etiology of Alzheimer's disease: A comprehensive review of the role of rare variants. Alz & Dem Diag Ass & Dis Mo. 2021;13(1):e12155. DOI: 10.1002/dad2.12155

xv. Serrano A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. The Lancet Neurology. 2021;20(1):68-80. DOI: 10.1016/S1474-4422(20)30412-9

xvi. Beitz J. Parkinson s disease a review. Front Biosci. 2014;S6(1):65-74. DOI: 10.2741/S415

xvii. Post B, Van Den Heuvel L, Van Prooije T, Van Ruissen X, Van De Warrenburg B, Nonnekes J. Young Onset Parkinson's Disease: A Modern and Tailored Approach Bloem BR, Brundin P, editors. JPD. 2020;10(s1):S29-S36. DOI: 10.3233/JPD-202135

xviii. Malek N, Weil R, Bresner C, Lawton M, Grosset K, Tan M, *et al.* Features of GBA -associated Parkinson's disease at presentation in the UK Tracking Parkinson's study. J Neurol Neurosurg Psychiatry. 2018;89(7):702-709. DOI: 10.1136/jnnp-2017-317348

xix. Creese B, Bell E, Johar I, Francis P, Ballard C, Aarsland D. Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses. American J of Med Genetics Pt B. 2018;177(2):232-241. DOI: 10.1002/ajmg.b.32549

xx. Yahalom G, Rigbi A, Israeli S, Krohn L, Rudakou U, Ruskey J, *et al.* Age at Onset of Parkinson's Disease Among Ashkenazi Jewish Patients: Contribution of Environmental

Factors, LRRK2 p.G2019S and GBA p.N370S Mutations. JPD. 2020;10(3):1123-1132. DOI: 10.3233/JPD-191829

xxi. Omer N, Giladi N, Gurevich T, Bar A, Gana M, Goldstein O, *et al.* A Possible Modifying Effect of the G2019S Mutation in the LRRK2 Gene on GBA Parkinson's Disease. Movement Disorders. 2020;35(7):1249-1253. DOI: 10.1002/mds.28066

xxii. Pang S, Lo RCN, Ho PW-L, Liu H-F, Chang EES, Leung C-T, *et al.* LRRK2, GBA and their interaction in the regulation of autophagy: implications on therapeutics in Parkinson's disease. Transl Neurodegener. 2022;11(1):5. DOI: 10.1186/s40035-022-00281-6

xxiii. Magistrelli L, Contaldi E, Comi C. The Impact of SNCA Variations and Its Product Alpha-Synuclein on Non-Motor Features of Parkinson's Disease. Life. 2021;11(8):804. DOI: 10.3390/life11080804

xxiv. Shu L, Zhang Y, Sun Q, Pan H, Guo J, Tang B. SNCA REP1 and Parkinson's disease. Neuroscience Letters. 2018;682:79-84. DOI: 10.1016/j.neulet.2018.05.043

xxv. Lesage S, Lunati A, Houot M, Romdhan S, Clot F, Tesson C, *et al.* Characterization of Recessive Parkinson Disease in a Large Multicenter Study. Annals of Neurology. 2020;88(4):843-850. DOI: 10.1002/ana.25787

xxvi. Kasten M, Hartmann C, Hampf J, Schaake S, Westenberger A, Vollstedt E, *et al.* Genotype-Phenotype Relations for the Parkinson's Disease Genes Parkin , PINK1, DJ1: MDSGene Systematic Review. Movement Disorders. 2018;33(5):730-741. DOI: 10.1002/mds.27352

xxvii. Aoki Y, Takahashi R, Suzuki Y, Pascual R, Kito Y, Hikida S, *et al.* EEG resting-state networks in Alzheimer's disease associated with clinical symptoms. Sci Rep. 2023;13(1):3964. DOI: 10.1038/s41598-023-30075-3

xxviii. Tellechea P, Pujol N, Esteve P, Echeveste B, García M, Arbizu J, *et al.* Enfermedad de Alzheimer de inicio precoz y de inicio tardío: ¿son la misma entidad? Neurología. 2018;33(4):244-253. DOI: 10.1016/j.nrl.2015.08.002

xxix. Baril A, Beiser A, Sanchez E, Mysliwiec V, Redline S, Gottlieb DJ, *et al.* Insomnia symptom severity and cognitive performance: Moderating role of APOE genotype. Alzheimer's & Dementia. 2022;18(3):408-421. DOI: 10.1002/alz.12405

xxx. Fray S, Achouri A, Belal S, Messaoud T. Missing apolipoprotein E **ε**4 allele associated with nonamnestic Alzheimer's disease in a Tunisian population. J Genet. 2022;101(2):41. DOI: 10.1007/s12041-022-01384-9

xxxi. Wu L, Rosa P, Hsiung G, Sadovnick A, Masellis M, Black S, *et al.* Early-Onset Familial Alzheimer's Disease (EOFAD). Can. J. Neurol. Sci. 2012;39(4):436-445. DOI: 10.1017/S0317167100013949

xxxii. Huang C, Hsiao I, Lin K, Huang K, Fung H, Liu C, *et al.* Amyloid PET pattern with dementia and amyloid angiopathy in Taiwan familial AD with D678H APP mutation. Journal of the Neurological Sciences. 2019;398:107-116. DOI: 10.1016/j.jns.2018.12.039

xxxiii. Zhang G, Xie Y, Wang W, Feng X, Jia J. Clinical characterization of an APP mutation (V717I) in five Han Chinese families with early-onset Alzheimer's disease. Journal of the Neurological Sciences. 2017;372:379-386. DOI: 10.1016/j.jns.2016.10.039

xxxiv. Qiu Q, Jia L, Wang Q, Zhao L, Jin H, Li T, *et al.* Identification of a novel PSEN1 Gly111Val missense mutation in a Chinese pedigree with early-onset Alzheimer's disease. Neurobiology of Aging. 2020;85:155.e1-155.e4. DOI: 10.1016/j.neurobiolaging.2019.05.018

xxxv. Dongxiao Li, Yupeng Liu, Yuan Ding, Xiyuan Li, Xun Wu, Jinqing Song, *et al.* A patient with initial symptom of epilepsy from age of 12 years old due to early-onset Alzheimer disease caused by presenilin 1 mutation. Chinese Journal of Obstetrics and Gynecology, 2016;12(6):621-626. DOI: 10.3877/CMAJ.ISSN.1673-5250.2016.06.001

xxxvi. Qiu Q, Shen L, Jia L, Wang Q, Li F, Li Y, *et al.* A Novel PSEN1 M139L Mutation Found in a Chinese Pedigree with Early-Onset Alzheimer's Disease Increases $A\beta_{42}/A\beta_{40}$ ratio. JAD. 2019;69(1):199-212. DOI: 10.3233/JAD-181291

xxxvii. Li Y, Yang Z, Zhang Y, Yang J, Shang D, Zhang S, *et al.* Two Novel Mutations and a de novo Mutation in PSEN1 in Early-onset Alzheimer's Disease. Aging and disease. 2019;10(4):908. DOI: 10.14336/AD.2018.1109

xxxviii. Pringsheim T, Day G, Smith D, Rae A, Licking N, Armstrong M, *et al.* Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary: A Report of the AAN Guideline Subcommittee. Neurology. 2021;97(20):942-957. DOI: 10.1212/WNL.0000000000012868

xxxix. Tolosa E, Vila M, Klein C, Rascol O. LRRK2 in Parkinson disease: challenges of clinical trials. Nat Rev Neurol. 2020;16(2):97-107. DOI: 10.1038/s41582-019-0301-2

xl. Li L, Lin H, Hua P, Yan L, Dong H, Li T, *et al.* Polymorphism of the Dopa-Decarboxylase Gene Modifies the Motor Response to Levodopa in Chinese Patients With Parkinson's Disease. Front. Neurol. 2020;11:520934. DOI: 10.3389/fneur.2020.520934

xli. Yin Y, Liu Y, Xu M, Zhang X, Li C. Association of COMT rs4680 and MAO-B rs1799836 polymorphisms with levodopa-induced dyskinesia in Parkinson's disease—a meta-

analysis. Neurol Sci. 2021;42(10):4085-4094. DOI: 10.1007/s10072-021-05509-3

xlii. Argueta N, Notari E, Szigeti K. Role of Pharmacogenomics in Individualizing Treatment for Alzheimer's Disease. CNS Drugs. 2022;36(4):365-376. DOI: 10.1007/s40263-022-00915-3

xliii. Zúñiga T, Yescas P, Fricke I, González M, Ortega A, López M. Estudios farmacogenéticos en la enfermedad de Alzheimer. Neurología. 2022;37(4):287-303. DOI: 10.1016/j.nrl.2018.03.025

xliv. Cheng Y, Huang Y, Liu H. Effect of Apolipoprotein E ε4 Carrier Status on Cognitive Response to Acetylcholinesterase Inhibitors in Patients with Alzheimer's Disease: A Systematic Review and Meta-Analysis. Dement Geriatr Cogn Disord. 2018;45(5-6):335-352. DOI: 10.1159/000490175

xlv. Jia J, Wei C, Chen W, Jia L, Zhou A, Wang F, *et al.* Safety and Efficacy of Donepezil 10 mg/day in Patients with Mild to Moderate Alzheimer's Disease. Journal of Alzheimer's Disease,. 2020;74(1):199-211. DOI: 10.3233/JAD-190940

xlvi. Cacabelos R. Pharmacogenetic considerations when prescribing cholinesterase inhibitors for the treatment of Alzheimer's disease. Expert Opinion on Drug Metabolism & Toxicology. 2020;16(8):673-701. DOI: 10.1080/17425255.2020.1779700

xlvii. Sonali N, Tripathi M, Sagar R, Velpandian T, Subbiah V. Clinical Effectiveness of Rivastigmine Monotherapy and Combination Therapy in Alzheimer's Patients. CNS Neurosci Ther. 2013;19(2):91-97. DOI: 10.1111/cns.12036

xlviii. Wallin Å, Minthon, Wattmo C. Galantamine treatment in Alzheimer's disease: response and long-term outcome in a routine clinical setting. NDT. 2011;7(1):565-576. DOI: 10.2147/NDT.S24196

xlix. Kondo T, Banno H, Okunomiya T, Amino Y, Endo K, Nakakura A, *et al.* Repurposing bromocriptine for Aβ metabolism in Alzheimer's disease (REBRAnD) study: randomised placebo-controlled double-blind comparative trial and open-label extension trial to investigate the safety and efficacy of bromocriptine in Alzheimer's disease with presenilin 1 (PSEN1) mutations. BMJ Open. 2021;11(6):e051343. DOI: 10.1136/bmjopen-2021-051343

l. Yat-Fung Shea, Leung-Wing Chu, Angel On-Kei Chan, Joyce Ha, Yan Li, You-Qiang Song. A systematic review of familial Alzheimer's disease: Differences in presentation of clinical features among three mutated genes and potential ethnic differences. Journal of the Formosan Medical Association. 2016;115(2):67-75. DOI: 10.1016/j.jfma.2015.08.004

Narrative review

Burnout Syndrome in Health Care Personnel During the COVID-19 Pandemic

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Síndrome de desgaste profesional en el personal de salud durante la pandemia de COVID-19

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Abstract
The WHO defines occupational stress as a reaction that may occur when a person is faced with work-related demands and pressures that test the individual's ability to cope with certain situations, and it exacerbates in healthcare personnel who provide care to patients with COVID-19. That is, what results from the imbalance between the pressures and demands that the individual faces, on the one hand, and the knowledge acquired on the other hand. Burnout syndrome is a type of work-related stress that encompasses a state of physical, emotional and mental exhaustion that leads to individual and social consequences. The objective of this systematic review is to identify the risk factors for the development of Burnout Syndrome in health personnel related to the care of patients with COVID-19. A search was carried out in the PubMed database, including original articles, randomized studies, systematic reviews, and textbooks in Spanish and English, published during the period 2020-2023. The main risk factors for the development of Burnout Syndrome identified in the literature were youth, female sex, singleness, workload and the level of job satisfaction of the professionals.

Keywords
COVID-19, Risk Factor, Health Personnel, Burnout Syndrome, Professional Burnout.

Resumen
La Organización Mundial de la Salud (OMS) define el estrés laboral como una reacción que puede manifestarse ante exigencias y presiones laborales que ponen a prueba la capacidad que tiene cada persona para afrontar ciertas situaciones y que se agravan en el personal de salud que atiende pacientes con la COVID-19. Es decir, lo que resulta del desequilibrio entre las presiones y exigencias a las que se enfrenta el individuo, por una parte, y los conocimientos adquiridos por otra parte. El Síndrome de desgaste profesional, conocido también como síndrome de agotamiento emocional o psicológico, o por el anglicismo *burnout*, es un tipo de estrés laboral que engloba un estado de agotamiento físico, emocional y mental que conlleva a consecuencias individuales y sociales. El objetivo de esta revisión narrativa es identificar los factores de riesgo para el desarrollo del Síndrome de desgaste profesional en el personal de salud relacionado con la atención de pacientes con la COVID-19. Se realizó una búsqueda en la base de datos PubMed, se incluyeron artículos originales, estudios aleatorizados, revisiones sistemáticas y otros textos en español e inglés, publicados durante el periodo 2020-2023. Los principales factores de riesgo identificados en la literatura para el desarrollo de Síndrome de desgaste profesional fueron la juventud, sexo femenino, la soltería, la carga de trabajo y el nivel de satisfacción laboral de los profesionales.

Palabras clave
COVID-19, Factores de Riesgo, Personal de Salud, Desgaste Profesional, Agotamiento Psicológico.

Introduction

Professional exhaustion is known by the anglicized term "burnout". It is an expression used by athletes to describe a situation in which, contrary to favorable prospects, an athlete fails to achieve the expected results, no matter how much preparation and effort they put into it.[i]

According to the *Diccionario de términos médicos de la Real Academia Nacional de Medicina de España*, professional burnout syndrome is the appropriate translation of the English word that literaly means "destroyed by heat".

In healthcare services it was first used in 1974 by Herbert Freudeberger, a psychiatrist working as a volunteer assistant in a New York drug addiction clinic.[i]

It has been scientifically proven that the professional burnout syndrome is composed of three factors or dimensions:[i]

1. Emotional exhaustion: this is a fundamental aspect and involves symptoms of loss of energy, physical and psychological exhaustion and a feeling of being at one's limit, of not being able to give more of oneself.[i]
2. Depersonalization: in this case, as a protective measure, the subject may develop a negative change in attitudes and responses towards others, especially towards the beneficiaries of one's own work, becoming distant, using derogatory labels to refer to others, or trying to blame them for their frustrations and decreased work commitment.
3. Low personal accomplishment: it is a feeling of personal professional inadequacy to perform the job. It involves feelings of inadequacy, low self-esteem and ideas of failure.[i]

Healthcare professionals and other public health decision-makers work beyond their potential to contain COVID-19. In such circumstances, healthcare professionals directly involved in the diagnosis and management of patients with COVID-19 are subject to various psychological stressors associated with the workplace.[ii]

Burnout is an element that threatens the general population, not just healthcare personnel. A positive observation is that, over the years, there has been an advance in knowledge about burnout.[iii]

This paper includes a review of original articles, randomized studies, systematic reviews, and texts in Spanish and English, published during the period 2020-2023, with the objective of identifying risk factors for the development of professional burnout syndrome in health personnel related to the care of patients with COVID-19.

Discussion

Burnout syndrome is a type of occupational stress that encompasses a state of physical, emotional, and mental exhaustion that leads to individual and social consequences. In 1977, during the annual congress of the American Psychological Association, the term burnout was established to describe a situation that occurred among human services workers consisting of the fact that, after months of work and dedication, they ended up becoming emotionally exhausted.[i]

Since its inception, burnout syndrome has been defined in many ways, being described by Maslach and Jackson as a syndrome characterized by emotional exhaustion, depersonalization, and low personal fulfillment at work, which can occur among individuals whose daily tasks are limited to the service of people.[iv]

Other authors, including Pines and Aronson, proposed a broader definition, not restricted to the helping professions: "It is the state of mental, physical and emotional exhaustion produced by chronic involvement in work in emotionally demanding situations".[v]

The SARS-CoV-2 pandemic caused a general increase in cases of anxiety, depression, and burnout syndrome in healthcare workers. This global health situation triggered an unprecedented health crisis with a high prevalence of psychological distress in healthcare workers, requiring the documentation of risk factors for the development of burnout syndrome among healthcare workers facing COVID-19.[iv] In many countries, this large-scale health situation resulted in the restructuring and reorganizing of health service delivery to support emergency services, medical intensive care units, and continuing care units.[v]

Healthcare professionals exposed to working with patients during the COVID-19 pandemic are at increased risk for short- and long-term mental health problems. Healthcare workers must receive psychosocial support to protect their mental well-being if they must continue providing high-quality patient care.[vi]

Some of the strategies adopted during the pandemic6 as risk factors to promote resilience include increasing the sense of control over the adverse situation, for example, increasing the perception that disease prevention measures can be managed, or controlling the possibility of becoming infected by protecting oneself with the resources that healthcare providers have at hand to care for infected patients.[vii]

Burnout is not a sudden onset of symptoms. Many people with burnout syndrome have a variety of thoughts, feelings, and actions that progress through a series of stages, often with options for prevention. It

is critical to understand the different stages of burnout syndrome to prevent it (honeymoon phase, stress onset, chronic illness, stress, and burnout).[viii]

The COVID-19 pandemic exerted considerable psychological pressure on front-line healthcare workers. Although the problem of burnout, which overlaps with symptoms of depression, remains urgent, few studies have addressed it comprehensively.[ix]

In a study, Castro *et al.* described risk factors associated with burnout syndrome in healthcare workers during the COVID-19 pandemic, as female sex, young age, being in contact with COVID-19 patients, previous history of depression or psychiatric illness, being nursing staff or resident medical staff, and longer work hours. It has also been reported that independent predictors of burnout syndrome are medical personnel and respiratory kinesiologist.[x]

Work time, fear of infection and infecting loved ones or patients, and concern about controlling the epidemic, among others, can be precipitating factors for an alteration in the mental health of healthcare professionals in times of COVID-19. Such alterations can be a serious problem on a personal scale, and an impairment in the professional performance, and can increase the risk of contagion and professional malpractice.[xi]

According to Matsuo T *et al.*, a study evaluated 488 healthcare workers; of these, 369 (75.6 %) responded to the survey, from which 57 (15.4 %) were excluded due to missing data. The final sample included 312 respondents, with a median age of 30.5 (26 to 40) years, with 223 (71.5 %) women, and median experience of 7.0 (3 to 15) years. The overall prevalence of burnout was 31.4 % (98 of 312). Of 82 physicians, 11 (11.2 %) experienced burnout; of 126 nurse personnel, 59 (46.8 %) experienced burnout; of 22 radiologic technologists, eight (36.4 %) experienced burnout; and of 19 pharmacists, seven (36.8 %) experienced burnout. It is worth noticing that nurse personnel working inwards with COVID-19 patients are psychologically affected by the consequences of the pandemic due to a higher workload and more time in direct contact with COVID-19 patients compared to physicians.[xii]

The COVID-19 pandemic caused enormous pressure on healthcare workers, with many implications for their physical and emotional well-being.[xii] Likewise, it is important to mention that it had a substantial impact on their mental health.[xiii] which is why healthcare personnel should become a priority for mental health strategies.[xiii]

In this scenario, understanding the consequences of the COVID-19 outbreak on the health of first-line healthcare professionals is urgent, and the root causes of the psychophysical impact related to emotional exhaustion and somatic symptoms should be sought.[xiv] Patient care is the first-factor causing stress, as well as job satisfaction. The suffering or stress of medical personnel is caused by identification with the anguish of the patients and their families, by the reactivation of their conflicts, and by the frustration of their diagnostic-therapeutic perspectives concerning the patient's condition. Therefore, adequate psychosocial training can enable the health professional to deal with the inevitable anxiety of the patient and family in a more satisfactory way.[iv]

Personal and familial implications

Healthcare workers are at high risk of developing physical and mental health impairments. The nature and frequency of these outcomes are undetermined. COVID-19 has had a substantial impact on the mental health of healthcare workers it must be a priority for health strategies since it has personal and occupational repercussions that, according to Salazar *et al.*, manifest themselves in symptoms such as chills, cough, diarrhea, dyspnea, fatigue, fever, headache, myalgia, nausea, and vomiting.[xiii]

It is suggested that the COVID-19 pandemic affected women with young children, with a higher prevalence of burnout among female physicians and nurse personnel, and physicians under 30 years old, accompanied by research suggesting that part-time work helps healthcare workers mitigate burnout.[xv]

It is noted that the nursing personnel experienced high levels of burnout during the COVID-19 pandemic and that various sociodemographic, occupational, psychological, and COVID-19-related factors played a role in this burnout syndrome[xiv]. Nurses experienced significant difficulties during the COVID-19 pandemic worldwide.[xvi]

In a study on COVID-19, it was shown that 80 % of health professionals suffer from low or moderate burnout syndrome, and 20 % suffer from severe burnout syndrome. Among nurses, the prevalence of burnout syndrome is around 70 %.[xvii]

Risk factors related to burnout syndrome

Occupational burnout syndrome is an adaptive disorder due to chronic work-related stress; it is a particular form of stress. There are many causes: family, economic, social, occupational, etc., and different reactions to stress.

However, burnout syndrome is a special form, motivated by the relationship between the person and his or her work; it occurs when work tasks are related to managing, relating to, or helping other people. According to Barello *et al.*, demographic risk factors are age, gender, marital status, job characteristics, work attitudes, and personality traits.[xiv]

The COVID-19 health emergency changed the lives of professionals and parents, increasing perceptions of stress and specific symptoms of exhaustion, emotional distancing, and depersonalization, as well as a decrease in feelings of satisfaction and fulfillment.[xviii,xix] Among health professionals caring for minors in therapeutic communities, the pandemic required numerous emotional tools and cognitive resources, so Peres *et al.* describe the professional characteristics of those who cared for patients with COVID-19.[i,xiii,xix]

Another study found that nursing personnel working with patients with COVID-19 are exposed to various stressors that can lead to professional burnout, and also demonstrated that working conditions with COVID-19-positive patients are associated with experiencing burnout symptoms.[xx] Another study in Ghana, Africa, demonstrated a high prevalence of burnout among healthcare workers in Accra, particularly during the onslaught of the COVID-19 pandemic.[xxi] Working night shifts and at the primary level of healthcare was significantly associated with a higher likelihood of experiencing burnout, so shift rotation for staff and adequate provision of resources for primary-level hospitals was recommended, showing that the high burnout syndrome could be caused by other factors such as bereavement caused by multiple losses and also by limited support resources for healthcare workers.[xxi]

Resilience, mentalization capacity, and burnout syndrome among healthcare workers are interrelated phenomena with important professional implications.[xxii] Education and training programs for healthcare workers should include knowledge and skills that are important for healthcare worker resilience in a pandemic.[xxii] It is important to be clear about one's purpose in life as a healthcare worker, which was most strongly associated with decreased levels of burnout.[xxiii]

A study confirmed a high incidence of burnout syndrome in the emotional exhaustion and depersonalization dimensions, among frontline nurse personnel working in COVID-19 care services during the outbreak,[xxiv] finding relevant data of history of previous psychiatric illness. Attention must be paid to the high prevalence of burnout among healthcare workers, not only in the frontline and during pandemics, should be addressed.[vii,xxiv]

Prevention of burnout syndrome

Burnout syndrome can be prevented or solved. It is possible to be mildly optimistic, although caution should exerted, especially when a person is suffering from burnout, given that it can be contagious and is easy to understand the permanent complaints, negative attitudes, suspicions, rejections, etc., in fact, it is noticeable that when there is a person with burnout in a group, the others are more at risk of suffering from it. It is therefore necessary to recognize it and help in the initial stages.[i]

In a study conducted during a pandemic in South Korea, it was shown that promoting the well-being and quality of work life of healthcare workers in response to a pandemic crisis contributed to reducing burnout among frontline nurses and enhancing the safety of healthcare workers and patients.[xxv,xxvi] This demonstrates the importance of considering the prevalence and predictors of burnout syndrome in nurses caring for patients with COVID-19.

Healthcare workers are critical to providing medical treatment in the community at large, especially during the COVID-19 pandemic, thus highlighting the importance of monitoring physical and mental well-being among all workers, not only among medical and nursing staff, who are the most visible frontline staff, as early identification of psychological distress and burnout syndrome, as well as increasing access to medical care for employees and family members can help decrease the negative effects impacting essential healthcare workers.[xxvii]

It is difficult to predict the duration of the pandemic's impact, but it could be an opportunity for healthcare institutions to review and improve their system to take a proactive role in mitigating professional burnout by recognizing the impacts, implementing work-life balance policies, and providing access to mental health services to alleviate professional burnout.[xxviii]

Both physical and psychological aspects of healthcare personnel must be considered to ensure their well-being. In addition, it is necessary to understand the relationship between the contribution of long working hours and the constant decrease in the quality of life of these personnel; therefore, an allocation of fixed working hours for healthcare personnel should be made.[xxix]

During the critical situation of the COVID-19 pandemic frontline staff who directly interacted with suspected and diagnosed COVID-19 patients were at high risk of becoming infected, which contributed to professional burnout.[xxx] This contrasts with a study from Mozambique, in which many healthcare workers reported a reduction in burnout, this may be associated with the lower number of COVID-19 cases observed during 2022.[xxxi]

Cognitive techniques for emotional self-care

Cognitive resources can also be used for the prevention of emotional disturbance or, in other words, mental healthcare. It is suggested that healthcare personnel could benefit from these techniques applied to practical cases. This approach offers an active preventive response to burnout.[i]

Among the various techniques is Socratic questioning or guided discovery, which is about asking inductive questions that help to change the "rigid perception" of reality into a state of curiosity. It is about realizing that there are other alternatives to the interpretation of what is happening. At times of disturbance, it may be difficult to do this to oneself. Even so, one can develop the habit of questioning cognitive distortions by asking oneself questions in writing.[i] Another important technique is selective abstraction or filtering (relative to the stimulus), which consists of focusing on a detail extracted from its context, ignoring other features of the situation, and considering the whole experience based on that fragment. A single detail is highlighted, and the rest is tinged by it.[i]

Existing programs and resources to facilitate healthcare provider´s wellness were inadequate before the pandemic, and despite the pandemic experience, they appear to remain insufficient.[xxxi] This situation is further complicated by the findings of this review, given that the healthcare personnel have less capacity to initiate, sustain, and complete interventions to improve their wellness.[xxxii]

In pandemic settings, clear communication of guidelines and precautionary measures reduces the likelihood of emotional distress, as does support from co-workers. Social support outside the workplace can also decrease stress, yet healthcare personnel often neglect relationships with friends and family because of workloads or concerns about infecting others due to their exposure to the virus.[xxxiii]

COVID-19 is a public health problem because of the high impact it has generated, and it has posed a challenge to economics and medicine worldwide,[xxvi] which makes it necessary to implement various psychological interventions for healthcare personnel, as such efforts could potentially mitigate the negative impacts of the pandemic on their mental health and prepare them for future risks.[xxxiv]

Burnout syndrome is associated with work overload, role conflict (ambiguity), lack of participation and control, clinical work (direct relationship with patients), and medical specialties with a predominance of chronic, critical, oncological, and terminal patients.[iv] It is worth mentioning that the syndrome is also associated with people who have suffered emotional conflicts in their childhood, which have made them narcissistic and ambitious, obsessive, anxious, or depressive.[iv]

The considerable prevalence of burnout syndrome in primary healthcare professionals in low- and middle-income countries has implications for patient safety, quality of care, and workforce planning.[xxvii]

Maintaining social contact is increasingly challenging in the context of distancing requirements. There are reports of healthcare workers experiencing social problems such as stigma and abuse due to public fears of contracting the virus from those with increased exposure, making it foremost to identify the biggest factors for the development of professional burnout syndrome in healthcare personnel who are in patient care with COVID-19. More cross-sectional studies are needed to help identify evidence-based solutions.[xviii]

Conclusions

The risk factors for the development of burnout syndrome in healthcare personnel related to patient care with COVID-19 found in the literature reviewed were age, observed more frequently among young people, and job satisfaction, which increases with age and is the major predictor of longevity. In terms of sex, women had more job stress than men. Regarding marital status, single people are more prone to the development of burnout linked to the profession since nursing personnel are more at risk of suffering burnout syndrome as they work closer with patients with COVID-19 and are affected psychologically by a heavier workload and more time in direct contact with patients with COVID-19, compared to medical personnel.

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References

i. González Correales Ramón, Gándara Martín JJ de la, González Rodríguez VM. El médico con burnout: conceptos básicos y habilidades prácticas para el médico de familia. Madrid: IM & C; 2004. 84 p.
ii. Caldichoury N, García Roncallo P, Saldías C, Zurita B, Castellanos C, Herrera Pino J, *et al.* Impacto psicológico del COVID-19 en los trabajadores sanitarios durante el segundo año de pandemia en Latinoamérica: estudio de encuesta transversal. Revista Colombiana de Psiquiatría. 2023. DOI: 10.1016/j.rcp.2023.04.010
iii. Vňuková MS, Sebalo I, Brečka T, Anders M, Ptáček R. Burnout syndrome in the Czech Republic: The decreasing trend over the years. Front. Public Health. 2023;11:1099528. DOI: 10.3389/fpubh.2023.1099528
iv. Olivares Faúndez V. Laudatio: Dra. Christina Maslach, Comprendiendo el Burnout. Cienc Trab. 2017;19(58):59-63. DOI: 10.4067/S0718-24492017000100059
v. Martínez Pérez A. El síndrome de Burnout. Evolución conceptual y estado actual de la cuestión. VA. 2010;112:42-80. DOI: 10.15178/va.2010.112.42-80
vi. Stuijfzand S, Deforges C, Sandoz V, Sajin C-T, Jaques C, Elmers J, Horsch A. Psychological impact of an epidemic/pandemic on the mental health of healthcare professionals: a rapid review. BMC Public Health. 2020;20(1):1230. DOI: 10.1186/s12889-020-09322-z
vii. Luceño Moreno L, Talavera Velasco B, García Albuerne Y, Martín García J. Symptoms of Posttraumatic Stress, Anxiety, Depression, Levels of Resilience and Burnout in Spanish Health Personnel during the COVID-19 Pandemic. IJERPH. 2020;17(15):5514. DOI: 10.3390/ijerph17155514
viii. Azoulay E, Lescale O. Burnout syndrome in healthcare providers: a preventable disease. Intensive Care Med. 2023;49(4):485-486. DOI: 10.1007/s00134-023-07017-8
ix. Matsuo T, Kobayashi D, Taki F, Sakamoto F, Uehara Y, Mori N, Fukui T. Prevalence of Health Care Worker Burnout During the Coronavirus Disease 2019 (COVID-19) Pandemic in Japan. JAMA Netw Open. 2020;3(8):e2017271. DOI: 10.1001/jamanetworkopen.2020.17271
x. Castro HM, Prieto MA, Muñoz AM. Prevalence of burnout in healthcare workers during the COVID-19 pandemic and associated factors. A cross-sectional study. Medicina (B Aires). 2022;82(4):479-486.
xi. García Iglesias JJ, Gómez Salgado J, Martín Pereira J, Fagundo Rivera J, Ayuso Murillo D, Martínez Riera JR, *et al.* [Impact of SARS-CoV-2 (Covid-19) on the mental health of healthcare professionals: a systematic review.]. Rev Esp Salud Publica. 2020;94:e202007088.
xii. Zerbini G, Ebigbo A, Reicherts P, Kunz M, Messman H. Psychosocial burden of healthcare professionals in times of COVID-19 - a survey conducted at the University Hospital Augsburg. GMS German Medical Science. 2020;18:Doc05. DOI: 10.3205/000281
xiii. Salazar De Pablo G, Vaquerizo Serrano J, Catalan A, Arango C, Moreno C, Ferre F, *et al.* Impact of coronavirus syndromes on physical and mental health of health care workers: Systematic review and meta-analysis. Journal of Affective Disorders. 2020;275:48-57. DOI: 10.1016/j.jad.2020.06.022
xiv. Barello S, Palamenghi L, Graffigna G. Burnout and somatic symptoms among frontline healthcare professionals at the peak of the Italian COVID-19 pandemic. Psychiatry Research. 2020;290:113129. DOI: 10.1016/j.psychres.2020.113129
xv. Innstrand ST. Burnout among Health Care Professionals during COVID-19. IJERPH. 2022;19(18):11807. DOI: 10.3390/ijerph191811807
xvi. Hur G, Cinar N, Suzan OK. Impact of COVID-19 pandemic on nurses' burnout and related factors: A rapid systematic review. Archives of Psychiatric Nursing. 2022;41:248-263. DOI: 10.1016/j.apnu.2022.09.002
xvii. Caillet A, Fillon M, Plou M, Tisson E, Vacheron C H, Allaouchiche B. Burnout Syndrome During COVID-19 Second Wave on ICU Caregivers. The Journal of Critical Care Medicine. 2022;8(4):266-272. DOI: 10.2478/jccm-2022-0026
xviii. Wright T, Mughal F, Babatunde O, Dikomitis L, Mallen C, Helliwell T. Burnout among primary health-care professionals in low- and middle-income countries: systematic review and meta-analysis. Bull World Health Organ. 2022;100(6):385-401A. DOI: 10.2471/BLT.22.288300
xix. Ferro L, Cariello M, Colombesi A, Segantini A, Centonze E, Baccini G, *et al.* Burnout Syndrome and COVID-19 Lockdown: Research on Residential Care Workers Who Assume Parental Roles with Youths.

IJERPH. 2022;19(23):16320. DOI: 10.3390/ijerph192316320

xx. Tomaszewska K, Majchrowicz B, Snarska K, Telega D. Stress and Occupational Burnout of Nurses Working with COVID-19 Patients. IJERPH. 2022;19(19):12688. DOI: 10.3390/ijerph191912688

xxi. Konlan KD, Asampong E, Dako-Gyeke P, Glozah FN. Burnout syndrome among healthcare workers during COVID-19 Pandemic in Accra, Ghana. PLoS ONE. 2022;17(6):e0268404. DOI: 10.1371/journal.pone.0268404

xxii. Safiye T, Vukčević B, Gutić M, Milidrag A, Dubljanin D, Dubljanin J, *et al.* Resilience, Mentalizing and Burnout Syndrome among Healthcare Workers during the COVID-19 Pandemic in Serbia. IJERPH. 2022;19(11):6577. DOI: 10.3390/ijerph19116577

xxiii. O'Higgins M, Rojas LA, Echeverria I, Roselló Jiménez L, Benito A, Haro G. Burnout, psychopathology and purpose in life in healthcare workers during COVID-19 pandemic. Front. Public Health. 2022;10:926328. DOI: 10.3389/fpubh.2022.926328

xxiv. Ulbrichtova R, Svihrova V, Tatarkova M, Svihra J, Novak M, Hudeckova H. Prevalence of Burnout Syndrome in COVID-19 and Non-COVID-19 Units in University Hospital: A Cross-Sectional Study. IJERPH. 2022;19(19):12664. DOI: 10.3390/ijerph191912664

xxv. Noh EY, Park YH, Chai YJ, Kim HJ, Kim E. Frontline nurses' burnout and its associated factors during the COVID-19 pandemic in South Korea. Applied Nursing Research. 2022;67:151622. DOI: 10.1016/j.apnr.2022.151622

xxvi. Molina Velásquez JI, Erazo Salas SP. ¿Se deben investigar los factores de riesgo para COVID-19 ante la probabilidad que sea endémica? Alerta. 2021;4(2):88-89. DOI: 10.5377/alerta.v4i2.11058

xxvii. Pala AN, Chuang JC, Chien A, Krauth DM, Leitner SA, Okoye NM, *et al.* Depression, anxiety, and burnout among hospital workers during the COVID-19 pandemic: A cross-sectional study. PLoS ONE. 2022;17(12):e0276861. DOI: 10.1371/journal.pone.0276861

xxviii. Alkhamees AA, Aljohani MS, Kalani S, Ali AM, Almatham F, Alwabili A, *et al.* Physician's Burnout during the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. IJERPH. 2023;20(5):4598. DOI: 10.3390/ijerph20054598

xxix. Marzo RR, Khaled Y, ElSherif M, Abdullah MSAMB, Zhu Thew H, Chong C, *et al.* Burnout, resilience and the quality of life among Malaysian healthcare workers during the COVID-19 pandemic. Front. Public Health. 2022;10:1021497. DOI: 10.3389/fpubh.2022.1021497

xxx. Mushtaque I, Raza AZ, Khan AA, Jafri QA. Medical Staff Work Burnout and Willingness to Work during COVID-19 Pandemic Situation in Pakistan. Hospital Topics. 2022;100(3):123-131. DOI: 10.1080/00185868.2021.1927922

xxxi. Feliciano P, Mootz JJ, Suleman A, Su AY, Khan S, Gouveia L, *et al.* The impact of COVID-19 on self-reported burnout and health and mental health services in Nampula, Mozambique. Front. Public Health. 2022;10:951270. DOI: 10.3389/fpubh.2022.951270

xxxii. Sexton JB, Adair KC, Proulx J, Profit J, Cui X, Bae J, *et al.* Emotional Exhaustion Among US Health Care Workers Before and During the COVID-19 Pandemic, 2019-2021. JAMA Netw Open. 2022;5(9):e2232748. DOI: 10.1001/jamanetworkopen.2022.32748

xxxiii. Amro TM, Arcos González P, Montero Viñuales E, Castro Delgado R. Impact of COVID-19 Pandemic on Stress and Burnout Levels amongst Emergency Medical Technicians: A Cross-Sectional Study in Spain. Annals of Medicine. 2022;54(1):3006-3015. DOI: 10.1080/07853890.2022.2137735

xxxiv. Restauri N, Sheridan AD. Burnout and Posttraumatic Stress Disorder in the Coronavirus Disease 2019 (COVID-19) Pandemic: Intersection, Impact, and Interventions. Journal of the American College of Radiology. 2020;17(7):921-926. DOI: 10.1016/j.jacr.2020.05.021

Narrative review

Clinical Use of Intravenous Lidocaine for Management of non-Oncologic Neuropathic Pain in Adults

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Uso clínico de lidocaína intravenosa para manejo de dolor neuropático no oncológico en adultos

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Abstract
Neuropathic pain is common in clinical practice; it is estimated that 2 to 3 % of the global population is affected; a considerable number of patients present pain refractory to existing treatments, making it a diagnostic and therapeutic challenge. The objective of this study is to describe the clinical use of intravenous lidocaine for the management of non-cancer neuropathic pain in adults. The information search was performed by consulting the HINARI, SciELO and PubMed databases. Articles with an obsolescence of no more than five years, both in English and Spanish, were selected. Original articles, clinical trials, bibliographic reviews and meta-analyses were used. The causes of neuropathic pain in which lidocaine has been used were postherpetic neuralgia, diabetic neuropathy, and trigeminal neuralgia. The use of intravenous lidocaine has been shown to decrease pain intensity; however, when compared with other first line drugs, there are no long-term differences. Most side effects occur in the nervous, gastrointestinal, and cardiovascular systems. Intravenous lidocaine as monotherapy for the management of non-cancer neuropathic pain, although effective in the short term with doses of 3-5 mg/Kg, does not have a persistent and long-lasting effect.

Keywords
Lidocaine, Infusions, Intravenous, Neuralgia, Analgesia.

Resumen
El dolor neuropático es común en la práctica clínica. Se estima que afecta entre el 2 y 3 % de la población a nivel global. Una cantidad considerable de pacientes presentan dolor refractario a tratamientos existentes, volviéndolo un reto diagnóstico y terapéutico. El objetivo de este estudio es describir el uso clínico de lidocaína intravenosa para manejo de dolor neuropático no oncológico en adultos. La búsqueda de información se realizó consultando las bases de datos HINARI, SciELO y PubMed. Se seleccionaron artículos en inglés y español de 2017 a 2021. Se utilizaron artículos originales, ensayos clínicos, revisiones bibliográficas y metaanálisis. Las causas de dolor neuropático en las que ha sido utilizada la lidocaína son la neuralgia posherpética, neuropatía diabética y neuralgia del trigémino. El uso de lidocaína intravenosa demostró que disminuye la intensidad del dolor; sin embargo, al compararlo con otros fármacos de primera línea no hay diferencias a largo plazo. La mayoría de efectos secundarios se presentan en el sistema nervioso, gastrointestinal y cardiovascular. La lidocaína intravenosa como monoterapia para manejo de dolor neuropático no oncológico, si bien fue eficaz a corto plazo con dosis de 3-5 mg/Kg, no tuvo un efecto persistente y duradero.

Palabras clave
Lidocaína, Infusiones Intravenosas, Neuralgia, Analgesia.

Introduction

The International Association for the Study and Treatment of Pain (IASP) defines neuropathic pain as pain caused by injury, dysfunction, or transient impairment of the nervous system. This pain is usually chronic, persisting continuously or intermittently.[i] It can result from etiologically diverse disorders affecting the peripheral or central system, depending on the location of the nerve lesion or dysfunction.[ii] Estimations of world population affected are between 2 to 3 %.[iii]

Its prevalence has been described in several countries, varying from 3.3 % in Austria to 6.9 % in France, 8 % in the United Kingdom, and Latin America, it is estimated to affect 2 % of the population.[iv]

Neuropathic pain can be responsible for a substantial financial burden for those affected, as total costs per patient ranged from 9305 EUR in Italy to 14 446 EUR per year in Germany, with the majority spent on indirect costs associated with care.[v,vi]

Neuropathic pain associated with symptoms such as allodynia, hyperalgesia and paresthesia[vii] impairs the patient's psychological and physical state. It is a common symptom in clinical practice and considerably affects people's quality of life. Many patients present pain that is refractory to existing treatments;[viii] observations of patients with similar etiology reported that not all respond in the same way to the same treatments, so there is no single specific treatment for neuropathic pain, being it considered a more complex entity that is difficult to control, which presents a health problem.[iii,x]

Over time, the use of drugs in the management of neuropathic pain, such as antiepileptics, NMDA receptor antagonists, and antidepressants, has proved to be useful; nevertheless, studies on efficacy and safety are still in progress. However, while 50 % of patients achieve a reduction of 30 to 40 % of their pain measured on a visual analog scale, between 40 to 70 % of patients do not achieve complete pain control.[xi,xii]

The IASP Neuropathic Pain Special Interest Group (NeuPSIG) Evaluation Committee proposes gamma-aminobutyric acid analogue anticonvulsants (gabapentin, pregabalin), tricyclic antidepressants (amitriptyline) and selective serotonin-norepinephrine reuptake inhibitors as first-line drugs. Intravenous lidocaine, capsaicin, and tramadol as second-line management, and opioids (morphine, oxycodone) were added as third-line treatment for neuropathic pain.[vii]

A study by Wang *et al.* compared the use of morphine and pregabalin as monotherapy and combination therapy for neuropathic pain management. From a total of 320 eligible patients, 265 were excluded due to the adverse effects of these drugs, concluding that, of the 55 patients selected, those who received combined therapy had a better safety and efficacy profile in the management of neuropathic pain ($p < 0.01$), compared to patients who received morphine or pregabalin in monotherapy.

Epidemiological surveys show that a large proportion of patients with neuropathic pain do not receive adequate treatment.[xiii] Evidence shows that less than 50 % of patients achieve appropriate pain control in the short term. It is increasingly important to reduce chronic complications and to comply with a sound safety profile.[xiv] Lidocaine infusion has an adequate safety profile with several desirable properties in the clinical setting.[xv]

Lidocaine is a local anesthetic of the amino amide type, which acts by decreasing the permeability of the neuronal membrane to sodium ions, inhibiting depolarization; therefore, it interrupts the propagation of the action potential and nerve conduction, resulting in a central anti-hyperalgesic effect.[xvi,xvii] In recent years, intravenous lidocaine has been used as an alternative for the management of neuropathic pain at low doses of 1.5 mg/Kg to 3 mg/Kg, achieving a significant decrease in pain by visual analog scale in the short term.[xviii]

In a study by Kim *et al.*, intravenous lidocaine administered at a dose of 3 mg/Kg for one hour was found to reduce the numerical pain rating scale scores in patients with postherpetic neuralgia or complex regional pain syndrome type II compared to the control group ($p = 0{,}011$).[xix]

This paper is a narrative literature review article. Information search was conducted by consulting HINARI, SciELO, and PubMed databases. Regarding data collection, published articles in Spanish and English from 2017 to 2021 were selected. Original articles, clinical trials, literature reviews, and meta-analyses using boolean connector AND: neuropathic pain AND intravenous lidocaine, lidocaine infusion, AND side effects were applied. The objective of this review is to describe the clinical use of intravenous lidocaine for the management of non-oncologic neuropathic pain in adults.

Discussion

Causes of non-oncologic neuropathic pain for which lidocaine is commonly used

Neuropathic pain is characterized by not directly affecting the pain receptors but rather, as a result of a lesion at the nervous system level: it can be of central or peripheral origin. Central origin causes are due to an alteration in the spinal cord or brain, such as multiple sclerosis, stroke, and spinal cord injury. They account for 1 to 12 % of neuropathic pain following the above-mentioned pathologies.[xx,xxi] As for peripheral origin, nerve plexuses, spinal cord roots, or directly to a peripheral nerve are affected,[xxii] the most frequent causes being polyneuropathy secondary to diabetes and HIV, post-herpetic neuralgia, post-surgical neuralgia, trigeminal neuralgia, and post-traumatic injury; the latter are the pathologies in which intravenous lidocaine has been used.[xxiii]

Postherpetic neuralgia is the most common complication of Herpes Zoster virus, affecting one in five patients. It is a pain that follows the dermatomic distribution; it presents as continuous or paroxysmal, evoked or spontaneous, lancinating with sensory alterations of the skin. Pain occurs in a sustained manner for at least 90 days; those over 60 years old are more likely (3.3 %) to develop the complication 12 months after infectionn.[xxiv,xxv]

Diabetic neuropathy is a loss of sensory function with onset in the distal parts of the extremities; most symptoms are numbness, weakness, and paresthesias. The early manifestations of this disease can often go unnoticed and may be detected at an irreversible point. At least 50 % of diabetic patients develop this complication.[xxvi,xxvii] Daykin *et al.* found significant reductions in pain in postherpetic neuralgia and diabetic neuropathy using doses of lidocaine 1 mg/Kg and 5 mg/Kg for 60 minutes and one week apart. They also reported significant changes compared to placebo, but there were no differences between the different doses of lidocaine.[xxviii] Yousefshashi *et al.* concluded that the use of intravenous lidocaine is effective in the management of postherpetic neuralgia and diabetic neuropathy in the short term, as opposed to 5 % lidocaine patches due to the limitation of not being able to cover the entire affected area.[xxix]

Trigeminal neuralgia refers to a short electric shock-like pain of abrupt onset and termination, which manifests in one or more divisions of the trigeminal nerve.[xxx]

In one study, Xu *et al.* performed a retrospective analysis of a cohort in which seven patients, refractory to surgical and pharmacological treatment for trigeminal neuralgia used the standard protocol of IV infusion of 1.25 g magnesium and 100 mg lidocaine in 100 mL of normal saline administered for one hour, once a week for a total of three weeks. They noted that all subjects experienced pain relief after combined intravenous infusion therapy using a numerical pain intensity scale at the end of four weeks.[xxxi]

Moore *et al.* evaluated the role of lidocaine infusion in a double-blind randomized controlled study in 20 patients; they compared lidocaine (5 mg/Kg) in 250 mL of 5 % dextrose solution against placebo in one hour and found that both lidocaine and placebo reduced pain intensity at the end of each session. However, lidocaine achieved a higher reduction compared to placebo ($p < 0.001$).[xxxii]

Fibromyalgia is a condition characterized by chronic musculoskeletal pain, hyperalgesia in different regions, and psychomotor symptoms such as anxiety, depression, and cognitive dysfunction, with a higher prevalence in women over 50 years old.[xxxiii] The pathophysiology or cause is not yet well established. Two theories under investigation mention alterations in the regulation of neurotransmitters or changes in the function of the immune system following a viral infection.[xxxiv]

In a randomized, double-blinded study, Albertoni *et al.* evaluated the effect of intravenous lidocaine compared to saline in 42 patients for pain relief in fibromyalgia. They used doses of 240 mg in one week for a duration of four weeks without obtaining a significant impact on pain relief.[xxxv]

Dose-response and most appropriate treatment timeframe

Neuropathic pain results from aberrant up-regulated sodium channels responsible for neuronal hyperexcitability after nerve injury.[xxxvi] Lidocaine blocks these channels, and several studies show that intravenous lidocaine infusion provides significant relief.[xxxvii] The dose usually used is 1 mg/Kg as an initial bolus, followed by a continuous infusion of 0.5 to 3 mg/Kg for one hour, with the most commonly used and best-described dose being a continuous infusion of 2 mg/Kg for one hour.[xxxviii]

In a retrospective study (n = 85) using intravenous lidocaine infusions at a dose of 5 mg/kg for 30 minutes once a week, Przeklasa *et al.* showed relief of pain symptoms using a numerical rating scale describing that the older the patients and the greater the number of infusions the better the therapeutic effect ($p < 0.05$, $p < 0.01$ respectively). (Table 1)[xxxix]

Regarding the duration of treatment, Tan *et al.* studied the therapeutic effects of daily intravenous infusion of lidocaine as monotherapy versus the usual therapy for postherpetic neuralgia in a population of n = 60, demonstrating that the one-hour infusion of 4 mg/kg for five consecutive days reduced the intensity of pain and the frequency of eruptive pain compared to the control group ($p < 0.001$). In addition, it reduced tramadol consumption in those patients who used this infusion ($p < 0.05$).[xl]

Clattenburg *et al.* compared the efficacy of intravenous lidocaine versus intravenous morphine in 32 patients in an unblinded, randomized, controlled study. They used bolus loading of 1.5 mg/Kg for 10 minutes, followed by 1.5 mg/Kg for 50 minutes for a total of approximately 3 mg/Kg/hr of lidocaine. They concluded that it provides clinically significant analgesia on the numerical

pain rating scale, with results similar to morphine, and also, it reduces opioid utilization. (Table 1)[xli]

Liu *et al.*, in a randomized double-blind study in 197 patients, compared the use of lidocaine at 5 mg/Kg for 1.5 hours versus placebo (normal saline) to assess analgesic efficacy and emotional response. They found that, although there was a reduction in the visual analog scale score for pain, it was not statistically significant versus control group ($p < 0.05$). In contrast, there was an statistical significant decrease in analgesic consumption in the group that received lidocaine infusions ($p < 0.05$).[xlii]

In contrast to the previous study in which only short-term infusions were used, Dwight *et al.* conducted a double-blind, randomized trial in patients with chronic neuropathic pain of peripheral nerve origin (n = 34), compared the use of intravenous lidocaine at a dose of 5 mg/Kg versus placebo (diphenhydramine), to determine significant relief of neuropathic pain and an improvement in quality of life in the long term (four weeks), concluding that there was no significant analgesic difference between the two groups in the long term ($p = 0.61$).[xliii]

Side effects and their frequency

Considering the benefits of intravenous lidocaine for the management of neuropathic pain, the safety profile regarding side effects and the dose used, should be kept in mind. According to the FDA, the dose of lidocaine without epinephrine should not exceed 5 mg/Kg; above these doses, plasma concentrations of 3 µg/mL, 5 µg/mL (paresthesias, fasciculations, tinnitus), and 7 µg/mL can be found, the latter being where convulsions, coma, and cardiorespiratory arrest appear.[xliv,xlv] Most side effects occur in the nervous, gastrointestinal, and cardiovascular systems; these adverse effects resolve when the infusion dose is lowered or stopped completely.[xlvi]

In a study conducted by Zavaleta *et al.*, in which they used intravenous lidocaine 2 % in acute postherpetic neuralgia in doses of 2 to 5 mg x Kg of weight, they observed that side effects occurred in 100 % of the patients, especially drowsiness and metallic taste ($p < 0.01$).[xlvii]

In another retrospective analysis of a sample of 233 patients, Iacob *et al.* documented that 46 % of the participants reported mild side effects, the most frequent being at the nervous system level. They also reported that the duration of these effects did not persist for more than three hours. The researchers consider it important to take electrocardiograms, and serum lidocaine levels, and monitor vital signs during infusions every 3 to 5 minutes.[xlviii] Guillén *et al.* reported no side effects using lidocaine at a

Table 1. Comparison of main articles in the literature review

Study	Type of study	n	Dosage	Clinical effect	Side effects
Reeves, DJ and Foster (2017)	Retrospective analysis	21	0.2-2.8 mg/Kg/h	Pain relief $p < 0.001$	Cognitive impairment, delirium, dizziness, perioral numbness and drowsiness.
Moulin *et al.* (2019)	Crossover , double-blind, randomized trial	34	5 mg/Kg	Pain relief $p = 0.61$	Drowsiness, xerostomia, abdominal discomfort and dizziness.
Zavaleta and Álvarez (2017)	Prospective, longitudinal, comparative and experimental	30	2-5 mg/Kg	Pain relief $p < 0.01$	Drowsiness, dysgeusia, hypotension, dizziness.
Iacob *et al.* (2018)	Retrospective analysis	233	1000 mg/h	Pain relief $p < 0.001$	Perioral numbness, dizziness, tinnitus, nausea, numbness.
Przeklasa *et al.* (2016)	Retrospective analysis	85	5 mg/Kg	Pain relief $p < 0.05$	None reported.
Guillén-Ramírez *et al.* (2019)	Controlled, randomized, triple-blind clinical trial	29	2 mg/Kg	Pain relief $p < 0.01$	None reported.
Kim *et al.* (2018)	Prospective parallel, double-blind, controlled, controlled study	42	3 mg/Kg	Pain relief $p = 0.011$	Chest tightness
Clattenburg E *et al.* (2019)	Controlled, randomized non-blind study	32	3 mg/Kg/h	Pain relief	Paresthesia, nausea, pruritus.
Liu *et al.* (2018)	Randomized double-blind study	197	5 mg/Kg/h	Pain relief $p < 0.05$	Dizziness, xerostomy, headache, drowsiness.
Tan *et al.* (2019)	Randomized double-blind study	60	4 mg/Kg/h	Pain relief $p < 0.001$	Drowsiness, xerostomy, paresthesias.

dose of 2 mg/Kg; they also suggested taking electrocardiograms and vital signs every 15 minutes during infusionss.[xlix]

Reeves *et al.* conducted a retrospective study of 21 patients with neuropathic pain using lidocaine at low doses of 0.5 to 2 mg/Kg; they reported side effects in five patients, at the nervous system and gastrointestinal level, such as drowsiness, dizziness, perioral numbness, among others. The researchers concluded that it is important to establish a specific dose for each patient and measure blood lidocaine levels; although no cardiac side effects were reported, they suggested having a history of cardiovascular medical history such as atrial fibrillation or sinus tachycardia should be available before administering the drug intravenously. (Tabla 1)[l]

If studies continue to show encouraging results, lidocaine infusion may be a viable option for patients who have long struggled to find relief from their symptoms.

Conclusion

According to the consulted literature, intravenous lidocaine has been used as monotherapy for the management of non-oncologic neuropathic pain. Although it is effective in short-term pain control with variable doses in the range of 3 to 5 mg/Kg, it does not have a persistent and lasting effect. Regarding its safety, no serious adverse effects were reported; however, it is associated with a higher frequency of mild side effects at the nervous system and gastrointestinal level compared to other drugs. Further research with standardized protocols on intravenous lidocaine infusion therapy in neuropathic pain is needed to fully understand the efficacy of this medication.

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References

i. Orozco H, Mercado MA. Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubiran." Arch. Surg. 2003;138(9):940. DOI: 10.1001/archsurg.138.9.940

ii. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, *et al.* The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. PAIN. 2019;160(1):53-59. DOI: 10.1097/j.pain.0000000000001365

iii. Rodríguez R, Loop R. Tratamiento farmacológico del dolor neuropático: actualización y controversias. Butlletí D'informació Ter. 2019;30(3):14-19. Available at: https://scientiasalut.gencat.cat/bitstream/handle/11351/4076/BIT_2019_30_03_cas.pdf?sequence=5&isAllowed=y

iv. Bouhassira D. Neuropathic pain: Definition, assessment and epidemiology. Revue Neurologique. 2019;175(1-2):16-25. DOI: 10.1016/j.neurol.2018.09.016

v. Abd-Elsayed A. Infusion Therapy: For Pain, Headache and Related Conditions. Cham. Springer International Publishing; 2019. 223 p.

vi. Udall M, Kudel I, Cappelleri JC, Sadosky A, King Concialdi K, Parsons B, *et al.* Epidemiology of physician-diagnosed neuropathic pain in Brazil. J. Pain Res. 2019;12:243-253. DOI: 10.2147/JPR.S160504

vii. Cavalli E, Mammana S, Nicoletti F, Bramanti P, Mazzon E. The neuropathic pain: An overview of the current treatment and future therapeutic approaches. Int. J. Immunopathol. Pharmacol. 2019;33:205873841983838. DOI: 10.1177/2058738419838383

viii. Macone A, Otis J. Neuropathic Pain. Semin. Neurol. 2018;38(6):644-653. DOI: 10.1055/s-0038-1673679

ix. St. John Smith E. Advances in understanding nociception and neuropathic pain. J. Neurol. 2018;265(2):231-238. DOI: 10.1007/s00415-017-8641-6

x. VanDenKerkhof EG, Mann EG, Torrance N, Smith BH, Johnson A, Gilron I. An Epidemiological Study of Neuropathic Pain Symptoms in Canadian Adults. Pain Res. Manag. 2016;2016:1-13. DOI: 10.1155/2016/9815750

xi. Bouchenaki H, Bégou M, Magy L, Hajj R, Demiot C. Les traitements pharmacologiques des douleurs neuropathiques. Therapies. 2019;74(6):633-643. DOI: 10.1016/j.therap.2019.04.003

xii. Neuropathic pain in adults: pharmacological management in non-specialist settings. London, England: NICE; 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK552848/

xiii. Guerrero G, Tapia D, Leyva R, Serrano I, García C. Infusión continua de lidocaína en pacientes operados de cirugía oncológica. Serie de casos. Multimed Rev. Médica Granma. 2018;22(3):650-660. Available at: https://revmultimed.sld.cu/index.php/mtm/article/view/895

xiv. Gierthmühlen J, Baron R. Neuropathic Pain. Semin. Neurol. 2016;36(5):462-468. DOI: 10.1055/s-0036-1584950

xv. González Obregón MP, Bedoya López MA, Ramírez AC, Vallejo Agudelo E. Lidocaine

infusion, basics and clinical issues. Colomb. J. Anesthesiol. 2021;50(2): e966. DOI: 10.5554/22562087.e966

xvi. Yang X, Wei X, Mu Y, Li Q, Liu J. A review of the mechanism of the central analgesic effect of lidocaine. Medicine (Baltimore). 2020;99(17):e19898. DOI: 10.1097/MD.0000000000019898

xvii. Estebe J-P. Intravenous lidocaine. Best Pract. Res. Clin. Anaesthesiol. 2017;31(4):513-521. DOI: 10.1016/j.bpa.2017.05.005

xviii. Martínez Cañas LG, Rodríguez Paz MA, Moreno EY, López Saca JM. Lidocaína para el alivio del dolor en pacientes de cuidados paliativos, una serie de casos. Alerta Rev. Científica Inst. Nac. Salud. 2023;6(2):179-184. DOI: 10.5377/alerta.v6i2.16413

xix. Kim Y-C, Castañeda AM, Lee C, Jin H-S, Park KS, Moon JY. Efficacy and Safety of Lidocaine Infusion Treatment for Neuropathic Pain: A Randomized, Double-Blind, and Placebo-Controlled Study. Reg. Anesth. Pain Med. 2018;43(4):415-424. DOI: 10.1097/AAP.0000000000000741

xx. Bendaña JE. Dolor neuropático: actualización en definiciones y su tratamiento farmacológico. Rev. Médica Hondureña. 2020;88(1):48-51. DOI: 10.5377/rmh.v88i1.11591

xxi. Pasero C. Intravenous Lidocaine for Acute Pain Treatment. J. Perianesth. Nurs. 2011;26(3):166-169. DOI: 10.1016/j.jopan.2011.03.002

xxii. Lara Solares A, Mayoral Rojals V, Guillén Núñez MDR, Villafaña Tello JDJS, Cantú Brito C, Genis Rondero MÁ, *et al.* Consenso multidisciplinario de diagnóstico y tratamiento del dolor neuropático periférico y localizado en México. Gac. Médica México. 2019;155(4):428-435. DOI: 10.24875/GMM.19005195

xxiii. Plancarte Sánchez R, Samano García M, Guillén Núñez MDR, Equihua Ortega A. Localized neuropathic pain. Gac. Médica México. 2023;157(3):302-308. DOI: 10.24875/GMM.M21000562

xxiv. Saguil A, Kane S, Mercado M, Lautters R. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. Am. Fam. Physician. 2017;96(10):556-663. Available at: https://www.aafp.org/pubs/afp/issues/2017/1115/p656.html

xxv. Lin CS. Interventional Treatments for PostherpeticNeuralgia: A Systematic Review. Pain Physician. 2019;3(22;3):209-228. DOI: 10.36076/ppj/2019.22.209

xxvi. Çakici N, Fakkel TM, Van Neck JW, Verhagen AP, Coert JH. Systematic review of treatments for diabetic peripheral neuropathy. Diabet. Med. 2016;33(11):1466-1476. DOI: 10.1111/dme.13083

xxvii. Selvarajah D, Kar D, Khunti K, Davies MJ, Scott AR, Walker J, *et al.* Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention. Lancet Diabetes Endocrinol. 2019;7(12):938-948. DOI: 10.1016/S2213-8587(19)30081-6

xxviii. Daykin H. The efficacy and safety of intravenous lidocaine for analgesia in the older adult: a literature review. Br. J. Pain. 2017;11(1):23-31. DOI: 10.1177/2049463716676205

xxix. Yousefshahi F, Predescu O, Francisco Asenjo J. The Efficacy of Systemic Lidocaine in the Management of Chronic Pain: A Literature Review. Anesthesiol. Pain Med. 2017;7(3):e44732. DOI: 10.5812/aapm.44732

xxx. Cruccu G. Trigeminal Neuralgia. Contin. Lifelong Learn. Neurol. 2017;23(2):396-420. DOI: 10.1212/CON.0000000000000451

xxxi. Xu M, Chen P, Zhu X, Wang C. Efficacy of intravenous lidocaine and magnesium in intractable trigeminal neuralgia: A preliminary report. J. Neurol. Sci. 2016;371:149-151. DOI: 10.1016/j.jns.2016.09.017

xxxii. Moore D, Chong MS, Shetty A, Zakrzewska JM. A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia. Br. J. Anaesth. 2019;123(2):e385-e396. DOI: 10.1016/j.bja.2019.05.026

xxxiii. Araújo FM, DeSantana JM. Physical therapy modalities for treating fibromyalgia. F1000Research. 2019;8:2030. DOI: 10.12688/f1000research.17176.1

xxxiv. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia Pathogenesis and Treatment Options Update. Curr. Pain Headache Rep. 2016;20(4):25. DOI: 10.1007/s11916-016-0556-x

xxxv. Albertoni Giraldes AL, Salomão R, Leal PDC, Brunialti MKC, Sakata RK. Effect of intravenous lidocaine combined with amitriptyline on pain intensity, clinical manifestations and the concentrations of IL -1, IL -6 and IL -8 in patients with fibromyalgia: A randomized double-blind study. Int. J. Rheum. Dis. 2016;19(10):946-953. DOI: 10.1111/1756-185X.12904

xxxvi. Meacham K, Shepherd A, Mohapatra DP, Haroutounian S. Neuropathic Pain: Central vs. Peripheral Mechanisms. Curr. Pain Headache Rep. 2017;21(6):28. DOI: 10.1007/s11916-017-0629-5

xxxvii. Challapalli V, Tremont Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst. Rev. 2005;2020(10). DOI: 10.1002/14651858.CD003345.pub2

xxxviii. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. BJA Educ. 2016;16(9):292-298. DOI: 10.1093/bjaed/mkw008

xxxix. Przeklasa Muszyńska A, Kocot Kępska M, Dobrogowski J, Wiatr M, Mika J. Intravenous lidocaine infusions in a multidirectional model of treatment of neuropathic pain patients. Pharmacol. Rep. 2016;68(5):1069-1075. DOI: 10.1016/j.pharep.2016.06.010

xl. Tan X, Ma L, Yuan J, Zhang D, Wang J, Zhou W, *et al.* Intravenous infusion of lidocaine enhances the efficacy of conventional treatment of postherpetic neuralgia. J. Pain Res. 2019;12:2537-2545. DOI: 10.2147/JPR.S213128

xli. Clattenburg EJ, Nguyen A, Yoo T, Flores S, Hailozian C, Louie D, *et al.* Intravenous Lidocaine Provides Similar Analgesia to Intravenous Morphine for Undifferentiated Severe Pain in the Emergency Department: A Pilot, Unblinded Randomized Controlled Trial. Pain Med. 2019;20(4):834-839. DOI: 10.1093/pm/pny031

xlii. Liu H, Lu F, Zhou D, Yin Y, Li J, Yang B, *et al.* The Analgesic and Emotional Response to Intravenous Lidocaine Infusion in the Treatment of Postherpetic Neuralgia: A Randomized, Double-Blinded, Placebo-controlled Study. Clin. J. Pain. 2018;34(11):1025-1031. DOI: 10.1097/AJP.0000000000000623

xliii. Moulin DE, Morley-Forster PK, Pirani Z, Rohfritsch C, Stitt L. Intravenous lidocaine in the management of chronic peripheral neuropathic pain: a randomized-controlled trial. Can. J. Anesth. Can. Anesth. 2019;66(7):820-827. DOI: 10.1007/s12630-019-01395-8

xliv. Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine. Anesthesiology. 2017;126(4):729-737. DOI: 10.1097/ALN.0000000000001527

xlv. Ochoa Anaya G, Aguirre Ibarra C, Franco Cabrera M. Lidocaína: aspectos generales y nuevas implicaciones en la inflamación. Rev. Mex. Anestesiol. 2017;40(3):220-225. Available at: https://www.medigraphic.com/pdfs/rma/cma-2017/cma173j.pdf

xlvi. Lancaster RJ, Wren K, Hudson A, Leavitt K, Albala M, Tischaefer D. Intravenous Lidocaine for Chronic Neuropathic Pain A Systematic Review Addressing Nursing Care. Pain Manag. Nurs. 2020;21(2):194-200. DOI: 10.1016/j.pmn.2019.06.008

xlvii. Zavaleta Avalos R. Eficacia de la lidocaína al 2% más triamcinolona por bloqueo en sábana y lidocaína intravenosa al 2% en neuralgia post herpética aguda. Tesis doctoral. Trujillo. Universidad privada Antenor Orrego; 2014. 54 p.

xlviii. Iacob E, Hagn EE, Sindt J, Brogan S, Tadler SC, Kennington KS, *et al.* Tertiary Care Clinical Experience with Intravenous Lidocaine Infusions for the Treatment of Chronic Pain. Pain Med. 2018;19(6):1245-1253. DOI: 10.1093/pm/pnx167

xlix. Guillén Ramírez NT, Jiménez Olvera M, Morales Águila MA, López López CO, RedingBernal A, Arista Villanueva JC, *et al.* Dexmedetomidina versus lidocaína intravenosa en el tratamiento del dolor irruptivo y la funcionalidad en pacientes con canal lumbar estrecho. Rev. Soc. Esp. Dolor. 2018;26(1):14-20. DOI: 10.20986/resed.2018.3656/2018

l. Reeves DJ, Foster AE. Continuous Intravenous Lidocaine Infusion for the Management of Pain Uncontrolled by Opioid Medications. J. Pain Palliat. Care Pharmacother. 2017;31(3-4):198-203. DOI: 10.1080/15360288.2017.1313356

Narrative review

Intermittent Fasting and Caloric Restriction as an Adjunctive Treatment in Alzheimer's Disease and Multiple Sclerosis

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Abstract
Alzheimer's disease and multiple sclerosis are neurodegenerative disorders with expensive and complex treatments aimed at reducing the progression of symptoms. However, due to the lack of adequate therapies and the possible adverse effects caused by first-line treatments, it's necessary to implement better complementary therapeutic approaches that do not produce major side effects and improve symptoms. Caloric restriction and intermittent fasting have been shown to be novel and beneficial strategies in neurodegenerative diseases, through immune, metabolic, and physiological mechanisms. To determine the use of intermittent fasting and caloric restriction as a new treatment in multiple sclerosis and Alzheimer's disease, a narrative review of original articles in both national and international scientific journals, in English and Spanish languages with no greater obsolescence than five years. The use of caloric restriction and intermittent fasting have generated positive changes, producing a decrease in pro-inflammatory states, oxidative stress, and aging. Approaches that modulate disease progression and improve cognitive function of adenosine monophosphate kinase, insulin-like growth factor, and sirtuin enzyme pathways are considered, generating a neuroprotective effect.

Keywords
Intermittent Fasting, Caloric Restriction, Multiple Sclerosis, Alzheimer Disease, Cognition.

Resumen
Las enfermedades de Alzheimer y esclerosis múltiple son neurodegenerativas, con tratamientos complejos y de costos elevados, orientados a disminuir la progresión de la sintomatología. Sin embargo, a causa de la falta de terapias adecuadas y de los posibles efectos adversos ocasionados por tratamientos de primera línea, es necesario implementar mejores abordajes terapéuticos complementarios que no produzcan mayores efectos secundarios y mejoren la sintomatología de dichas patologías. La restricción calórica y el ayuno intermitente han demostrado ser estrategias novedosas y beneficiosas en enfermedades neurodegenerativas, a través de mecanismos inmunitarios, metabólicos y fisiológicos. Con el objetivo de determinar el uso del ayuno intermitente y la restricción calórica como tratamiento coadyuvante en esclerosis múltiple y enfermedad de Alzheimer, se realizó una revisión narrativa de artículos originales en revistas científicas, en idiomas inglés y español, de 2018 a 2022. El uso de la restricción calórica y ayuno intermitente han generado cambios positivos produciendo disminución de estados proinflamatorios, estrés oxidativo y envejecimiento. Se consideran abordajes que modulan la progresión de la enfermedad y mejoran la función cognitiva por vías de señalización de monofosfato de adenosina cinasa, factor de crecimiento similar a la insulina y la enzima sirtuina, generando un efecto neuroprotector.

Palabras clave
Ayuno Intermitente, Restricción Calórica, Esclerosis Múltiple, Enfermedad de Alzheimer, Cognición.

OPEN ACCESS

Ayuno intermitente y restricción calórica como tratamiento coadyuvante en enfermedad de Alzheimer y esclerosis múltiple

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Introduction

Neurodegenerative diseases such as multiple sclerosis (MS) and Alzheimer's disease (AD) are characterized by a progressive loss of neurons and white matter that can lead to brain atrophy and different types of disability. Both diseases represent a health problem, as their prevalence has been increasing, and their treatments are considered complex.[i]

It is estimated that a total of 2.8 million people are living with MS worldwide, i.e. 35.9 per 100 000 population.[ii] MS is considered one of the main causes of disability in young patients, and its diagnosis is usually in the fourth decade of life.[iii] Regarding AD, the average age at which diagnosis is established is 65 years, although its onset at a younger age is increasingly frequent.[iv] In addition, it has been shown that AD is the cause of 60 to 80 % of all cases of dementia worldwide. The World Health Organization establishes that Latin America and the Caribbean will be the most affected, reaching 7.6 million patients by 2030.[v]

There are several drugs approved for MS, interferons being the first line of therapy, which cause flu-like effects in most patients.[vi] For this reason, it becomes necessary to find therapeutic alternatives that do not entail major side effects and can improve the symptomatology of these patients.[vii] Different nutritional approaches have been currently described as neuroprotective strategies for neurodegenerative diseases, but their mechanism of action is still under study.[viii]

Caloric restriction (CR) and intermittent fasting (IF) have been proposed as adjuvant treatments. However, the majority of clinical trials in which they are implemented have focused on overweight, metabolically compromised, or middle-aged populations. Therefore, it is necessary to adequately assess the potential benefits of these nutritional approaches.[ix]

The use of ketogenic diets such as IF and CR have demonstrated certain benefits in neurodegenerative pathologies and have been proposed as a novel strategy to improve symptoms in these chronic diseases.[x,xi] The relevance of these diets is greater due to the multiple benefits observed in patients with different metabolic pathologies. These diets also have been shown to significantly reduce cardiometabolic risk.[xii] In addition, these nutritional interventions have the advantage of not presenting side effects in addition to those caused by conventional treatment and even reducing them.[xiii]

The relationship between caloric intake, diet quality, and meal frequency with the gut microbiota and its role in regulating cellular pathways in diseases such as AD and MS has been described.[xiv] This regulation is believed to positively impact these diseases by promoting normal aging and delaying disease progression.[xv,xvi]

Methodology

A narrative literature review article was prepared by searching for original and review articles of clinical and preclinical studies in international scientific journals in English and Spanish, in databases such as PubMed, Embase, and sites of international organizations related to the topic of interest. The search terms used were "Intermittent fasting", "Caloric restriction", "Multiple sclerosis", "Alzheimer disease", and "cognition"; Boolean operators (AND, OR, and NOT) were incorporated to limit the bibliographic search. Articles with obsolescence not older than five years of publication, from 2018 to 2022, were cited.

Nutritional interventions in neurodegenerative diseases have a promising approach because of their ease of use, the paucity of associated adverse effects, and the theoretical improvement posed by their appropriate use. However, further investigation of these intervention strategies in neurodegenerative diseases is needed. For this reason, the present work seeks to determine the use of intermittent fasting and caloric restriction as adjuvant treatments for Alzheimer's disease and multiple sclerosis.

Results

Overview of intermittent fasting and caloric restrict

Obesity and overweight are among the most studied health problems with more non-pharmacological therapeutic alternatives. Among the diets that have emerged from different studies are IF and CR. The common results of these diets are weight reduction, lower oxidative stress, and improved cardiovascular health.[xvii] Both diets are considered ketogenic; they produce ketones from fatty acids metabolized by a glucose deficit. However, certain mechanisms differentiate these diets and by which they may be beneficial.[xviii]

IF consists of a pattern of food intake consisting of two periods: one of them is fasting, where no food is ingested, only non-caloric beverages or water; the other one

consists of the time in which food intake is allowed in a controlled manner. There are different modalities of IF depending on the number of hours in which the fasting is performed. Unlike CR, there is no limit to the number of calories ingested, only the time in which they are consumed.[xix]

Fasting periods in IF can vary from 12 hours to a full day. One of the most commonly used methods is 24 hours fasting followed by a full day with a regular eating pattern.[xx] Another protocol that can be classified as IF is the 5:2 method, in which fasting is for one day twice each week and eating food on a regular basis for the remaining five days. The fasting can also be for a certain number of hours, such as 12, 16, or 18 hours each day, and for the rest of the hours, only two meals are taken. While fasting for a full day produces more ketones, all methods have beneficial health effects.[xxi]

In IF, stored fatty acids are converted to ketones, which become the main energy source of the brain. These begin to be produced after 12 hours of fasting, as glycogen is consumed in the liver by glucagon. After a period of IF, insulin levels decrease due to reduced glucose utilization, thus regulating metabolism and improving insulin resistance. This was observed by Sutton *et al.* in their study, which showed that after IF insulin function was improved and insulin peaks were reduced. This metabolic change is what leads to a lower inflammatory state and overall better life prognosis caused by autophagy, a process by which damaged proteins and organelles in cells are eliminated.[xxii]

CR is also considered a ketogenic diet. Its main objective is the reduction of total caloric intake, up to 30 % less, without falling into malnutrition. Although its protective effects on the cardiovascular system are not as well studied as in IF, it has been shown in preclinical studies in mice that CR has a positive effect on weight reduction and increased longevity.[xxiii] A study by Il'yasova *et al.* showed that after two years of CR, oxidative stress levels decreased significantly, concluding that it improves the quality and prognosis of life.[xxiv] The same was corroborated by Redman *et al.*, who observed that patients with CR produced a lower amount of cellular oxidation markers.[xxv]

In CR, autophagy is the primary mechanism that generates the intended benefits of this diet. However, in this case, it is produced by the deficit of acetyl-CoA that leads to the deacetylation of the damaged proteins, which subsequently produces their destruction. This leads to an increased production of acetyl-CoA, which does not come directly from the diet but instead produces energy in the form of ATP. In addition, studies by Most *et al.* have shown that, in healthy adults, CR decreases circulating levels of tumor necrosis factor-alpha and cardiometabolic risk factors.[xxvi]

The effect of both CR and AI on weight, diabetes, obesity, hypertension and even some types of cancer has been extensively studied. In addition, several researches point out that these ketogenic diets, carried out in a controlled way, can lead to increase the average lifespan and prevent different diseases.[xxvii] The potential benefits on the prevention and progression of cognitive disorders of CR and AI through metabolic as well as immune and neurological mechanisms have now been highlighted.[xxviii] Such benefits of CR and AI on Alzheimer's disease and multiple sclerosis, as well as the possible physiological mechanisms involved, are discussed below.

Metabolic and immunologic effect of intermittent fasting and caloric restriction

Nutritional interventions aimed at the production of ketone bodies have shown benefits in neurodegenerative diseases. As previously mentioned, both proposed diets produce ketones, which are valuable sources of energy during periods of glucose deficiency. There are studies with animal models that show that the memory of animals with ketogenic diet was better than those with normal diet, suggesting that these dietary approaches may be beneficial in diseases such as AD and MS.[xxix] The mechanisms by which the neuromodulation process is achieved are: decreased glycolysis, change in oxidative stress, increased signaling and number of mitochondria and decreased molecules involved in neuroinflammation.[xxx]

Neuroinflammation is a defense mechanism that initially protects the brain, removing pathogens; however, when it persists, it is part of the pathophysiology in certain diseases,[xxxi] where both the innate and acquired immune systems are involved. For example, in MS, the acquired immune system prevails due to the invasion of T and B cells that characterize the disease.[xxxii] In AD, its occurrence is related to innate immunity since several regulators of this pathway are genetic risk factors for the development of the disease, while acquired immunity participates in the progression.[xxxiii]

The progression of these diseases can be modulated by anti-inflammatory mechanisms related to metabolism. The gut-brain axis, which represents a bidirectional system

between the central nervous system (CNS) and the gastrointestinal system, regulates inflammation and protects against oxidative damage.[xxxiv] In patients who practice IF and CR, it has been related to greater enrichment of the microbiota, increasing the levels of bacteria, mainly from families such as Lactobacillaceae, Bacteroidaceae, and Prevotellaceae, related to anti-inflammatory mechanisms.[xxxv]

Cignerella *et al.* describe the importance of the gut-brain axis, microbiota, caloric restriction, and their relationship in the clinical improvement of the autoimmune encephalomyelitis (EAI) model of MS in mice. After presenting their results found by histology and cytometry, they determined that CR generates an increase in regulatory T cells, anti-oxidative processes, less infiltration of inflammatory cells, and improvement in demyelination; establishing that these changes are caused by the microbiota exposed to CR. To prove this, they transplanted this microbiota to unexposed mice. The results were similar: demyelination studied by myelin basic protein, axonal damage studied by SMI-32+ protein and inflammatory cytokines IL-12 and IFN-Y were lower in these mice.[xxxvi]

Nutritional interventions have been successful in decreasing lymphocyte infiltration into the spinal cord, resulting in reduced demyelination after two cycles of CR in mice. Bai *et al.* subjected mice with EAI to CR with a 33 % decrease in calories three days a week, which generated a neuroprotective process with a decrease and regression in the accumulation of TDC4+ and IFN-Y cells in the CNS. Likewise, the proliferation rate increased, and the expression of neurotrophic factors and remyelination markers improved, generating a benefit in the inflammatory response and recovery of tissue damaged by demyelination in the CNS.[xxxvii]

In 2022, Fitzgerald *et al.* conducted a clinical study involving 36 MS patients who were followed for eight weeks. Different interventions were performed using three comparison groups: one group with daily caloric restriction in which patients received 78 % of their total calories, seven days a week; the second group with intermittent caloric restriction 5:2, decreasing calories two days a week to 25 % of the total and the control group where they received 100 % of their calories seven days a week. Lymphocyte levels were studied by flow cytometry at weeks 0, 4, and 8 in the three groups. It was found that patients in the intermittent CR group had significant reductions in TCD8+ and Th1 effector cells, a decrease in memory T cells, and an increase in immature T cells.[xxxviii]

Continuous monitoring of neuronal injury is key to determining the recurrence or remission of MS, which can be determined by neurofilament chains, being a marker of acute damage.[xxxix] Bock *et al.* conducted a study exploring serum neurofilaments in MS patients, finding that ketogenic diets for a period of six months decreased these markers of inflammation.[xl] Aging, oxidative stress, and inflammatory response are factors that are part of the pathophysiology of Alzheimer's disease. CR and IF regulate the above by modulating deacetylation activities and the inflammatory response.[xli] The aging process is an important factor as age is inversely proportional to neurogenesis. However, CR has been shown to mitigate microglia activation, thus alleviating chronic inflammation and preserving neurogenesis longer.[xlii]

Physiological effects of intermittent fasting and caloric restriction on cognitive function

It has been shown that through IF, a metabolic change is initiated in which there is a preference for energy extraction through lipolysis. In other words, there is greater utilization of stored fat in the form of lipids, which are subsequently metabolized into ketones, generating signaling effects and regulation of transcription factors in the neurons of the brain.[xliii] As previously mentioned, IF and CR affect the microbiota-gut-brain axis, relating directly to cognitive function through neural, endocrine, and immune pathways.[xliv]

AD is pathologically characterized by the presence of β-amyloid plaques that lead to neuronal death, leading to a decrease in cognitive abilities, from mild cognitive impairment to dementia.[xlv] Ooi *et al.* conducted a study with a three-year follow-up in 99 patients with mild cognitive impairment, divided into three groups: patients who performed IF regularly, another group that practiced IF irregularly, and those who did not perform IF. They determined that regular IF improves cognitive function through ketogenesis since ketone bodies act as a source of energy and increase the survival of neurons under hypoxemia conditions. In addition, it is related to the reduction of DNA damage through the production of repair enzymes, improving cognitive impairment by 73 % in those who performed IA regularly, compared to 2.7 % in the group that did not perform it ($p < 0.05$).[xlvi]

CR and IF are equally associated with blocking the accumulation of β-amyloid

in neurons. In the study by Shut *et al.* conducted in groups of mice injected with amyloid β in the hippocampus, it was shown that when these nutritional approaches were performed, there was a reduction in oxidative stress and improvement of synaptic plasticity, which was related to the protection of memory impairment.[xlvii]

Currently, there are theories of delayed aging related to the signaling pathways of adenosine monophosphate kinase (AMPK), insulin-like growth factor, and the enzyme sirtuin (SIRT1). The mechanism of such delay has not been fully determined; however, Ma *et al.* propose that the AMPK pathway is the most important in the delay of aging. To verify this, they performed an experiment with mice that were intervened in different nutritional ways, in which they found that in mice subjected to CR, learning and memory were increased, which was accompanied by an increase in the expression of AMPK, thus associating this kinase with a neuroprotective effect.[xlviii]

Patients with MS clinically show manifestations of cognitive impairment, including deficits in information processing and attention, impaired information processing speed, impaired working and long-term memory, and verbal fluency.[xlix] Wingo *et al.*, in a pilot study with 12 patients who underwent IF for eight weeks, determined that cognitive function in patients with relapsing-remitting MS improved through reduced inflammation and activation of autophagy. Similarly, this study attributes the importance of conducting more clinical trials in patients to determine the effects of this nutritional approach since the existing ones are in the preclinical phase.[l]

Conclusion

Intermittent fasting and caloric restriction are approaches that modulate the progression of Alzheimer's disease and multiple sclerosis through metabolism-related anti-inflammatory mechanisms via the gut-brain axis. In addition, they regulate antioxidative processes and decrease the infiltration of inflammatory cells into the nervous system. Similarly, CR and IF have demonstrated benefits in cognitive function through the AMPK, insulin-like growth factor and sirtuin enzyme pathways, generating delayed aging and a neuroprotective effect. However, most of the research is still in the preclinical phase, and many of these studies highlight the importance of conducting trials in patients to adequately define the effects of these nutritional interventions.

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References

i. Erkkinen MG, Kim MO, Geschwind MD. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. Cold Spring Harb Perspect Biol. 2018;10(4):a033118. DOI: 10.1101/cshperspect.a033118

ii. Federación Internacional de Esclerosis Múltiple (MSIF). Atlas de EM 3.ª edición. Londres. Federación Internacional de Esclerosis Múltiple. 2020. 37 p. Available at: https://www.msif.org/wp-content/uploads/2020/10/Atlas-Epidemiology-report-Sept-2020-Final-ES.pdf

iii. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, *et al.* Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler J. 2020;26(14):1816-1821. DOI: 10.1177/1352458520970841

iv. Ayodele T, Rogaeva E, Kurup JT, Beecham G, Reitz C. Early-Onset Alzheimer's Disease: What Is Missing in Research? Curr Neurol Neurosci Rep. 2021;21(2):4. DOI: 10.1007/s11910-020-01090-y

v. World Health Organization. Dementia.2023. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia

vi. Rafiee Zadeh A, Askari M, Azadani NN, Ataei A, Ghadimi K, Tavoosi N, *et al.* Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 1. Int J Physiol Pathophysiol Pharmacol. 2019;11(4):95-104. Available at: https://pubmed.ncbi.nlm.nih.gov/31523357/

vii. Dugger BN, Dickson DW. Pathology of Neurodegenerative Diseases. Cold Spring Harb Perspect Biol. 2017;9(7):a028035. DOI: 10.1101/cshperspect.a028035

viii. Longo VD, Di Tano M, Mattson MP, Guidi N. Intermittent and periodic fasting, longevity and disease. Nat Aging. 2021;1(1):47-59. DOI: 10.1038/s43587-020-00013-3

ix. Hofer SJ, Carmona-Gutierrez D, Mueller MI, Madeo F. The ups and downs of caloric restriction and fasting: from molecular effects to clinical application. EMBO Mol

Med. 2022;14(1):e14418. DOI: 10.15252/emmm.202114418

x. Almendáriz-Palacios C, Mousseau DD, Eskiw CH, Gillespie ZE. Still Living Better through Chemistry: An Update on Caloric Restriction and Caloric Restriction Mimetics as Tools to Promote Health and Lifespan. Int J Mol Sci. 2020;21(23):9220. DOI: 10.3390/ijms21239220

xi. Forslund SK. Fasting intervention and its clinical effects on the human host and microbiome. J Intern Med. 2023;293(2):166-83. DOI: 10.1111/joim.13574

xii. Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, *et al.* 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7(9):673-683. DOI: 10.1016/S2213-8587(19)30151-2

xiii. Stekovic S, Hofer SJ, Tripolt N, Aon MA, Royer P, Pein L, *et al.* Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans. Cell Metab. 2019;30(3):462-476.e6. DOI: 10.1016/j.cmet.2019.07.016

xiv. Fontana L, Ghezzi L, Cross AH, Piccio L. Effects of dietary restriction on neuroinflammation in neurodegenerative diseases. J Exp Med. 2021;218(2):e20190086. DOI: 10.1084/jem.20190086

xv. Lobo F, Haase J, Brandhorst S. The Effects of Dietary Interventions on Brain Aging and Neurological Diseases. Nutrients. 2022;14(23):5086. DOI: 10.3390/nu14235086

xvi. Kritsilis M, V. Rizou S, Koutsoudaki P, Evangelou K, Gorgoulis V, Papadopoulos D. Ageing, Cellular Senescence and Neurodegenerative Disease. Int J Mol Sci. 2018;19(10):2937. DOI: 10.3390/ijms19102937

xvii. Wang HH, Lee DK, Liu M, Portincasa P, Wang DQH. Novel Insights into the Pathogenesis and Management of the Metabolic Syndrome. Pediatr Gastroenterol Hepatol Nutr. 2020;23(3):189-230. DOI: 10.5223/pghn.2020.23.3.189

xviii. Świątkiewicz I, Woźniak A, Taub PR. Time-Restricted Eating and Metabolic Syndrome: Current Status and Future Perspectives. Nutrients. 2021;13(1):221. DOI: 10.3390/nu13010221

xix. Kroeger CM, Trepanowski JF, Klempel MC, Barnosky A, Bhutani S, Gabel K, *et al.* Eating behavior traits of successful weight losers during 12 months of alternate-day fasting: An exploratory analysis of a randomized controlled trial. Nutr Health. 2018;24(1):5-10. DOI: 10.1177/0260106017753487

xx. Nowosad K, Sujka M. Effect of Various Types of Intermittent Fasting (IF) on Weight Loss and Improvement of Diabetic Parameters in Human. Curr Nutr Rep. 2021;10(2):146-154. DOI: 10.1007/s13668-021-00353-5

xxi. Vasim I, Majeed CN, DeBoer MD. Intermittent Fasting and Metabolic Health. Nutrients. 2022;14(3):631. DOI: 10.3390/nu14030631

xxii. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even Without Weight Loss in Men with Prediabetes. Cell Metab. 2018;27(6):1212-1221.e3. DOI: 10.1016/j.cmet.2018.04.010

xxiii. Acosta Rodríguez V, Rijo Ferreira F, Izumo M, Xu P, Wight Carter M, Green CB, *et al.* Circadian alignment of early onset caloric restriction promotes longevity in male C57BL/6J mice. Science. 2022;376(6598):1192-1202. DOI: 10.1126/science.abk0297

xxiv. Il'yasova D, Fontana L, Bhapkar M, Pieper CF, Spasojevic I, Redman LM, *et al.* Effects of 2 years of caloric restriction on oxidative status assessed by urinary F2-isoprostanes: The CALERIE 2 randomized clinical trial. Aging Cell. 2018 Apr;17(2):e12719. DOI: 10.1111/acel.12719

xxv. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Supports the Rate of Living and Oxidative Damage Theories of Aging. Cell Metab. 2018;27(4):805-815. DOI: 10.1016/j.cmet.2018.02.019

xxvi. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. Am J Physiol Endocrinol Metab. 2018;314(4):E396-405. DOI: 10.1152/ajpendo.00261.2017

xxvii. Kunduraci YE, Ozbek H. Does the Energy Restriction Intermittent Fasting Diet Alleviate Metabolic Syndrome Biomarkers? A Randomized Controlled Trial. Nutrients. 2020;12(10):3213. DOI: 10.3390/nu12103213

xxviii. Gudden J, Arias A, Bloemendaal M. The Effects of Intermittent Fasting on Brain and Cognitive Function. Nutrients. 2021;13(9):3166. DOI: 10.3390/nu13093166

xxix. Park S, Zhang T, Wu X, Yi Qiu J. Ketone production by ketogenic diet and by intermittent fasting has different effects on the gut microbiota and disease progression in an Alzheimer's disease rat model. J Clin Biochem Nutr. 2020;67(2):188-198. DOI: 10.3164/jcbn.19-87

xxx. Field R, Field T, Pourkazemi F, Rooney K. Ketogenic diets and the nervous system: a

scoping review of neurological outcomes from nutritional ketosis in animal studies. Nutr Res Rev. 2022;35(2):268-281. DOI: 10.1017/S0954422421000214

xxxi. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener. 2020;9(1):42. DOI: 10.1186/s40035-020-00221-2

xxxii. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS neurodegenerative diseases. Immunology. 2018;154(2):204-219. DOI: 10.1111/imm.12922

xxxiii. Chen X, Holtzman DM. Emerging roles of innate and adaptive immunity in Alzheimer's disease. Immunity. 2022; 55(12):2236-2254. DOI: 10.1016/j.immuni.2022.10.016

xxxiv. Lombardi VC, De Meirleir KL, Subramanian K, Nourani SM, Dagda RK, *et al.* Nutritional modulation of the intestinal microbiota; future opportunities for the prevention and treatment of neuroimmune and neuroinflammatory disease. J Nutr Biochem. 2018; 61:1-16. DOI: 10.1016/j.jnutbio.2018.04.004

xxxv. Schepici G, Silvestro S, Bramanti P, Mazzon E. The Gut Microbiota in Multiple Sclerosis: An Overview of Clinical Trials. Cell Transplant. 2019;28(12):1507-1527. DOI: 10.1177/0963689719873890

xxxvi. Cignarella F, Cantoni C, Ghezzi L, Cross AH, Zhou Y, Piccio L, *et al.* Intermittent Fasting Confers Protection in CNS Autoimmunity by Altering the Gut Microbiota. Cell Metab. 2018; 27(6):1222-1235.e6. DOI: 10.1016/j.cmet.2018.05.006

xxxvii. Bai M, Wang Y, Han R, Xu L, Huang M, Zhao J, *et al.* Intermittent caloric restriction with a modified fasting-mimicking diet ameliorates autoimmunity and promotes recovery in a mouse model of multiple sclerosis. J Nutr Biochem;. 2021; 87:108493. DOI: 10.1016/j.jnutbio.2020.108493

xxxviii. Fitzgerald KC, Bhargava P, Smith MD, Vizthum D, Barron B, Kornberg MD, *et al.* Intermittent calorie restriction alters T cell subsets and metabolic markers in people with multiple sclerosis. EBioMedicine. 2022; 82:104-124. DOI: 10.1016/j.ebiom.2022.104124

xxxix. Siller N, Kuhle J, Muthuraman M, Barro C, Uphaus T, Groppa S, *et al.* Serum neurofilament light chain is a biomarker of acute and chronic neuronal damage in early multiple sclerosis. Mult Scler. 2019;25(5):678-686. DOI: 10.1177/1352458518765666

xl. Bock M, Steffen F. Impact of Dietary Intervention on Serum Neurofilament Light Chain in Multiple Sclerosis. Neurology Neuroinm&neuroinflamattion. 2021;9(1):e1102. DOI: 10.1212/NXI.0000000000001102

xli. Yang H, Shan W, Zhu F, Wu J, Wang Q. Ketone Bodies in Neurological Diseases: Focus on Neuroprotection and Underlying Mechanisms. Front Neurol. 2019;10:585. DOI: 10.3389/fneur.2019.00585

xlii. Apple DM, Mahesula S, Fonseca RS, Zhu C, Kokovay E. Calorie restriction protects neural stem cells from age-related deficits in the subventricular zone. Aging. 2019;11(1):115-126. DOI: 10.18632/aging.101731

xliii. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci. 2018;19(2):81-94. DOI: 10.1038/nrn.2017.156

xliv. Stoiloudis P, Kesidou E, Bakirtzis C, Sintila SA, Konstantinidou N, Boziki M, Grigoriadis N. The Role of Diet and Interventions on Multiple Sclerosis: A Review. Nutrients. 2022;14(6):1150. DOI: 10.3390/nu14061150

xlv. McGrattan AM, McGuinness B, McKinley MC, Kee F, Passmore P, *et al.* Diet and Inflammation in Cognitive Ageing and Alzheimer's Disease. Curr Nutr Rep. 2019;8(2):53-65. DOI: 10.1007/s13668-019-0271-4

xlvi. Ooi TC, Meramat A, Rajab NF, Shahar S, Ismail IS, Azam AA, *et al.* Intermittent Fasting Enhanced the Cognitive Function in Older Adults with Mild Cognitive Impairment by Inducing Biochemical and Metabolic changes: A 3-Year Progressive Study. Nutrients. 2020;12(9):2644. DOI: 10.3390/nu12092644

xlvii. Shin BK, Kang S, Kim DS, Park S. Intermittent fasting protects against the deterioration of cognitive function, energy metabolism and dyslipidemia in Alzheimer's disease-induced estrogen deficient rats. Exp Biol Med. 2018;243(4):334-343. DOI: 10.1177/1535370217751610

xlviii. Ma L, Wang R, Dong W, Zhao Z. Caloric restriction can improve learning and memory in C57/BL mice probably via regulation of the AMPK signaling pathway. Exp Gerontol. 2018;102:28-35. DOI: 10.1016/j.exger.2017.11.013

xlix. Doskas T, Vavougios G, Karampetsou P, Kormas C, Synadinakis E, Stavrogianni K, *et al.* Neurocognitive impairment and social cognition in multiple sclerosis. Int J Neurosci. 2022;132(12):1229-1244. DOI: 10.1080/00207454.2021.1879066

l. Wingo BC, Rinker JR 2nd, Green K, Peterson CM. Feasibility and acceptability of time-restricted eating in a group of adults with multiple sclerosis. Front Neurol. 2023;13:1087126. DOI: 10.3389/fneur.2022.1087126

Narrative review

Seroprevalence of *Toxoplasma gondii* and its Relationship with Mental Disorders in the Adult Population

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Abstract
Toxoplasma gondii is a parasite that is found in approximately 30 % of the human population. In recent years, it has been shown that latent infection can be a risk factor for the development of mental disorders; particularly schizophrenia, anxiety, bipolar disorders, and conduct disorders. The association with neuropsychiatric disorders can be explained by the influence of the parasite on the expression of multiple neurotransmitters; among them, dopamine has received the most attention. A narrative bibliographic review article was done with the search of original and review articles in international scientific journals, in English and Spanish listing the relationship between the seroprevalence of *T. gondii* and the development of mental disorders in the adult population. The relationship between mental disorders in the adult population with *Toxoplasma gondii* infection is present and increases the possibility of developing schizophrenia and depression in individuals with no previous history, including the ability to worsen previous psychiatric conditions, making it difficult for standard management. Not all statistical data establish a direct relationship, some studies show an association and certain data are discordant, which opens a door for future research.

Keywords
Toxoplasmosis, Mental Disorders, Cognitive Disorders, Schizophrenia.

Resumen
El *Toxoplasma gondii* es un parásito que se encuentra, aproximadamente, en el 30 % de la población humana. Durante los últimos años se ha evidenciado que la infección latente puede ser un factor de riesgo para el desarrollo de trastornos mentales; particularmente para la esquizofrenia, ansiedad, trastornos bipolares y trastornos de conducta. La asociación con los trastornos neuropsiquiátricos pueden explicarse por la influencia que tiene el parásito sobre la expresión de múltiples neurotransmisores; entre ellos la dopamina. Se realizó una búsqueda en las bases de datos PubMed y SciELO de 2015 a 2023, se seleccionaron artículos originales y de revisión de revistas científicas internacionales, en idiomas inglés y español con el objetivo de describir la relación entre la seroprevalencia de *T. gondii* y el desarrollo de trastornos mentales en población adulta. Existe relación entre los trastornos mentales en la población adulta con la infección por *Toxoplasma gondii* y este aumenta la posibilidad de desarrollar esquizofrenia y depresión en individuos sin historial previo, y que podría exacerbar cuadros psiquiátricos previos con dificultad en el tratamiento. Sin embargo, no todos los datos estadísticos establecen una relación directa, algunos estudios demuestran una asociación, ciertos datos son discordantes, lo que abre una puerta para futuras investigaciones.

Palabras clave
Toxoplasmosis, Trastornos mentales, Trastornos cognitivos, Esquizofrenia, *Toxoplasma gondii*.

OPEN ACCESS

Seroprevalencia de *Toxoplasma gondii* y su relación con trastornos mentales en adultos

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The authors declare there are no conflicts of interest.

Introduction

Toxoplasma gondii is a protozoan parasite found in approximately 30 % of the human population and has historically been a problem as congenital toxoplasmosis and disease in immunocompromised patients.[i]

Some studies have shown that this parasite produces biological alterations in the human brain.[ii] Likewise, a direct association between patients' seropositivity is a causal factor in the development of mental illnesses.[iii]

Latent toxoplasmosis has been associated as a risk factor for the development of mental disorders, particularly schizophrenia, anxiety, bipolar disorders, and conduct disorders.[iv,v] Schizophrenia affects one in 300 people worldwide and has a significant impact on their life expectancy.[vi]

The high incidence rate of latent toxoplasmosis contributes to the difficulty of clinical diagnosis and specific pharmacological treatment and makes it a community problem.[vii] Seropositivity rates have been increasing in recent years, reaching 90 % depending on the country or region.[viii,ix] Due to the growing number of associations between *T. gondii* and mental disorders, the impact of this parasite in different investigations has been largely underestimated, and more studies are needed to strengthen this association.[vi]

A narrative literature review article was prepared by searching for original and review articles in scientific journals, in English and Spanish, in databases such as PubMed, SciELO, and sites of international organizations related to the topic of interest. The search terms used were "Latent toxoplasmosis", "Mental disorders", "Seroprevalence of toxoplasmosis", "Cognitive disorders", "Schizophrenia" and "*Toxoplasma gondii*"; with the incorporation of Boolean operators (AND, OR & NOT). Original articles, meta-analyses and review articles published between 2015 and 2023 were cited. This investigation seeks to explore the connection between the prevalence of *T. gondii* and the emergence of mental health issues in the adult population.

Discussion

Pathophysiology and effects of *Toxoplasma gondii* at the brain level

T. gondii uses a complicated mechanism to gain access to the central nervous system (CNS); when it manages to invade it, it can affect different brain cells, such as astrocytes and neurons, where it forms cysts.[x] The mechanism of invasion into the CNS has not been extensively studied, and there is still no consensus on how this parasite crosses the blood-brain barrier.[i] Different mechanisms used by *T. gondii* to cross the blood-brain barrier have been explored; one of the best-known mechanisms is transendothelial migration through integrins. It is also possible that the parasite enters the CNS on its own through transcytosis or parasitosis.[xi] Another mechanism that has been studied *in vitro* is the Trojan horse mechanism, which consists of parasite transport by a cell, for example, a leukocyte.[xi]

The association between *T. gondii* and neuropsychiatric disorders can be largely explained by the parasite's influence on the expression of multiple neurotransmitters. The neurotransmitter dopamine has received the most attention due to the parasite's ability to synthesize tyrosine hydrolase, an enzyme involved in dopamine biosynthesis.[xii] Increased levels of dopamine in and around parasite cysts generated by multiple pathways are responsible for the positive symptoms of schizophrenia.[xiii] *T. gondii* also alters the expression of other neurotransmitters, such as glutamate, gamma-aminobutyric acid, serotonin, and noradrenaline.[xii] These effects on neurotransmitters can be explained by the encystation of bradyzoites in brain cells, especially microglia or neuronal cells, causing alterations in host neurochemistry and receptor expression.[i]

The presence of this parasite in the brain parenchyma is also related to the secretion of proinflammatory cytokines and mediators from neurons, astrocytes, and microglia. Persistent neuroinflammation has also been related to alterations in neurotransmitter release.[xiv]

Psychiatric disorders associated with latent infection with *T. gondii*

Nessim *et al.* mention that the percentage of the population associated with *T. gondii* seropositivity and schizophrenia is 20.4 %, bipolar disorder 27.3 %, and suicidal behavior 0.29 % ; however, these percentages are subject to variations by geographical area due to regionally prevalent risk factors. For example, the risk factors for toxoplasmosis associated with mental illness were water contamination in Africa, and cooking conditions of meats in the European region.[xv]

According to Lindgren *et al.*, there is an association between *T. gondii* infection and psychotic symptoms ($p = 0.001$) to the head, predominantly auditory hallucinations; these events considerably increase the risk of suffering psychosis in the future, even if they are transitory. Even if a DSM-V-diagnosed psychosis does not develop, these isolated events are associated with a worse functional capacity and general health in the population.[xvi]

The relationship between toxoplasmosis and schizophrenia has been demonstrated by Stepanova *et al.* in a prevalence study conducted in Russia, where there is an incidence of schizophrenia of 0.82 %,[xvii] and which showed that patients with underlying neuropsychiatric diseases had twice the inci-

dence of being infected by *T. gondii* (40 %), compared to the control group (25 %) with statistical significance (p = 0.007). However, the direct role of the parasite in the etiology is still questionable. Few longitudinal studies have examined the causal relationship between *T. gondii* and schizophrenia.[xviii]

Contopoulos-Ioannidis *et al.* examined 66 studies published in the last two decades, involving 11 540 patients with schizophrenia and 69 491 controls, to study the relationship between *T. gondii* and schizophrenia. Although there was heterogeneity across studies in the types of toxoplasmosis exposure and schizophrenia outcomes, on average, 45 % of schizophrenia patients were seropositive for *Toxoplasma* IgG (or IgG/IgM) versus 30 % of the control group. *Toxoplasma* IgG (or IgG/IgM) seropositivity increased the odds of schizophrenia by 1.91-fold.[xix]

Although schizophrenia is a multicausal disease, risk factors for developing schizophrenia have been identified, including seropositivity to *T. gondii* (IgG). In an umbrella study by Radua *et al.* in which multiple published systematic reviews and meta-analyses were compiled, suggestive class III evidence for *T. gondii* (IgG) seropositivity was found.[xx]

T. gondii-infected individuals with schizophrenia often exhibit significant impairment in multiple cognitive domains; Guimarães *et al.* note that patients with positive IgG for *T. gondii* may experience deficits in verbal learning, social cognition, and even visual memory, in contrast to digital cognitive learning in those who showed improved adherence.[xxi]

In a study conducted by Veleva *et al.* on 89 patients who had been diagnosed with schizophrenia, they discovered that seropositive patients had worse visual memory and executive functions. At the same time, seroprevalence was linked to a higher score on the Positive and Negative Syndrome Scale, which measures the prevalence of both positive and negative symptoms in schizophrenia.[xxii]

Delusions and alogia were the most common symptoms in a cohort study by Fong *et al.* that examined ten community centers and 250 clinically stable patients diagnosed with schizophrenia. The study also found that latent infection with *Toxoplasma gondii* is associated with a higher score on the Positive and Negative Syndrome Scale. Latent *T. gondii* infection did not significantly correlate with age, gender, or the age at which schizophrenia first manifested itself in this study.[xxiii]

Liu *et al.* present the results of their research, where they identified that schizophrenia, bipolar disorder, depression and recurrent depressive disorder were associated with *T. gondii* serological positivity, except for dissociative depressive disorder. Likewise, a potential association was found between depression or recurrent depressive disorder and *T. gondii* infection, and there was evidence that infection affects the susceptibility and severity of depression in children, adolescents, and pregnant women.[xxiv]

The etiology of major depressive disorder is multifactorial, consisting of genetic and environmental factors.[xxv] According to the manuscript by Sapmaz *et al.*, a significant association was found between *T. gondii* seropositivity and the presence of clinical depression (p = 0.046). In addition, the data indicated that patients who reported suicide attempts and suicidal ideation had higher levels of antibodies that could be associated.[xxvi]

A study by Nasirpour *et al.* found a higher prevalence of antibodies against *T. gondii* in patients with depression, which shows the possible impact of this parasite on the cause of depression and the intensity of its symptoms. On the other hand, it was found that the frequency of antibodies against *T. gondii* IgG was 59.8 % in patients with depression and 56.3 % in the control groups, and it was determined that the risk of depression in people with positive serology tests was 1.5 times more than with a negative response.[xxvii]

Currently, the relationship between *T. gondii* seropositivity and depression is related to the geographical site of the study and the conditions of the study. Lin *et al.* found that both clinical depression and anxiety have a greater risk of developing in infected patients. However, he mentions that there are some differences between the results because infection may favor depression in different degrees of severity for each individual.[xxviii]

A cross-sectional case-control study including 384 patients over 18 years of age with a diagnosis of depression and 400 healthy subjects found that patients with current depression have higher anti-G antibody positivity for *T. gondii* compared to healthy individuals. It was also shown that seropositive individuals with depression have a higher severity index with a higher risk of suffering a suicide attempt. Furthermore, it has been shown that the seroprevalence of *T. gondii* is related to higher suicide attempts compared to healthy individuals.[xxix]

Bahceci *et al.* recruited 100 patients diagnosed as depressed with suicidal ideation, 100 patients with depression without suicidal ideation, and 100 healthy patients in whom they assessed depression and

suicide risk with assessment instruments such as the Hamilton depression scale and suicide scales. It was found that seropositivity for *T. gondii* in depressed patients with and without suicidal ideation is higher than in healthy patients.[xxx] Likewise, a case-control study by Bak *et al.* of 155 patients with suicidal attempts and 135 healthy individuals found IgG antibodies to *T. gondii* in 13.5 % in the case group compared to 5.9 % in the controls. Also, higher severity values were found in seropositive cases compared to controls. The results of this study suggest a relationship between seropositivity and suicidal behavior.[xxxi]

There is evidence that treatment against *T. gondii* in seropositive patients with underlying psychiatric disease has significantly improved their symptoms and has demonstrated a decrease in antibodies against *toxoplasma* in diseases such as depression, obsessive-compulsive disorder, and schizophrenia. It has been shown that several drugs, including antipsychotics and sodium valproate, have an *in vitro* effect on preventing parasites from replicating in cell cultures.[xxxii]

Antipsychotic drugs such as haloperidol, chlorpromazine, and valproic acid have been shown to inhibit the *in vitro* growth of *T. gondii* as well. Nevertheless, Kezai *et al.* describe that *T. gondii* could interfere with the effectiveness of antipsychotic treatment; individuals with therapy-resistant forms of schizophrenia had a higher prevalence of anti-*toxoplasma* antibodies, in contrast to the control group with non-drug-resistant forms of schizophrenia ($p = < 0.0001$).[xxxiii,xxiv]

In patients with a diagnosis of schizophrenia and seroprevalence for toxoplasmosis, antiparasitic drugs have not demonstrated clinical improvement in the severity of schizophrenia symptoms.[xxxv,xxxvi]

T. gondii seroprevalence and cognitive changes

It has been demonstrated that the seroprevalence of *T. gondii* is associated with alterations in cognitive functions, mainly in working memory tests. This result was identified through a questionnaire called "National Health and Nutrition Examination Survey 2013-2014" and the analysis of cognitive tests performed on a group of adults over 60 years of age with positive IgG to *T. gondii*.[xxxvii]

Similarly, *T. gondii* seropositivity was linked to worse reasoning and pattern completion, including with arithmetic tasks, in a community study involving individuals aged 40 to 70 years. Although few tests for memory assessment were conducted in this cohort, the executive component of cognitive function, such as decision-making, was primarily affected.[xxxviii]

Haan *et al.* conducted a meta-analysis that included 13 studies with 12 289 healthy individuals, in which an association was observed between seropositivity to *Toxoplasma gondii* and impairment in cognitive tests affecting processing speed, working memory, and executive functioning.[xxxix]

The role of *T. gondii* in the development of neurological diseases that affect memory remains unclear; Mendy *et al.* analyzed the database of the United States Center for Disease Control in which 4485 people over 60 years of age participated, in whom a significant difference in seroprevalence of *T. gondii* was observed with short-term memory impairment, but not long-term.[xl] In contrast, Wyman *et al.* analyzed 117 older adults without a diagnosis of dementia without finding evidence of a significant association between *T. gondii* seropositivity and memory impairment.[xli]

Another study in laboratory mice showed that *T. gondii* infection significantly alters behavior, decreases fear of predators, decreases anxiety, and consequently produces immune and inflammatory reactions in the brain. In humans, other types of behavioral changes have been found, such as increased suicidal behavior, aggressiveness, and increased risk of traffic accidents.[xlii]

On the other hand, Zouei *et al.*, in their study, showed that the population infected by *T. gondii* had hormonal alterations, regardless of sex, with a significant increase in testosterone levels ($p = 0.02$ and $p = 0.04$ for men and women, respectively) in contrast to the control group, which did not show this increase. The increase in testosterone has been associated with behavioral changes, such as antisocial behavior, aggressiveness, and dominant behaviors, as well as immunosuppressive reactions.[xliii]

According to Postolache *et al.*, there is an increased incidence of suicide attempts in the *T. gondii*-infected population, ranging from 39 % to 57 % in seropositive individuals, regardless of any underlying mental disorder. Similarly, impulsive conduct throughout life has been linked to *T. gondii* infection and is a risk factor for suicide attempts.[xliv]

Similarly, Johnson *et al.* found that *T. gondii* infection is associated with a lower fear of failure and a stronger inclination to take chances. Under this concept, infection can be biased toward specific activities, demonstrating that modifying some behaviors can have a holistic impact on the human being.[xlv] Although not all statistical data

prove a direct relationship, certain studies show an association, which is a significant health problem for future investigation.

Conclusion

In the adult population, there is a relationship between mental disorders and *Toxoplasma gondii* infection, which increases the possibility of developing schizophrenia and depression in individuals with no previous history, with a risk of exacerbation of previous psychiatric conditions that are difficult to treat. The pathophysiological mechanisms that support such claims are mostly based on the parasite's ability to produce biochemical reactions at the CNS level. These mechanisms also include increases in neurotransmitters such as dopamine, glutamate, gamma-aminobutyric acid, serotonin, and noradrenaline. These biochemical changes are responsible for predisposing to predominantly impulsive and aggressive behaviors, suicidal tendencies, and cognitive changes such as altered memory, cognitive speed, and executive functioning.

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References

i. Milne G, Webster JP, Walker M. *Toxoplasma gondii*: An Underestimated Threat? Trends Parasitol. 2020;36(12):959-969. DOI: 10.1016/j.pt.2020.08.005

ii. Xiao J, Li Y, Gressitt KL, He H, Kannan G, Schultz TL, *et al.* Cerebral complement C1q activation in chronic Toxoplasma infection. Brain. Behav. Immun. 2016;58:52-56. DOI: 10.1016/j.bbi.2016.04.009

iii. Burgdorf KS, Trabjerg BB, Pedersen MG, Nissen J, Banasik K, Pedersen OB, *et al.* Large-scale study of Toxoplasma and Cytomegalovirus shows an association between infection and serious psychiatric disorders. Brain. Behav. Immun. 2019;79:152-158. DOI: 10.1016/j.bbi.2019.01.026

iv. Flegr J, Escudero DQ. Impaired health status and increased incidence of diseases in Toxoplasma -seropositive subjects - an explorative cross-sectional study. Parasitology. 2016;143(14):1974-1989. DOI: 10.1017/S0031182016001785

v. Bay-Richter C, Buttenschøn HN, Mors O, Eskelund A, Budac D, Kærlev L, *et al.* Latent toxoplasmosis and psychiatric symptoms - A role of tryptophan metabolism? J. Psychiatr. Res. 2019;110:45-50. DOI: 10.1016/j.jpsychires.2018.12.016

vi. World Health Organization. Mental disorders. World Health Organization. 2022. Date of citation: November 3, 2023. Available at: https://www.who.int/news-room/fact-sheets/detail/mental-disorders

vii. Sutterland AL, Mounir DA, Ribbens JJ, Kuiper B, van Gool T, de Haan L. *Toxoplasma gondii* Infection and Clinical Characteristics of Patients With Schizophrenia: A Systematic Review and Meta-analysis. Schizophr. Bull. Open. 2020;1(1). DOI: 10.1093/schizbullopen/sgaa042

viii. Sanchez SG, Besteiro S. The pathogenicity and virulence of *Toxoplasma gondii*. Virulence. 2021;12(1):3095-3114. DOI: 10.1080/21505594.2021.2012346

ix. Flegr J, Horáček J. Negative Effects of Latent Toxoplasmosis on Mental Health. Front. Psychiatry. 2020;10:1012. DOI: 10.3389/fpsyt.2019.01012

x. Nayeri Chegeni T, Sharif M, Sarvi S, Moosazadeh M, Montazeri M, Aghayan SA, *et al.* Is there any association between *Toxoplasma gondii* infection and depression? A systematic review and meta-analysis. PLoS ONE. 2019;14(6):e0218524. DOI: 10.1371/journal.pone.0218524

xi. Ross EC, Olivera GC, Barragan A. Early passage of *Toxoplasma gondii* across the blood-brain barrier. Trends Parasitol. 2022;38(6):450-461. DOI: 10.1016/j.pt.2022.02.003

xii. Wohlfert EA, Blader IJ, Wilson EH. Brains and Brawn: Toxoplasma Infections of the Central Nervous System and Skeletal Muscle. Trends Parasitol. 2017;33(7):519-531. DOI: 10.1016/j.pt.2017.04.001

xiii. Chaudhury A, Ramana BV. Schizophrenia and bipolar disorders: The Toxoplasma connection. Trop. Parasitol. 2019;9(2):71-76. DOI: 10.4103/tp.TP_28_19

xiv. Samojłowicz D, Twarowska-Małczyńska J, Borowska-Solonynko A, Poniatowski ŁA, Sharma N, Olczak M. Presence of *Toxoplasma gondii* infection in brain as a potential cause of risky behavior: a report of 102 autopsy cases. Eur. J. Clin. Microbiol. Infect. Dis. 2019;38(2):305-317. DOI: 10.1007/s10096-018-3427-z

xv. Nessim J, Luna Ramirez JC, Moreno Gómez GA, Galvis Soto DM, Gomez Marin JE. Estimations of the number people with mental diseases associated

with toxoplasmosis and identification of risk factors by continent. Psychiatry Res. 2023;323:115130. DOI: 10.1016/j.psychres.2023.115130

xvi. Lindgren M, Torniainen-Holm M, Härkänen T, Dickerson F, Yolken RH, Suvisaari J. The association between toxoplasma and the psychosis continuum in a general population setting. Schizophr. Res. 2018;193:329-335. DOI: 10.1016/j.schres.2017.06.052

xvii. World Health Organization. Mental Health ATLAS 2017. Geneva. World Health Organization. 2018. 62 p. Available at: https://iris.who.int/bitstream/handle/10665/272735/9789241514019-eng.pdf?sequence=1

xviii. Stepanova EV, Kondrashin AV, Sergiev VP, Morozova LF, Turbabina NA, Maksimova MS, *et al.* Toxoplasmosis and mental disorders in the Russian Federation (with special reference to schizophrenia). PLOS ONE. 2019;14(7):e0219454. DOI: 10.1371/journal.pone.0219454

xix. Contopoulos-Ioannidis DG, Gianniki M, Ai-Nhi Truong A, Montoya JG. Toxoplasmosis and Schizophrenia: A Systematic Review and Meta-Analysis of Prevalence and Associations and Future Directions. Psychiatr. Res. Clin. Pract. 2022;4(2):48-60. DOI: 10.1176/appi.prcp.20210041

xx. Radua J, Ramella Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, *et al.* What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry. 2018;17(1):49-66. DOI: 10.1002/wps.20490

xxi. Guimarães AL, Araujo Coelho DR, Scoriels L, Mambrini J, Do Valle Antonelli LR, Henriques P, *et al.* Effects of *Toxoplasma gondii* infection on cognition, symptoms, and response to digital cognitive training in schizophrenia. Schizophrenia. 2022;8(1):104. DOI: 10.1038/s41537-022-00292-2

xxii. Veleva I, Stoychev K, Stoimenova Popova M, Stoyanov L, Mineva Dimitrova E, Angelov I. *Toxoplasma gondii* seropositivity and cognitive function in adults with schizophrenia. Schizophr. Res. Cogn. 2022;30:100269. DOI: 10.1016/j.scog.2022.100269

xxiii. Fond G, Boyer L, Schürhoff F, Berna F, Godin O, Bulzacka E, *et al.* Latent toxoplasma infection in real-world schizophrenia: Results from the national FACE-SZ cohort. Schizophr. Res. 2018;201:373-380. DOI: 10.1016/j.schres.2018.05.007

xxiv. Liu T, Gao P, Bu D, Liu D. Association between *Toxoplasma gondii* infection and psychiatric disorders: a cross-sectional study in China. Sci. Rep. 2022;12(1):15092. DOI: 10.1038/s41598-022-16420-y

xxv. Chand SP, Arif H. Depression. PubMed. 2023. Date of citation: January 22, 2024. Available at: https://pubmed.ncbi.nlm.nih.gov/28613597/

xxvi. Yalın Sapmaz Ş, Şen S, Özkan Y, Kandemir H. Relationship between *Toxoplasma gondii* seropositivity and depression in children and adolescents. Psychiatry Res. 2019;278:263-267. DOI: 10.1016/j.psychres.2019.06.031

xxvii. Nasirpour S, Kheirandish F, Fallahi S. Depression and *Toxoplasma gondii* infection: assess the possible relationship through a seromolecular case-control study. Arch. Microbiol. 2020;202(10):2689-2695. DOI: 10.1007/s00203-020-01993-x

xxviii. Lin HA, Chien WC, Huang KY, Chung CH, Chen LC, Lin HC, *et al.* Infection with *Toxoplasma gondii* increases the risk of psychiatric disorders in Taiwan: a nationwide population-based cohort study. Parasitology. 2020;147(13):1577-1586. DOI: 10.1017/S0031182020001183

xxix. Kamal AM, Kamal AM, Abd AS, Rizk MM, Hassan EE. Latent Toxoplasmosis is Associated with Depression and Suicidal Behavior. Arch. Suicide Res. 2022;26(2):819-830. DOI: 10.1080/13811118.2020.1838368

xxx. Bahceci I, Bahceci B, Senturk S, Yildiz IE, Yazici ZA. Correlation of Suicidal Thoughts and Toxoplasmosis in Patients With Depression. Cureus. 2021;13(2): e13369. DOI: 10.7759/cureus.13369

xxxi. Bak J, Shim SH, Kwon YJ, Lee HY, Kim JS, Yoon H, *et al.* The Association between Suicide Attempts and *Toxoplasma gondii* Infection. Clin. Psychopharmacol. Neurosci. 2018;16(1):95-102. DOI: 10.9758/cpn.2018.16.1.95

xxxii. Ibrahim I, Tobar S, Fathi W, ElSayed H, Yassein A, Eissa A, *et al.* Randomized controlled trial of adjunctive Valproate for cognitive remediation in early course schizophrenia. J. Psychiatr. Res. 2019;118:66-72. DOI: 10.1016/j.jpsychires.2019.08.011

xxxiii. Daher D, Shaghlil A, Sobh E, Hamie M, Hassan ME, Moumneh MB, *et al.* Comprehensive Overview of *Toxoplasma gondii*-Induced and Associated Diseases. Pathogens. 2021;10(11):1351. DOI: 10.3390/pathogens10111351

xxxiv. Deeb A, Hassan AA, Tolba ME, Huseein EA. The Effects of Two Antipsychotic Drugs and Prolactin on *Toxoplasma gondii* Tachyzoites in Vivo. J. Egypt. Soc. Parasitol. 2021;51(2):355-364. DOI: 10.21608/jesp.2021.193315

xxxv. Kezai AM, Lecoeur C, Hot D, Bounechada M, Alouani ML, Marion S. Association between schizophrenia and *Toxoplasma*

gondii infection in Algeria. Psychiatry Res. 2020;291:113293. DOI: 10.1016/j.psychres.2020.113293

xxxvi. Chorlton SD. *Toxoplasma gondii* and schizophrenia: a review of published RCTs. Parasitol. Res. 2017;116(7):1793-1799. DOI: 10.1007/s00436-017-5478-y

xxxvii. Wiener RC, Waters C, Bhandari R. The association of *Toxoplasma gondii* IgG and cognitive function scores: NHANES 2013-2014. Parasitol. Int. 2020;78:102123. DOI: 10.1016/j.parint.2020.102123

xxxviii. Gale SD, Erickson LD, Thacker EL, Mitchell EL, Brown BL, Hedges DW. *Toxoplasma gondii* seropositivity and serointensity and cognitive function in adults. PLoS Negl. Trop. Dis. 2020;14(10):e0008733. DOI: 10.1371/journal.pntd.0008733

xxxix. Haan L de, Sutterland AL, Schotborgh JV, Schirmbeck F, Haan L de. Association of *Toxoplasma gondii* Seropositivity With Cognitive Function in Healthy People: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021;78(10):1103-1112. DOI: 10.1001/jamapsychiatry.2021.1590

xl. Mendy A, Vieira ER, Albatineh AN, Gasana J. Immediate rather than delayed memory impairment in older adults with latent toxoplasmosis. Brain. Behav. Immun. 2015;45:36-40. DOI: 10.1016/j.bbi.2014.12.006

xli. Wyman CP, Gale SD, Hedges Muncy A, Erickson LD, Wilson E, Hedges DW. Association between *Toxoplasma gondii* Seropositivity and Memory Function in Non-Demented Older Adults. Neurobiol. Aging. 2017;53:76-82. DOI: 10.1016/j.neurobiolaging.2017.01.018

xlii. Boillat M, Hammoudi PM, Dogga SK, Pagès S, Goubran M, Rodriguez I, *et al.* Neuroinflammation-Associated Aspecific Manipulation of Mouse Predator Fear by *Toxoplasma gondii*. Cell Rep. 2020;30(2):320-334.e6. DOI: 10.1016/j.celrep.2019.12.019

xliii. Zouei N, Shojaee S, Mohebali M, Keshavarz H. The association of latent toxoplasmosis and level of serum testosterone in humans. BMC Res. Notes. 2018;11(1):365. DOI: 10.1186/s13104-018-3468-5

xliv. Postolache TT, Wadhawan A, Rujescu D, Hoisington AJ, Dagdag A, Baca-Garcia E, *et al. Toxoplasma gondii*, Suicidal Behavior, and Intermediate Phenotypes for Suicidal Behavior. Front. Psychiatry. 2021;12:665682. DOI: 10.3389/fpsyt.2021.665682

xlv. Johnson SK, Fitza MA, Lerner DA, Calhoun DM, Beldon MA, Chan ET, *et al.* Risky business: *Toxoplasma gondii* infection and entrepreneurship behaviours across individuals and countries. Proc. R. Soc. B Biol. Sci. 2018;285(1883):20180822. DOI: 10.1098/rspb.2018.0822

Letter to editor

Effective Communication as a Contribution of Linguistics Applied to Health Services

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La comunicación efectiva como un aporte de la lingüística aplicada a los servicios de salud

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Dear Editor:

Human communication is a natural act in which things happen.[i] A concern arises when thinking about how this act goes among people who relate to each other in healthcare institutions since we cannot avoid talking to each other throughout the day. It is precisely in this context that this analysis aims to understand some ideas on the use of language in the professional environment from the approach of applied linguistics, to consider its contributions, changing paradigms, and acquiring skills for effective communication.

When we have a conversation, phenomena that seem imperceptible often occur, such as body synchronization, which "happens when two people get into a rhythm," but there are also people who interrupt during the conversation; in linguistics, this is known as overlapping: "when two or more people speak simultaneously for a short period."[i]

Dr. Pilar Ospina analyzed reasons why physicians interrupt patients after an average of 11 seconds from the moment attention begins.[ii] In her article, she emphasizes that the cause may be the limited time for the treatment provided in the service, the fatigue of the medical staff, and the language barriers between the two. However, the point to emphasize is the purpose of the interruption and the way it is done. It is of interest to mention another example: what about interruptions between colleagues who, during meetings, discuss healthcare problems?

These are two different moments in which this phenomenon happens: disruption. It is relevant to consider whether the overlapping is collaborative or competitive. It is said to be collaborative when the purpose of interrupting is to support the idea, and to add elements that reinforce it. It usually occurs in conversations between friends and people with a lot of trust and none of the speakers is intimidated or annoyed. But in the competitive one, the purpose is "to be antagonistic with the speaker, as they try to steal the turn and divert the topic to another aspect."[i]

It is at this moment when the relationship between the conversational partners ceases to be empathetic and becomes "metaphorically as aggressive and invading my space" because we perceive that he or she "interrupts us because he can," after all, he or she is an expert (case of doctor and patient), giving the perception that "you will only speak when I tell you to, and you will shut up when I tell you to." In a conversation between boss and collaborator, the perception is usually not so different, especially if the interrupter is a man and if the speaker is a woman, even when the overlap is collaborative because power relations are decisive when it comes to yielding and retaining the floor.[i,iii]

In the healthcare system, humanization is not possible if we have conversations that, far from being healing, make people feel violence in their treatment, inequality, and disrespect, taking us away from our raison d'être: to improve people's health and work as a team. Applying a very simple skill such

as apologizing when interrupting "leads to a polite withdrawal from the conversational terrain of the other and we reestablish interpersonal balance," even though the interruption may be justified.[i]

Another aspect to consider if we want to improve communication is to bear in mind that "to have a conversation is to know how to listen," as Estrella Montolío, professor of Spanish Language, says. It implies not only keeping silent, but being present in the dialogue with attention to recognize when to intervene or yield the floor. She points out the importance of using non-verbal strategies such as looking into the eyes, nodding to show approval, minimal statements such as "yes," "of course!" or collaborative reactions such as "wow!" "Really?" which confirms to the interlocutor that attention is being paid and an effective connection has been established."[i]

According to Herbert Paul Grice, during the conversation, it is essential to observe a phenomenon that he calls the "cooperative principle" since he asserts that when two or more people engage in dialogue, there is implicit cooperation where certain rules or "conversational premises are applied: contribute with the necessary information, do not say what you believe to be false and lack adequate evidence, be relevant, be brief, be clear, avoid ambiguity."[iv]

These rules are necessary to achieve the objective of the conversation. If these are not complied with, they can produce confusing and false messages, so that a patient goes home with the wrong message or an associate performs functions with confusing instructions, resulting in outcomes that affect healthcare services.

During the conversation, the way the message is delivered, and the choice of words (for example, the use of personal pronouns) have such complex implications that they generate work and emotional stress in healthcare personnel at moments, when they have to communicate bad news to the patient and family.[v] How do I start the conversation: with an "I," or a "you?" These simple words can be the key to improving the transmission of the message in these difficult conversations.[vi]

Sometimes, one uses metaphors so that the message is understood.[vi] Based on cognitive linguistics and the Theory of Conceptual Metaphors developed by George Lakoff and Mark Johnson, which intend to facilitate understanding and communicative effectiveness concerning the target domain, it is interesting to reflect on how the analysis of the use of metaphors in the understanding of, for example, schizophrenia, by those affected and their treating physicians, can improve the results of treatment and recovery.[vii]

In short, just as we improve our diet and other aspects that make us healthy and happy, it is important to pay attention to what we speak and what words we use since language results from a continuous and daily learning process. We should consider these contributions as an additional tool that can improve the communication skills of healthcare personnel.

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References

i. Montolío E. Cosas que pasan cuando conversamos. 1era Edición. Barcelona. Editorial Planeta, S.A.; 2020. Capítulo 1, Las cosas que pasan cuando dos hablan a la vez. 25-49

ii. Ortega P. Physicians Interrupting Patients. USA. Journal of general internal medicine.2019; 34(10):1961-1962. DOI: 10.1007/s11606-019-05139-8

iii. Bisbee J, Fraccaroli N, Kern A. Yellin' at Yellen: Gender Bias in the Federal Reserve Congressional Hearings. USA. SSRN eJournals. 2022; 37. DOI: 10.2139/ssrn.4030121

iv. Khusna FA, Aliyah SL, Asyifah DA. Investigating the use of maxims in the efl class presentation: a pragmatic study. SAGA. 2021;2(2):133-44. DOI: 10.21460/saga.2021.22.80

v. Almonacid L, Rueda G, Eduardo F, Herrera S, Miguel J. Conversaciones difíciles en medicina: el profesionalismo y humanismo en el arte de comunicar malas noticias. Universitas Medica. 2020;61(1). DOI: 10.11144/javeriana.umed61-1.conv

vi. Álvarez C. Una reseña acerca de "Cosas que pasan cuando conversamos". Chile. Rev.Chil. Fonoaudiol. 2021; 20(1):1-2. DOI: 10.5354/0719-4692.2021.65423

vii. Coll-Florit M, Miranda X, Climent S. Metáforas de la esquizofrenia: Un estudio sobre el discurso de afectados y profesionales. Revista Española de Lingüística Aplicada.2019; 32(1):1-31. DOI: 10.1075/resla.16003.col

Letter to editor

Dietary Education of Parents and Caregivers Promotes Healthy Lifestyles for Children

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La educación alimentaria de padres y cuidadores promueve estilos de vida saludables en los niños

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Ms. Editor:

On July 20, 2022, the article on "Oral diagnosis in preschool children living in a marginal urban area" was published, where a high frequency of dental caries was found in the population studied, which can cause short and long term repercussions, not only in dental health but also in general health.[i]

Therefore, it is important to treat it promptly to prevent physical and psychological health problems in patients. This clinical picture causes complex dental alterations that involve pain, esthetic alterations, malnutrition, halitosis, and diminished self-esteem, among others.[i,ii]

This pathology is multifactorial and has been described in various studies, among which the following stand out: poor dental hygiene, genetic predisposition, and low attendance at prevention programs.[i-iii]

At this point, a notorious cause is the frequent consumption of cariogenic foods, which are part of the children's diet at home and school.[i,ii] Cariogenic foods are high in sugar, which generates acids and tooth demineralization to the point of their possible destruction.[ii]

The problem is that the children's food choices are made by their caregivers, parents, or teachers, who often do not have an adequate nutritional dietary orientation but rather unhealthy habits that have lasted all their lives.[iii]

In the preschool and school stages, children begin to develop their preferences for foods and discriminate against those that are not palatable, so it is important that they become accustomed to eating nutritious foods with less sugar, fat, and salt at this age.[iv]

These feeding practices are influenced by the cultural, social, and even emotional context that the caregivers have acquired; thus, they are transmitted to new generations.[iii]

This lack of knowledge among adults is added to the pressure of energy-dense food advertising, which offers a wide variety of products with high cariogenic potential, such as sweets and fast food products with high cariogenic potential. They are also low-cost and even come with toys or other gifts as part of the advertising.[ii,iv]

Children do not have enough knowledge to reflect on the damage caused to their health by consuming these foods; they will not understand an explanation of the amount of calories and the percentage of fat a cookie contains. The only thing they will remember is its pleasant taste, compared to the taste of carrots, which are also sweet.[v]

Equally important is the misguided practice of caregivers providing children with sugary and carbonated beverages, candy, and other snacks to reward achievement or control children's negative emotions, such as temper tantrums.[v]

Given this situation, it is necessary to change the habits of caregivers so that children acquire healthy lifestyles. Parents must know what foods to buy, read and understand nutritional labels, and prepare and cook.[v]

As the parents develop competencies and skills in nutrition, they can decide on their family's diet according to their needs

and socioeconomic context. Eating patterns are born within the family and are imitated in other places, such as school.[v]

Health-promoting dietary behaviors will enable children to develop healthy lifestyle habits and prevent non-communicable diseases such as dental caries, among others.[iii,iv]

At the international level, there have been efforts to ensure adequate child nutrition and to correct dietary problems in the early stages of childhood. Thus, dietary guidelines and child feeding manuals have emerged, but efforts to educate caregivers have not been sufficient.[iii,v]

Health professionals of the different branches must inform caregivers about healthy eating habits. It is not enough to say, during healthcare: "do not eat this or that"; it is important to explain in simple words the short and long-term consequences of not eating healthily and choose the most appropriate foods according to the age group and other concomitant health conditions.[v]

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References

i. Arévalo Y, Rodríguez J. Diagnóstico bucodental en niños de parvularia residentes de una zona urbanomarginal. Alerta. 2022;5(2):153-158. DOI: 10.5377/alerta.v5i2.12813

ii. Guzmán J, Loza J, Flores C, Crespo E. Influencia del consumo de alimentos cariogénicos y presencia de caries dental en la etapa escolar. RUSXXI. 2023;3(9):30-42. DOI: 10.57246/rusxxi.v3i9.64

iii. Giraldo O. Prácticas de alimentación de los padres y conductas alimentarias en niños: ¿Existe información suficiente para el abordaje de los problemas de alimentación? 2014. 2014;6(1):57-74. Available at: http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S2145-48922014000100005

iv. Andrade L, De Pablo C, Córdova R, Armijos J. La dieta y su influencia en las caries de infantes en la educación urbana-rural. Salud y Vida. 2022;6(3):337-349. DOI: 10.35381/s.v.v6i3.2250

v. Nazar G, Petermann F, Martínez M, Leiva A, Labraña A, Ramírez K, *et al.* Actitudes y prácticas parentales de alimentación infantil: Una revisión de la literatura. Rev. chil. nutr. 2020;47(4):669-676. DOI: 10.4067/S0717-75182020000400669

Letter to editor

Regional Integration in Health in Central America and Dominican Republic: Achievents and Opportunities

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Dear Editor:

Integration is a broad process that involves social, political, economic, cultural, scientific, diplomatic, and even military links between two or more nations.[i] It is an opportunity to advance in the construction of the well-being of people, representing an excellent strategy for resolving severe regional social inequalities to move towards a more just, humane, and supportive development model.

Since years now, health has taken a prominent place in regional integration efforts, despite encountering various limitations. The regions of Central America and the Dominican Republic, due to their proximity, offer an area par excellence for addressing common problems that cross borders. This approach allows an adequate framework to undertake actions that, from the social determinants of health (SDH), not only consider the social determinants of health but also enable socio-sanitary and environmental issues, for the adoption of technical and legal instruments, joining efforts and promoting collective and diplomatic actions in the field of health. It should be noted that the region has a long history of regional integration projects, which survive and recover despite recurrent crises.[ii] Consequently, the complexity of this region should not be underestimated. There are ideological differences, various levels of development and institutional factors specific to each country, cultural diversity, and vulnerable groups such as indigenous peoples and migrant groups, among others.

In Central America, the latest regionalism strategy implemented is the current Central American Integration System (SICA), created more than three decades ago.[iii] It is a multidimensional integration initiative. The Tegucigalpa protocol sets out economic, political, social, cultural, educational, and environmental dimensions, based on five pillars: security and democracy, prevention and mitigation of natural disasters, social integration, economic integration, and institutional strengthening.

As a result, it included the establishment of Sectoral Councils of Ministers, among which is the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA). Since 2007, it has been a fundamental pillar of governance through the Executive Secretariat (SE-COMISCA), based in El Salvador, which is an instance for the formulation of technical proposals, projects, and follow-up of the agreements of the ministers, as well as an active protagonist for building strategic alliances and mobilizing funds for regional projects.

COMISCA's regional strategy rests on the periodic meetings of the Ministers of Health, which provide an appropriate framework for discussion and dissemination of information, in addition to building consensus and promoting joint strategies to overcome public health access barriers. It also facilitates the identification of cross-border health problems, the management of responses, and the evaluation of lessons learned in health policies, thus promoting a virtuous circle for policy formulation and decision-making.

Regional integration in health in Central America has enabled the development of common strategies in response to epidemics

(such as the COVID-19 pandemic, influenza, dengue, yellow fever, and adolescent pregnancy, among others) and the strengthening of national capacities of the member countries. It has also launched important regional cooperation projects for access to medications in areas related to global health, epidemiological surveillance, laboratory surveillance, migration, and healthy eating, among others.

Among the achievements of the health integration process in Central America, it is worth citing the following:

Identification of common problems: certain problems transcend the national borders of the countries, which requires the structuring of shared responses. An example of these actions are the cross-border binational agreements for the elimination of malaria, under the framework of the Regional Initiative for the Elimination of Malaria.

Common addressing criteria for diseases: an example of this occurred in the context of the COVID-19 pandemic. Guidelines were proposed to strengthen mental health and biosecurity; a regional contingency plan in addition to periodic regional reports.

Production of regional public goods: the identification of common problems and shared responses has generated the possibility of innovation for a common good whose appropriation by one country does not harm the other. For example, the FACEDRA regional pharmacovigilance system for monitoring adverse drug reactions, used by the eight pharmacovigilance centers of the member States, reports weekly to the World Health Organization's international drug monitoring program.

Appropriate mechanism for public health emergencies, epidemics, and pandemics: in response to the COVID-19 pandemic and public health contingencies caused by natural disasters, SE-COMISCA is promoting capacity building in the countries in areas such as laboratory, epidemiological surveillance, and others. At present, a proposal is being discussed for a mechanism to help Member States coordinate regionally to mobilize the cooperation of partners and facilitate horizontal cooperation in the event that a rapid response is required in any type of health emergency or multi-hazard situation.

Information and knowledge production: there are mechanisms for the exchange of information on certain prioritized diseases, as well as on the policies to respond to them, which constitutes a window of opportunity to provide feedback for policy formulation processes and transnational cooperation through COMISCA's operational bodies. These bodies are commissions, networks, or specialized technical groups composed of experts from the eight Member States, facilitated by SE-COMISCA.

Consensus building: the region has a privileged opportunity to build consensus based on the principles of equity and solidarity that place health as a fundamental right.

Regional negotiations and access to medicines: the COMISCA Joint Negotiation emerged in 2007, with the support of international cooperation until its institutionalization and self-sustainability, to become a procurement mechanism that facilitates access to quality and efficacy medicines at more favorable prices for member states. This process facilitates cost containment and economies of scale, and has its own regulatory framework. The price negotiation processes have the value of a national tender therefore, the member states can execute their contracts based on the prices negotiated at the regional level. COMISCA Joint Negotiation reduces drug prices by an average of 30 %. In 13 years of implementation, it has resulted in savings of US$120 million for SICA member states.

Effective global health diplomacy: within the framework of COMISCA, joint positions have been issued on addressing non-communicable diseases, tuberculosis, and other health threats, through the adoption of joint declarations issued within the framework of the United Nations General Assembly.

Networking: allows for a horizontal cooperation model with focal points from the various Ministries of Health of Central America and Domincan Republic to join efforts around common problems of regional interest, which favors the strengthening of the capacities of these ministries. Health integration in Central America and the Dominican Republic is a process that has been consolidated since the creation of SICA, through the momentum that COMISCA has offered by binding political decisions on prioritized issues.

The organization of COMISCA is formed by different bodies which, through the regional technical commissions, networks, specialized technical groups, and regional coordination mechanisms generate technical work and horizontal cooperation among the countries. These working mechanisms operate in accordance with the Guidelines for the Organization and Functioning of the Regional Technical Commissions, Technical Committee, Specialized Technical Groups, Networks and Regional Mechanisms of COMISCA and contribute with their actions and proposals to the execution of the ongoing Health Plan for Central America and

the Dominican Republic and other political and technical instruments.

The COMISCA sessions have made possible the construction of a regional health community that shares challenges, is concerned about common problems and has developed a common episteme, such as the importance of social determination and health, with projects, policies and activities to address them.

The institutional and legal framework of the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA), as the decision-making body of SICA, allows the ministers of health of the eight member States, to make binding decisions by consensus.

The health integration process in Central America and the Dominican Republic has been progressing by building a governance with well-defined game rules, leading to the development of important policies such as the recently approved PRSS 2023-2030. Therefore, one can conclude that the health integration processes in Central America and the Dominican Republic have been consolidated with a governance that reflects the scope of cooperation, taking advantage of its structure, recognizing the articulations with the rest of the Central American Integration System, coordinating regional actions with the Pan American Health Organization (PAHO), the Economic Commission for Latin America and the Caribbean (ECLAC), the United States Center for Disease Control (CDC) and other strategic allies, and harmonizing cooperation agendas on health and its determinants.

After all, as an ancient thinker once said: "Men are angels with only one wing. To fly, they need to embrace each other."

References

i. Venegas San Martín F. Pensar la integración regional desde los márgenes: la importancia y desafíos de la dimensión subestatal en América Latina desde la experiencia chileno-argentina. Si Somos Americanos. 2019;19(2):69-88. DOI: 10.4067/S0719-09482019000200069

ii. Nolte D. Lo bueno, lo malo, lo feo - y lo necesario: Pasado, presente y futuro del regionalismo latinoamericano. Rev. Urug. Cienc. Polít. 2019;28(1)131-156. DOI: 10.26851/RUCP.28.1.5

iii. Arriaza RS. Integración centroamericana, una (re)visión crítica y estratégica. Revista Con-Secuencias. 2023;(4):4-62. Available at: https://revistas.ues.edu.sv/index.php/rcs/article/view/2579

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Original article

Research works that have not been published or proposed for revision in other journals and provide information to understand or propose solutions to the main health problems. Case series studies, descriptive and analytical cross-sectional studies, case-control studies, cohort studies, and randomized controlled trials are considered for publication. Results must be original.

The article must have the following structure: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 4000 words and a minimum of 3000, not including references, abstract and text of figures and tables. The abstract must have a maximum of 250 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 35 references and a minimum of 25 are allowed. 65 % of references must not be older than five years since their publication date. Only 10 % of grey literature is allowed as part of references. Tables and figures must not be more than five in total.

For observational studies, it is recommended the format according to STROBE guidelines. For randomized controlled trials, it is recommended the format according to the CONSORT statement.

Review article

Review articles that present the result of an analysis of recent information or a thematic update of interest in public health, following any of the accepted methodologies for this purpose. It is required to indicate that it is a narrative or systematic review.

Systematic review and meta-analysis

Systematic reviews representing a synthesis of evidence, original, quantitative or qualitative studies, that use a rigorous process to minimize biases and that identify, evaluate and synthesize studies to answer a specific clinical question are accepted. The search process for the original studies, the criteria used for the selection of those that were included in the review and the procedures used in the synthesis of the results obtained by the reviewed studies must be described in detail.

The article must have the following sections: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 4000 words and a minimum of 3000, not including references, abstract and text of figures and tables. The abstract must have a maximum of 250 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and references in the abstract is not allowed. There is no limit to the number of references. 75 % of them must not be older than five years since their publication date. The use of grey literature as part of references is not permitted. Tables and figures cannot be more than five in total.

Recommended format: PRISMA guide.

Narrative or critical review

Narrative or critical review must have descriptive writing and make a comprehensive presentation and discussion of topics of scientific interest in the field of public health. A clear formulation of a scientific object of interest with logical argumentation must be presented.

The article must have the following sections: abstract, keywords, introduction, discussion, conclusion and references. The text must have a maximum of 3500 words and a minimum of 2500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words. Use of acronyms, abbreviations and references in the abstract is not allowed. A maximum of 50 references and a minimum of 30 are allowed. 70 % of them must not be older than five years since their publication date. Only 15 % of grey literature is allowed as part of references. Tables and figures cannot be more than three in total.

Brief communication

This type of scientific paper is shorter than an original article. They are works that aim to publish data of interest in the health situation on a report of a research in development and innovative techniques or methodologies, among others.

The article must have the following sections: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 2000 words and a minimum of 1500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 20 references and a minimum of 15 are allowed. 65 % of them must not be older than five years since their publication date. Only 5 % of grey literature is allowed as part of references. Tables and figures cannot be more than three in total.

Case report

This type of text refers to the presentation of clinical cases that meet established criteria and whose diagnostic and treatment aspects make a considerable contribution to scientific knowledge on the subject. It must respect the provisions of the Declaration of Helsinki and international ethics guidelines ffor health-related research involving human beings.

The text must have the following sections: abstract, keywords, introduction, case presentation, treatment, outcome, clinical diagnosis, discussion, ethical aspects and references. The text must have a maximum of 2000 words and a minimum of 1500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words and must be structured in case presentation, treatment and outcome. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 20 references and a minimum of 15 is allowed. 70 % of them must not be older than five years since their publication date. Only 5 % of grey literature is allowed as part of references. Tables and figures cannot be more than five in total.

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Letter to the editor

Letter to the editor or the editorial committee clarifying, discussing or commenting on the content presented in previous issues of this journal. Comment letters on specific public health issues may also be accepted. Letters must have the following sections: title and object of correspondence. It can have a maximum of 1000 words and a minimum of 700. Tables and figures are not accepted. A maximum of five references and a minimum of three are accepted.

Summary of the characteristics of the different articles

General format for the presentation of articles					
Type of manuscript		Word count	References	Abstract	Tables or figures
Original articles		3000 – 4000	25 – 35	250 words (structured)	Up to 5
Review articles	Systematic	3000 – 4000	As appropiate	250 words (structured)	Up to 5
	Narrative	2500 – 3500	30 – 50	200 words	Up to 3
Brief communications		1500 – 2000	15 – 20	200 words (structured)	Up to 3
Case report		1500 – 2000	15 – 20	200 words (structured)	Up to 5
Letter to editor		700 – 1000	3 – 5	No	No

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