Impact of COVID-19 on mental health in Uruguay

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Scientific excellence for the consolidation of the national health systems

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In the past few years, we have witnessed a growing interest and awareness surrounding mental health because of the COVID-19 pandemic. It is becoming evident that mental health publications play a critical role in promoting a more informed and empathetic society. In this regard, it is important to recognize the direct impact that these publications have on public health.

Mental health affects people of all ages and socioeconomic backgrounds. However, it has long been stigmatized[1] and relegated to the background compared to other areas of medicine. Fortunately, this is changing thanks to the tireless work of dedicated professionals and committed organizations within El Salvador's National Integrated Health System.

Mental health publications that you are about to read in Volume 6, Nº. 2 of Alerta journal play an influential role in providing accurate and up-to-date information on a diverse array of topics. This issue includes five case reports, two original articles on mental health during the pandemic, one from Uruguay and one from Spain, a brief communication on lidocaine management in palliative care patients, five narrative reviews and three correspondences, including one from Peru on occupational stress in frontline staff in the care of COVID-19.

The objective of this publication is not only to educate health personnel and the general public about the challenges faced by people with mental health disorders but also to provide an invaluable tool for professionals in this field about the need to generate new, rigorous, and exhaustive research, relevant clinical studies and innovative therapeutic advances that will continuously improve the quality of care in this area of health.

These scientific papers also foster the exchange of knowledge among experts, which in turn promotes research and development in mental health. Increasing awareness and understanding of the issues in this critical area of health contributes to reducing stigma and promoting a more inclusive environment for those with mental illness.

In addition, by providing accurate, evidence-based information, publications contribute to better decision-making by health professionals, which translates into more effective and personalized care. It is important to emphasize that all these publications should be available in different formats and languages, in journals that, like this one, are open access.

It is everyone's responsibility to support and value these kinds of publications, as they represent a fundamental tool to improve our collective understanding of mental health and promote positive change in our society.

Finally, this issue of Alerta journal publishes a correspondence on simulation-based education in pediatrics, another transcendental topic to improve the quality of health care through learning and development of clinical skills and abilities in a controlled and safe environment for professionals in the public health care sector. This provides the opportunity to acquire theoretical and practical knowledge more effectively, as they can experience different clinical scenarios without putting people's lives at risk, encourages decision-making and teamwork as an effective tool to face
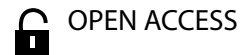
complex clinical situations, and improve the quality of pediatric care.

It is with joy that we present today Volume 6, No. 2, whose content reflects our interest in discussing topics that are of great concern to the National Institute of Health: mental health and the education of health personnel in health issues. The latter has been possible by employing simulation as a learning technique through the National Simulation Center, not to mention the recent publication of the results of the National Mental Health Survey, the first of its kind in El Salvador[2].

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Respiratory failure in a patient with Sézary syndrome

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Abstract

Case presentation. A 44 year old female patient, with no preexisting underlying disease, with a history of approximately ten months of presenting pruritic erythematous-desquamative lesions initially localized in the lower extremities and latter generalized throughout the body, associated with weight loss of 15 kg. **Treatment.** Initial management consisted of topical corticosteroids and oral antihistamines with little clinical response. A dermatology work-up was initiated, and the initial diagnosis of malignant T-cell neoplasm was confirmed. A bone marrow smear was performed, in which "cerebriform" cells were identified, confirming the diagnosis of Sézary syndrome. The patient received cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone chemotherapy. **Outcome.** The initial response was favorable, with hospital discharge and outpatient follow-up. After three months of treatment, the patient consulted for a febrile episode, productive cough plus respiratory distress associated with bilateral basal rales, presented respiratory failure, and during induction of mechanical ventilation suffered cardiorespiratory arrest and died.

Keywords

Lymphoma, Sezary Syndrome, Mycosis Fungoides, Dermatitis Exfoliative.

Resumen

Presentación del caso. Paciente de 44 años de sexo femenino, sin ninguna enfermedad de base preexistente, con una historia de aproximadamente de diez meses de presentar lesiones eritemato-descamativas pruriginosas inicialmente localizadas en extremidades inferiores y que luego se generalizaron en todo el cuerpo, asociándose a la pérdida de peso de aproximadamente 15 kg. **Intervención terapéutica.** El manejo inicial consistió en corticoides tópicos y antihistamínicos orales con poca respuesta clínica. Se inició el estudio por dermatología y se confirmó el diagnóstico inicial de neoplasia cutánea maligna de células T. Luego se realizó el frotis de médula ósea, en el que se identificaron células «cerebriformes» que confirmaron el diagnóstico de síndrome de Sézary. La paciente recibió esquema de quimioterapia ciclofosfamida, doxorrubicina, vincristina, etopósido y prednisona. **Evolución clínica.** La respuesta inicial fue favorable, con alta hospitalaria y seguimiento en la consulta externa. Transcurridos tres meses de tratamiento, la paciente consultó por episodio febril, tos productiva más distrés respiratorio asociado a estertores basales bilaterales, presentó insuficiencia respiratoria y durante la inducción a la ventilación mecánica sufrió un paro cardiorrespiratorio y falleció.

Palabras clave

Linfoma, Síndrome de Sézary, Micosis Fungoide, Dermatitis Exfoliativa.

Introduction

Cutaneous T-cell lymphoma is a general term to identify non-Hodgkin's T-cell lymphomas that primarily affect the skin. There are many subtypes of cutaneous T-cell lymphoma, the most common of which are mycosis fungoides and Sézary syndrome (SS). They can simulate benign skin disorders, making them a diagnostic challenge for dermatologists[1,2].

SS and mycosis fungoides are closely related entities, with mycosis fungoides being considered the indolent form and SS its aggressive leukemic phase. Therefore, it is hypothesized that SS may evolve gradually from mycosis fungoides or occur spontaneously, although some authors now consider them to be different entities[2].

SS is a malignant neoplasm originating from T lymphocytes, which involves the skin and can extend to the bone marrow, blood lymphocytes, lymph nodes, and various organs, characterized by erythroderma, superficial adenopathy, and atypical cells in the blood[1].

Regarding the epidemiological distribution of this syndrome, it predominates in men with a 2:1 ratio between 60 and 70 years of age[1,3] and has an annual incidence rate of one every ten millions, representing 3 % of all cutaneous lymphomas[4]. This syndrome affects the white population more than African-Americans and does not present a genetic predisposition[2].

The prevalence of primary cutaneous lymphomas recorded between 1986 and 2002 in the Netherlands and Austria was 3 %[5], which represents similar data to those reported by the World Health Organisation, Organisation for Research and Treatment of Cancer (WHO/EORTC)[6]. In Argentina, a prevalence of 0.13 % was reported in a specialized dermatological center from 2006 to 2016[7].

Case presentation

A 44 year old female patient and a teacher; with no preexisting underlying disease, neither family nor surgical history. She consulted with a ten-month history of generalized pruritus, without visible skin lesions, accompanied by unquantified febrile episodes, fatigue, and decreased appetite, with a weight loss of 15 kg, which led to multiple consultations in which she had been prescribed laboratory tests and had received treatment with oral antihistamines. In addition, she had two months of onset with scaly, pruritic, progressive and generalized skin lesions (Figure 1 and 2), and was treated with oral antihistamines and topical steroids without improvement. Physical examination revealed marked xerosis, signs of grattage, intense generalized erythema and palpable cervical and inguinal lymphadenopathy.

She was evaluated by a dermatologist in private practice who decided to perform a skin biopsy of the dorsal and anterior chest region. The results of the skin biopsy with immunohistochemical (IHC) assessment revealed: CD20 negative, CD3 positive, CD5 positive, CD7 negative, CD8 positive in 10 % with a diagnosis of malignant cutaneous T-cell neoplasm (Sézary Syndrome).

Due to the persistence of the febrile process and the worsening of the patient's general condition, it was decided to transfer her to the Medical-Surgical Hospital of the Salvadoran Social Security Institute (ISSS), where laboratory tests reported marked leukocytosis (leukemoid reaction), in peripheral blood smear: Decreased erythrocyte line with moderate anemia, normocytic, normochromic, immature cells from 8 % to 10 % with characteristics of large lymphocyte-like cells with abundant cytoplasm and irregular nuclei (Table 1).

Chest X-ray showed mediastinal widening without evidence of consolidating lesions in both lung fields (Figure 2). In addition, palpable cervical and inguinal adenopathies were identified on physical examination. As a result, inpatient management was decided to complete the study.

Computed tomography of the neck, thorax, abdomen and pelvis highlighted the presence of conglomerate lymphadenopathy in both jugular chains, posterior neck, supraclavicular and inguinal triangles without areas of necrosis or calcifications. These findings led to the suspicion of lymphoproliferative syndrome (Figure 3).

Upon admission to the hospitalization service, she was evaluated by the hematology unit where a bone marrow aspirate was indicated for smear processing and biopsy (Figure 4), which showed the presence of hypercellularity with the presence of megakaryocytes, myeloid series with 60 % predominance of adult forms,

Figure 1. Erythematous scaly plaques with a tendency to confluence interspersed with areas of healthy skin, involving extensive areas of the anterior and dorsal region of the thorax.
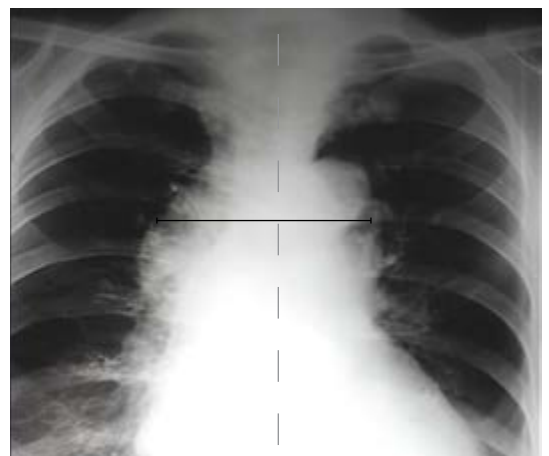
Figure 2. Chest X-ray images show the widening of the mediastinum related to a possible lymphoproliferative hematopoietic neoplasm

Table 1. Laboratory test results on admission

Hemogram	
White cells	$54{,}0 \times 10^6/mm^3$
Neutrophils	33,6 %
Lymphocytes	43,2 %
Monocytes	20,7 %
Hemoglobin	9,9 g/dL
Hematocrit	30,3 %
Platelets	362×10^3
Blood Chemistry	
Glucose	84,5 mg/dL
Creatinine	0,59 mg/dL
Urea nitrogen	9,3 mg/dL
Urea	20 mg/dL
Sodium	133 mEq/L
Potassium	4,1 mEq/L
C-reactive protein	20,2
Erythrocyte sedimentation rate	53 mm/h
Tiempos de coagulación	
Partial Thromboplastin time	38,6 segundos
Prothrombin time	13,3 segundos
International normalized ratio (INR)	1,2

EUrine test: yellow, density: 1020 pH: 6; protein: 0 mg/dl; leukocytes 10-15 per field; leukocyte esterase and urine sediment: negative
Blood and urine cultures: negative
Electrocardiogram: no abnormalities.

although with a slight increase of juvenile forms and toxic granulation. The erythroid series with normal shape and size but decreased in 20 %; lymphoid series with 20 % presented irregular nuclei, some with condensed chromatin and "cerebriform" appearance, a pathognomonic finding in this disease. The bone marrow biopsy was negative for lymphoma.

Flow cytometry reported that 76 % of all events are lymphocytes, 97 % of T lymphocytes are CD4 and express CD3, CD4, CD5, CD2, CD25 heterogeneous and CD7 negative, CD34, CD10, and CD56 negative with immunophenotype reading of adult T-cell lymphoma-leukemia or anaplastic lymphoma.

Therapeutic intervention

The initiation of the chemotherapy regimen available at the institutional level was indicated, with cyclophospha-mide, doxorubicin, vincristine, etoposide and prednisone (CHOEP).

Five days after the start of chemotherapy, she presented febrile peaks of 38. 5°C, documented leukopenia/neutropenia associated with chemotherapy, so reverse isolation was implemented, a prophylactic antibiotic regimen was started with: 2 g of ceftriaxone, intravenously every day, plus 900 mg of clindamycin, orally every eight hours. The febrile peaks persisted, and *Acinetobacter baumannii*, with sensitivity to carbapenems, was preliminarily identified in blood cultures (Table 2). This data was confirmed in the definitive report. The patient consulted with the infectious disease specialist, who indicated treatment with 500 mg of imipenem intrave-

Figure 3. Axial abdominal CT scan identifying multiple clusters of retroperitoneal para-aortic adenopathy (arrows)
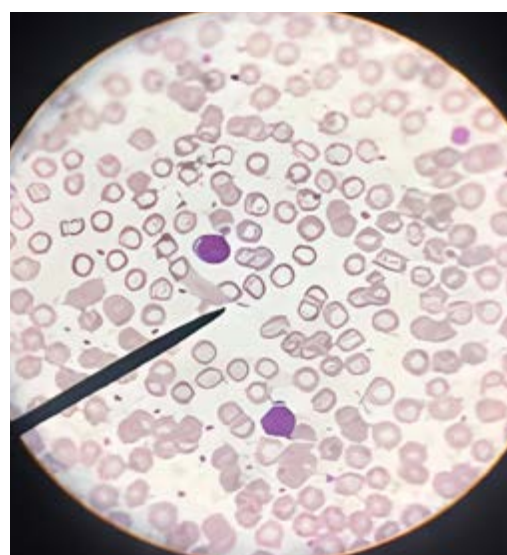
Figure 4. Bone marrow aspirate smear, atypical mononuclear cells (lymphocytes) with "cerebriform" nuclei, also called Sézary cells

nously every six hours for 14 days. The fever subsided on the second day of treatment.

Clinical evolution

The patient was discharged from the hospital due to clinical improvement with an increase in the number of white blood cells (Table 2). In addition, the outpatient follow-up plan by the hematology specialty was indicated.

After three months of oncological treatment, the patient consulted due to a week of unquantified febrile episodes, productive cough and dyspnea. The physical examination revealed bilateral basal rales and subcostal tension. As such, the patient management was in the area of maximum urgency, where she presented episodes of desaturation and frank respiratory distress. Therefore, starting mechanical ventilation was decided. During induction, the patient presented a cardiorespiratory arrest that was not reversed with resuscitation maneuvers, so she died.

Clinical diagnosis

The presence of cutaneous lesions associated with Sézary cells in bone marrow aspirate smears and the aberrant expression of markers in T lymphocytes by flow cytometry confirmed the diagnosis of Sézary syndrome as a variant of cutaneous T-cell lymphoma, eventually complicated by respiratory failure.

Discussion

SS was first described in 1938 by Sézary and Bouvrian, who described the Sézary syndrome triad, characterized by erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells in the skin, lymph nodes, and peripheral blood[6,8].

SS corresponds to stages IVA2 and IVB of cutaneous T-cell lymphoma (T 1-4, N 0-3, M 0-1, B 0-2) according to the specific staging and classification TNMB (Table 3) proposed since 2007 by the consensus between the International Cutaneous Lymphoma Society and the Cutaneous Lymphoma Working Group of the European Organization for Research and Treatment of Cancer (ISCL/EORTC)[9-11].

SS patients present extensive and infiltrative erythroderma often manifesting with leonine facies and intense pruritus, and may also present alopecia, ectropion, mild palmo-plantar keratoderma and nail onychodystrophy[2,9]. Adenopathy, hepatosplenomegaly, associated with more than 1000/mm³ (or >10 %) atypical mononuclear cells circulating in the bloodstream with "cerebriform" nuclei (Sézary cells), these cells can be: CD4+, CD7-, CD26- with a CD4+/CD8+ T-cell ratio >10[7,9].

Genetic factors have been implicated in its etiopathogenesis, in particular, rearrangements in the 6q23-27 region that lead to alterations in the MYB proto-oncogene and in the gene of interleukin-22 receptor subunit alpha-2 (IL22RA2)[4]; infectious factors such as human T-cell lymphotropic virus type 1, Epstein-Barr virus, cytomegalovirus and human herpesvirus type 8; immunological factors, including the lack of cytokine regulation, which influences tumor cells, where CD4 (Th2) T cells and their clones produce IL-4, IL-5, IL-6, and IL-10; and environmental factors, although their etiology remains unclear[7].

The diagnostic criteria for SS are: 80 % of erythroderma over of the body surface, abnormal lymphocyte count, presence of Sézary cells >1000 cells/mm³, increased CD4+ cells in peripheral blood, and a CD4/CD8 ratio >10.5 % to 35 %[7,11]. A skin biopsy may be inconclusive in slightly more than half of the cases (60 %)[12]. Evidence of clonal expansion of CD4+/CD7- ≥ 40 % or CD4+/CD26- ≥30 % is also considered sufficient for diagnosis[9].

The differential diagnosis of SS includes mycosis fungoides, psoriasis, pityriasis rubra pilaris, dermatitis, hypereosinophilic syndrome and adult T-cell leukemia, primary skin disorders such as scabies, adverse drug reactions and graft-versus-host disease[2,7,13]. It is frequently delayed in diagnosis (up to six years from initial presentation) as it can mimic benign inflammatory diseases[6].

Initial evaluation of these patients includes CBC, renal function, liver function tests, lactate dehydrogenase (LDH),

Table 2. Laboratory test results for febrile process

	Febrile process	Hospital discharge
White blood cells	3,28 x 10⁶/mm³	4,08 x ,10⁶/mm³
Neutrophils	13,6 %	63,6 %
Lymphocytes	23,1 %	27,2 %
Monocytes	10,2 %	7,7 %
Hemoglobin	9,8 g/dl	10,4 g/dL
Hematocrit	30,3 %	32,3 %
Platelets	368x10³	211x10³

Urine test and negative urine cultures
Chest X-rays, without alveolar occupancy evidence
Blood cultures: isolated Acinetobacter baumannii sensitive to carbapenems..

chest X-ray, CT, MRI and PET-CT scans, and initial lymph node biopsy[6].

The treatment depends on the stage of the disease; those with stage IA-IIA are initiated with skin-directed therapies, such as topical steroids or phototherapy (psoralen-UV-A [PUVA] or narrow-band UVB). In stage IIB patients, localized radiotherapy can be used if they are single lesions, or gemcitabine or doxorubicin in monotherapy in multiple lesions[2,7,9]. In patients with advanced stages, chemotherapy with liposomal doxorubicin, gemcitabine or alemtuzumab can be considered. If the patients are young, consider hematopoietic stem cell transplantation or therapy with mogamulizumab, a monoclonal antibody directed against the C-C chemokine receptor 4 (CCR4), a transmembrane cell surface receptor for the chemokines CCL17 and CCL22, which play a role in cell migration and trafficking of various lymphocyte subpopulations to the skin[12,14,15].

The prognosis is poor, with an approximate five year survival of no more than 30-40 % reported[9,11].

Ethical aspects

This case report was conducted by the principles of the Declaration of Helsinki. Patient confidentiality and nonmaleficence were considered.

Acknowledgments

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Case report

Idiopathic atrophoderma of Pasini and Pierini, an unusual approach

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Abstract
Idiopathic atrophoderma of Pasini and Pierini is a rare entity of unclear etiology, occurring as much as six times more frequently in women than in men, with a possible association with localized scleroderma (morphea). Case presentation. It is about a 30 years old woman who consulted with an asymptomatic lesion of two years of evolution on the left gluteal region. Physical examination revealed an oval plaque, depressed and acromic in its center, measuring five by ten centimeters. A 30 years old female patient who consulted about an asymptomatic lesion of two years of evolution on the left gluteal region. Physical examination revealed an oval plaque, depressed and acromic in its center, measuring five by ten centimeters. The patient was previously treated with multiple topical therapies without clinical improvement. **Treatment.** Skin biopsy showed minimal changes in the epidermis, homogenization, and thinning of the collagen without adnexal involvement. After a correlation was made with the clinical findings, starting treatment with high-potency intralesional steroids (triamcinolone acetonide) was recommended. **Outcome.** After administering two applications of the drug, four weeks apart, the complete resolution of the dermatosis was evidenced. One month after the last dose, the patient showed no recurrence.
Keywords
Atrophy, localized scleroderma, steroids, atrophoderma.

Resumen
La atrofodermia idiopática de Pasini y Pierini es una entidad poco frecuente y de etiología aún no esclarecida, se presenta con una frecuencia hasta seis veces mayor en mujeres que en hombres y una posible asociación con la esclerodermia localizada (morfea). **Presentación del caso.** Paciente femenina de 30 años, quien consultó por una lesión asintomática de dos años de evolución en el glúteo izquierdo. En el examen físico se evidenció una placa ovalada, deprimida y acrómica en su centro, que mide cinco por diez centímetros. La paciente había sido tratada previamente con múltiples terapias tópicas sin obtener mejoría clínica. **Intervención terapéutica.** Se realizó la biopsia de piel que demostraba cambios mínimos en epidermis, homogenización y adelgazamiento de colágeno sin afección de anexos. Se hizo correlación con los hallazgos clínicos y se decidió iniciar tratamiento con esteroides intralesionales de alta potencia (acetónido de triamcinolona). **Evolución clínica.** Posterior a la administración de dos aplicaciones del medicamento, con cuatro semanas de diferencia entre ellas, se evidenció la resolución completa de la dermatosis. Un mes después de la última dosis la paciente no mostró recidivas.

Palabras clave
Atrofia, esclerodermia localizada, esteroides, atrofodermia.

Introduction

Idiopathic atrophoderma of Pasini and Pierini (IAPP) is an infrequent dermatosis that affects the organization of dermal collagen fibers. It manifests clinically as areas of atrophy. Nontheless, these features are not evident in all cases[1]. Although some authors consider it a localized variant of morphea, others consider it a tatally distinct nosological entity[2]. IAPP is a single or multiple well-delimited, hyperpigmented, non-indurated patches with a slight depression of the skin, which may converge and form a confluent area with subsequent atrophy[3]. It was first described in 1923 by Pasini, who assigned it the name "progressive idiopathic atrophoderma." Thirteen years later, Luis Pierini studied this dermatosis and established a possible relationship with localized scleroderma. Subsequently, Canizares assigned it the term idiopathic atrophoderma of Pasini and Pierini[1]. Its etiology still remains uncertain.

AIPP usually occurs more frequently in women than men, with a 6:1[4] ratio, mainly in young people between the second and third decade of life, albeit there are reports of congenital cases. There appears to be no predominance in any specific geographic region or ethnicity[4-5]. The lesions remain without significant changes and evolve asymptomatically during the course of the disease, increasing in size and acquiring their definitive characteristics. Once established, they do not regress spontaneously.

At the present time, there are few cases of successful therapeutic approaches reported in the literature, and their treatment is a challenge for dermatological practice, which is why those therapeutic approaches that appear to be promising are of great interest[1-4].

Case presentation

This case is about a 30 year old female patient who consulted at the Specialized Health Unit of San Jacinto, San Salvador, El Salvador, with a history of presenting an atrophic, acromic, and asymptomatic lesion for over two years. Physical examination revealed a dermatosis localized on the upper and lower outer quadrants in the left gluteus region. The dermatosis consisted of a smooth surface, depressed oval-shaped, atrophic plaque with defined cliff borders measuring 5 × 10 centimeters. Inside it, there was an oval acromic macule, with laking clear limits, measuring 3.8 x 7.5 centimeters, with a soft consistency, chronic evolution, and asymptomatic (Figure 1).

The patient had no relevant personal or family medical history. Multiple previous treatments administered included topical steroids, emollient creams, and systemic antibiotics, with no evidence of improvement. Skin biopsy reported mild perivascular and interstitial lymphocytic inflammatory infiltrate in the dermis. In the middle dermis, there was minimal homogenization of the collagen with no involvement of the adnexa skin. There were no significant changes in the epidermis (Figure 2).

Therapeutic intervention

Due to the previous topical therapeutic failure, the decision favored the use of the intralesional route with triamcinolone acetonide (50 mg vial in 5 mL) in two sessions with a difference of four weeks between applications. In each session, two milliliters of triamcinolone and one milliliter of lidocaine 2 % were applied to improve pain tolerance during the application.

Outcome

In the second control (four weeks after applying the first dose), the evolution of the lesion was assessed, noticing a marked clinical improvement. At this moment, the second dose of steroids was administered (Figure 3).

The patient was called for further follow-up four weeks after the second dose, and the complete resolution of the dermatosis was evidenced two months after starting the treatment (Figure 4).

One month after the end of the treatment, the satisfactory therapeutic results remained stable (absence of atrophy), with a slight residual hypercromia in the treated area.

Figura 1. Lesión atrófica, ovalada, de bordes netos en acantilado. a. Presencia de área de piel acrómica en su interior, blanda a la palpación y asintomática. b. Mayor aumento

Clinical diagnosis

The histological findings on skin biopsy were non-specific and did not constitute a definitive diagnostic criterion by themselves. Therefore, they were correlated with the characteristics and time of evolution of the dermatosis in the clinical context of the patient, which led to the diagnosis of an idiopathic atrophoderma of Pasini and Pierini.

Discussion

Nowadays, IAPP remains a challenge in terms of its etiology and appropriate clinical and histological diagnostic criteria[4-6]. Since its original description by Pasini in 1923, different etiologies have emerged, even though none has enough weight to be accepted as a definitive explanation for this dermatosis[4-7].
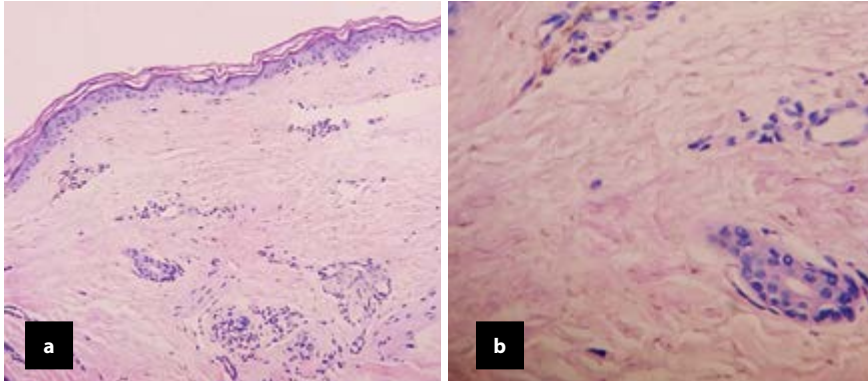
Figura 2. Hematoxilina y eosina. Epidermis sin cambios significativos. A nivel de la dermis superficial se observa leve infiltrado inflamatorio linfocitario perivascular. a. En dermis media se observa homogenización mínima de la colágena. No hay compromiso de los anexos (10x). b. Mayor aumento (40x). Fibras de colágeno homogenizado y adelgazado
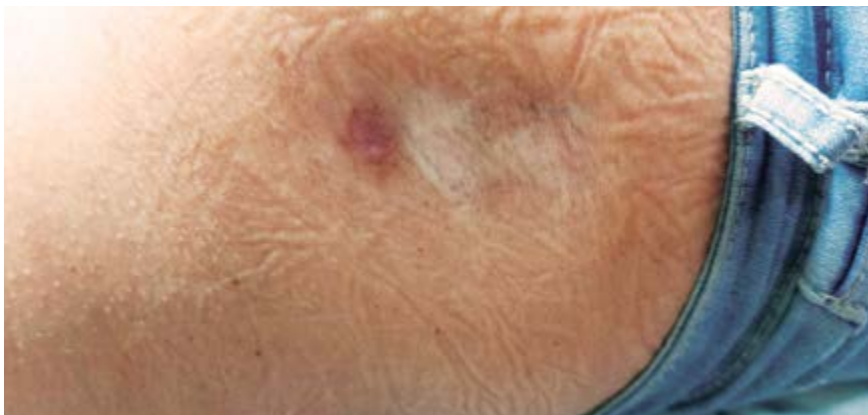
Figura 3. Lesión ligeramente deprimida, con disminución notable de área de piel acrómica

Figura 4. Resolución completa de la dermatosis

The neurogenic or zosteriform theory, which suggests some factors linked to a predisposition to errors in the migration of nerve cells from the neural crest during the embryonic period, might cause the appearance of atrophic lesions with unilateral distribution and zosteriform involvement based on a series of cases reported over the years[8-9]. On the contrary, the genetic theory supposes the existence of elements related to genetics that could allow hereditary transmission of the dermatosis. Weiner and Gant report the occurrence of IAPP in two siblings[10]. Kim Sung Kwon describes the case of a two years old girl whose dermatosis was present at birth; however, a similar clinical manifestation is not reported in another family member[11].

On the other hand, the infectious theory suggests that the association with a simultaneous infection by *Borrelia burgdorferi*. Different authors have described the presence of abnormally high antibody titles IgM and IgG against *B. burgdorferi*. Regardless of this, these patients did not meet the criteria for Lyme disease. A (discrete) clinical improvement is described in these patients when they were treated with antibiotics derived from penicillin, both orally and parenterally[9].

Although for many authors, IAPP is an "abortive" form (incomplete presentation, because it does not meet all the clinical and histologic criteria) of localized morphea, it is more appropriate to establish a classification that somehow facilitates the approach to this dilemma. The Argentine school (Pierini and Borda) proposes a classification into two variants of dermatosis: "true" IAPP, which remains unchanged in clinical and histological findings over the years; the other, a variant that seems to be clinically and histologically related to morphea. Of the latter, different forms of presentation are known: (1) IAPP with clinical and histological features that are similar to morphea ("abortive" variant); (2) IAPP presenting simultaneously with morphea lesions; (3) IAPP with lesions that over the years acquire typical morphea features; (4) IAPP progressing to systemic sclerosis[12-13].

The authors of this study consider that the patient falls into the first of the variants ("true"). The latter is based on the clinical evolution and histopathologic findings, which despite the length of the development remained unchanged in skin texture, a crucial element in the diagnosis of localized scleroderma. Also, knowing that the most relevant changes in the patient's dermatosis were the progressive size of the lesion and the accentuation of the accompanying dyschromia, the diagnosis can be oriented towards a "true" IAPP.

The lesions evolve asymptomatically during the progression of the disease, increasing in size and acquiring their characteristics. Once established, they do not reverse spontaneously. The most frequently involved anatomical sites are the trunk, back, thorax, abdomen, and arms, in order from highest to lowest. The face, hands, and feet are usually not compromised. Usually, the lesions are bilateral and symmetrical, although cases of zosteriform distribution have been described.

The dermatosis consists of depressed, hyperchromic, or skin-colored plaques. However, in this case, acromic areas may develop within the lesions. The borders are usually well delimited, giving it a "cliff" or "inverted plate" appearance. They can range in size, from two to five centimeters, but in rare cases, they can confluence and grow to a larger size, acquiring a crateriform appearance. In IAPP, the skin at the periphery of the lesions is normal, and there is no hyperchromic halo, which contributes to its distinction from morphea. On palpation, a slightly indurated consistency and a sclerotic appearance have been reported, but there may be no change in this appearance[1,4,9,14].

The primary differential diagnosis with which IAPP shares certain clinical and histologic features is localized morphea. However, there is no consensus on whether IAPP is a variant of morphea or a distinct entity[1,4,7,15]. Despite this, and based on various studies, the authors believe IAPP should be considered an independent entity from localized scleroderma[1,13,16]. In the case of the patient described above, and taking into consideration the clinical and histological characteristics, the diagnosis of IAPP seems appropriate since it meets many of the criteria, among which are the following: early age of onset, female sex, chronic evolution, clinical and histological aspects of the lesion compatible with IAPP, and no tendency to spontaneous resolution6. Other differential diagnoses may include primary anetoderma and linear atrophoderma of Moulin, each with differential histologic patterns[1,4,17].

Skin biopsy findings are usually minimal and non-specific and consist of a normally or slightly atrophic epidermis, with possible hyperpigmentation of the basal layer. A minimal perivascular and interstitial inflammatory infiltrate composed of lymphocytes, histiocytes, and plasma cells may be present in the papillary and mid-dermis. The collagen fibers present minimal changes consisting of thickening and homogenization at the level of the reticular dermis and

edema in the interior of these fibers in their upper segments[1,6,12,18], stressing that these findings are non-specific and are not a definitive diagnostic criterion by themselves. However, they can help when establishing a differential diagnosis with morphea. In the patient's case, many of the elements mentioned above were present, favoring the diagnosis of IAPP[4-6].

So far, this entity remains a challenge to treatment[4-6]. There are reports of variable data regarding the use of systemic antibiotics under the assumption that B. Burgdorferi is involved in the pathogenesis in patients with positive IgG antibodies. Oral penicillin and doxycycline 200 mg/day orally for two to three weeks have been used at variable doses with favorable results[5,9,14]. The use of antimalarial drugs is effective in a few cases[4,14,19]. Topical steroids do not seem to offer any improvement in these patientss[19].

The administration of intralesional corticosteroids is an approach that until now has not been used in this dermatosis, although topical and systemic steroids tend to be a relatively frequent approach. In several studies, this is now considered a first-line approach[4,6,19], due to its immunosuppressive and anti-inflammatory mechanism. Notwithstanding, the results were excellent in the patient when used intralesionally, caution should be applied, and further research must be conducted[4-6].

In hyperpigmented lesions, the use of a Q-switched laser has been suggested to potentially improve the condition[13].

Ethical aspects

For the presentation of this case, the patient's consent was requested and confidentiallity was respected; her approval was obtained through informed consent and it was developed in accordance with the principles of the Declaration of Helsinki.

Funding

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Acute chest pain in young patients: report of two cases

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Abstract

Two clinical cases of young patients with acute chest pain are presented, where the multidisciplinary approach and cardiac magnetic resonance played a crucial role in diagnosis and treatment. **Case presentation 1**. A 20 year old patient with precordial pain and palpitations showed elevated cardiac enzyme levels on laboratory examination. Coronary angiography revealed no significant stenosis. However, the diagnosis of myocarditis was confirmed by cardiac magnetic resonance imaging, which led to the initiation of drug treatment to achieve adequate cardiac function and prevention of disease progression. His clinical evolution was favorable. **Case presentation 2**. 19 year old patient presented with severe chest pain radiating to the left arm and jaw. Laboratory tests reported elevated troponin levels, which raised the suspicion of acute coronary syndrome. Cardiac magnetic resonance imaging confirmed the diagnosis of acute myocardial infarction, and coronary angiography revealed significant stenosis in the anterior descending artery and subsequent ectasia. During hospitalization, a comprehensive therapeutic approach with medication administration, monitoring, pain control, and prevention of complications was provided, and the patient showed a favorable clinical evolution.

Keywords

Chest Pain, Magnetic Resonance Imaging, Acute Coronary Syndrome, Myocardial Infarction, Myocarditis.

Resumen

Se presentan dos casos clínicos de pacientes jóvenes con dolor torácico agudo, en ellos, el enfoque multidisciplinario y la resonancia magnética cardíaca jugaron un papel crucial en el diagnóstico y tratamiento. **Presentación del caso 1**. Un paciente de 20 años con dolor precordial y palpitaciones que mostró elevación de los niveles de enzimas cardíacas en los exámenes de laboratorio. La angiografía coronaria no reveló estenosis significativas. Sin embargo, se confirmó el diagnóstico de miocarditis a través de la resonancia magnética cardíaca, lo que llevó al inicio del tratamiento con medicamentos para lograr una función cardíaca adecuada y la prevención del progreso de la enfermedad. Su evolución clínica fue favorable. **Presentación del caso 2**. Un paciente de 19 años que presentó un dolor torácico intenso que se irradiaba al brazo izquierdo y mandíbula. Los exámenes de laboratorio reportaron elevación de los niveles de troponinas, que generaron la sospecha de un síndrome coronario agudo. La resonancia magnética cardíaca confirmó el diagnóstico de un infarto agudo de miocardio, y la angiografía coronaria reveló una estenosis significativa en la arteria descendente anterior y una ectasia subsiguiente. Durante la hospitalización, se brindó un enfoque terapéutico integral con la administración de medicamentos, monitoreo, control del dolor y prevención de complicaciones, y el paciente mostró una evolución clínica favorable.

Palabras clave

Dolor torácico, Imagen de Resonancia Magnética, Síndrome Coronario Agudo, Infarto Agudo de Miocardio, Miocarditis.

Introduction

Chest pain is defined as an unpleasant or uncomfortable sensation experienced in the chest that may indicate the presence of a cardiac problem. It is characterized by pressure, tightness, heaviness, and burning and may radiate to the jaw, neck, shoulder, arm, or upper abdomen[1,2]. In the context of studies related to cardiovascular disease, young patients are those under the age of 45 years, as they have a lower cardiovascular risk[33].

Acute chest pain in young patients is a frequent reason for consultation in the emergency department. In the United States, it is the second most common reason for consultation after trauma.; it accounts for more than seven million emergency department visits per year, equivalent to 5 % of all emergency department visits[4,5]. In addition, it causes almost four million outpatient visits per year[1,2].

There are various causes of chest pain, ranging from musculoskeletal disorders to life-threatening cardiac diseases[1,2]. Due to the complexity of possible causes, timely diagnosis and appropriate treatment are essential to avoid serious consequences. In the young patient, non-cardiac origin is the most frequent, more than 90 % of cases, and it is estimated that 36 % of cases have an idiopathic cause, musculoskeletal 25 %, psychological 16 %, and gastrointestinal 10 %[1,2].

The initial assessment of patients includes a complete medical history, thorough physical examination, and diagnostic tests such as electrocardiogram (ECG), blood tests, and chest X-ray. However, in some cases, these tests may be insufficient to detect the underlying cause of the pain. In recent years, cardiac magnetic resonance imaging (CMR) has become a valuable tool for the diagnosis of acute chest pain. It allows a more accurate assessment of the possible causes of pain, which can lead to a faster and more accurate diagnosis[6,7].

This article presents two clinical cases of young patients with acute chest pain that were evaluated at the Rosales National Hospital in El Salvador. Magnetic resonance imaging was used as a complementary study and proved to be a valuable tool in the diagnosis and management of the conditions.

Case presentation 1

A 20 year old male patient referred from a peripheral hospital with a history of 17 hours of precordial pain accompanied by diaphoresis and palpitations. The precordial pain was oppressive and of moderate intensity, radiating to the left arm. The patient denied having had energy drinks, alcohol, drugs, or tobacco. He had no personal pathological history.

On physical examination, the patient was in good general condition. He had a heart rate of 72 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 100/70 mm/Hg, temperature of 37 °C, and oxygen saturation of 98 %. At the thoracic level, symmetry was observed, with no pain or masses on palpation. MRI was normal on percussion, and auscultation showed no abnormal respiratory sounds. A cardiovascular examination revealed a regular heart rhythm with no murmurs. Peripheral pulses were present.

Laboratory tests showed elevated creatine phosphokinase-MB values as well as positive troponins I and T, while all other results were within normal ranges (Table 1). In addition, the ECG showed ST-segment elevation in leads DII, DIII, and aVF (Figure 1). The echocardiogram showed normal function and morphology and a left ventricular ejection fraction (LVEF): 65.5 %. Moreover, coronary angiography revealed no significant stenosis.

Additionally, CMR was performed (Figure 2), which confirmed the diagnosis of myocarditis, excluding an ischaemic pattern. CMR imaging revealed subepicardial oedema in the inferior and inferoseptal region of the mid and apical segments, and late subepicardial gadolinium enhancement was observed. These findings provided valuable information on the extent of inflammation and the presence of structural changes in the myocardium.

Treatment

Medical treatment was started with enalapril 2.5 mg every 12 hours and carvedilol 6.25 mg every day to reduce afterload and preload, improve ventricular contractile function and prevent the progression of myocarditis.

Outcome

The patient showed a favorable clinical evolution with medical treatment, with significant improvement of symptoms. After four days of hospitalization, he was discharged in a stable and symptom-free condition, with a recommendation for outpatient follow-up.

After three months, he attended a follow-up consultation where clinical improvement was evident, and CMR showed a decrease in the area of oedema and a reduction in late gadolinium enhancement.

Diagnosis

Myocarditis was confirmed by cardiac magnetic resonance imaging.

Case presentation 2

The patient was a 19 year old male who presented with one hour of severe, sudden onset, oppressive retrosternal chest pain radiating to the left arm, jaw, and posterior thorax. He also reported palpitations and a feeling of anguish in the days before the onset. The patient denied having energy

Table 1. Laboratory values, case 1

Laboratory tests	Values	Laboratory tests	Values
CPK-MB	100 ng/mL	Platelets	253 x 10³ mm³
Troponine I	Positive	Creatinine	0.79 mg/dL
Troponine T	Positive	Urea nitrogen	6.9 mg/dL
Leukocytes	7.73 x 10³ mm³	Glucose	80 mg/dL
Neutrophils	71.3 %	Sodium	145 mEq/L
Lymphocytes	20.7 %	Calcium	6.73 mg/dL
Hemoglobin	16.5 g/dL	Potassium	3.4 mEq/L
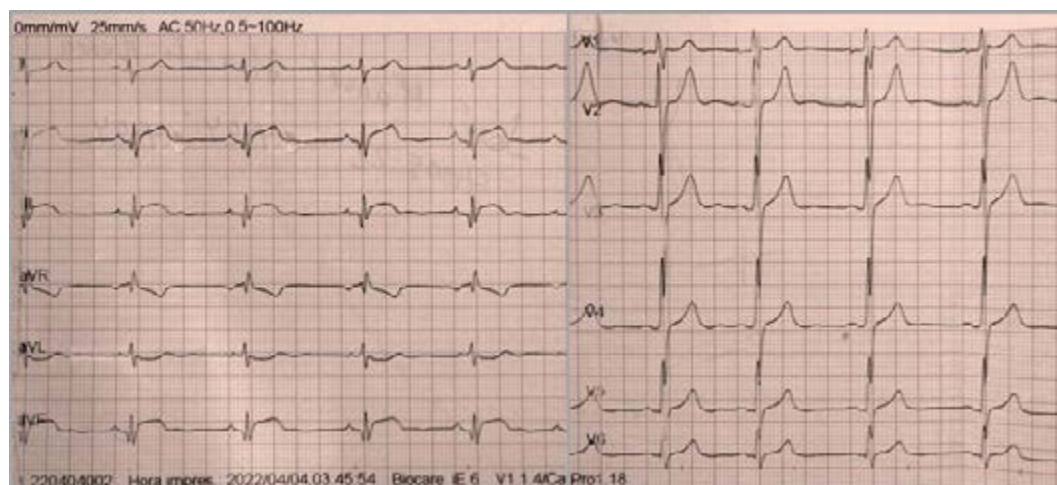
Figure 1. Electrocardiogram. Sinus rhythm, ST-segment elevation in leads DII, DIII, and aVF, and ST-segment elevation in aVL
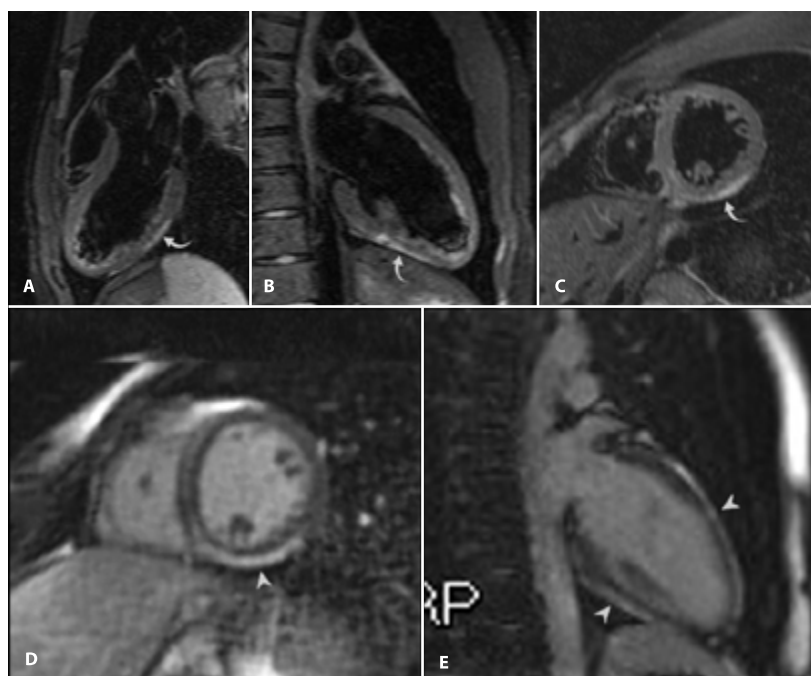
Figure 2. Cardiac CMR. T2-weighted STIR sequence, three-chamber (A), two-chamber (B), and medial short axis (C) slices. Late enhancement T1-IR sequence with gadolinium, medial short axis (D), and two chambers (E). The images show an increased signal on T2/STIR due to subepicardial oedema (curved arrow) at the level of the inferior and inferoseptal regions of the mid and apical segments (A-C). The images show an increased signal on T2/STIR due to subepicardial oedema (curved arrow) at the level of the inferior and inferoseptal regions of the mid and apical segments (A-C)

or stimulants, alcohol, or drugs. He had no personal medical history.

The patient was acutely ill, haemodynamically stable on the physical examination. He was noted to be in grade I obesity. Vital signs with a heart rate of 72 beats per minute, respiratory rate of 18 breaths per minute, blood pressure of 140/90 mmHg, temperature of 36.0 °C, and oxygen saturation of 93 %. Abnormal breath sounds were not detected. A regular heart rhythm was auscultated with no murmurs, third murmurs, or rubs on cardiovascular examination. Peripheral pulses were palpable, and significant abnormalities were not detected on the rest of the physical examination.

On further examination, an ECG was performed, which showed ST-segment elevation and Q-wave in leads V1-V6 and Q with embryonic R in DI-aVL that indicates a transmural infarction (Figure 3). In addition, troponins I and T were positive and C-reactive protein values were elevated, while all other laboratory tests were normal (Table 2). Therefore, it was classified as acute coronary syndrome (ACS) with ST elevation. An echocardiogram was performed to assess cardiac function and structure, which revealed motility disorders in the apical segment of the heart. CMR was performed due to the possibility of myocarditis or Takotsubo syndrome.

Complementary CMR (Figure 4) confirmed the diagnosis of acute myocardial infarction (AMI) in the territory of the anterior descending artery. Non-viable myocardial tissue was observed, and microvascular obstruction was shown, which indicates severe myocardial injury. In addition, a decreased left ventricular ejection fraction (LVEF) of 41.7 % was observed

A coronary angiography was performed to determine the underlying cause of the acute myocardial infarction. It revealed 80 % stenosis of ostioproximal of the anterior descending artery with subsequent segment ectasia and a sudden transition to an angiographically normal distal segment (Figure 5). These findings suggested the possibility of a sequela of inadvertent Kawasaki disease during childhood.

Therapeutic intervention

Thrombolysis with streptokinase was performed, and supportive care was provided with continuous monitoring, pain control, oxygen administration and prevention of thromboembolic complications during hospitalization. In addition, continuous medication with enalapril 10 mg and carvedilol 6.25 mg, both every 12 hours, plus spironolactone 25 mg, clopidogrel 75 mg, atorvastatin 80 mg, furosemide 40 mg and acetylsalicylic acid 100 mg in daily doses.

Clinical evolution

The patient showed a favorable clinical evolution with significant improvement of symptoms. The patient was discharged in stable condition after seven days of hospital stay with an outpatient follow-up plan.

Diagnosis

Acute myocardial infarction in the territory of the anterior descending artery.

Discussion

The evaluation of acute chest pain in young patients is a diagnostic challenge due to the wide variety of potential causes. In young patients the non-cardiac cause is more frequent. Therefore, it may have
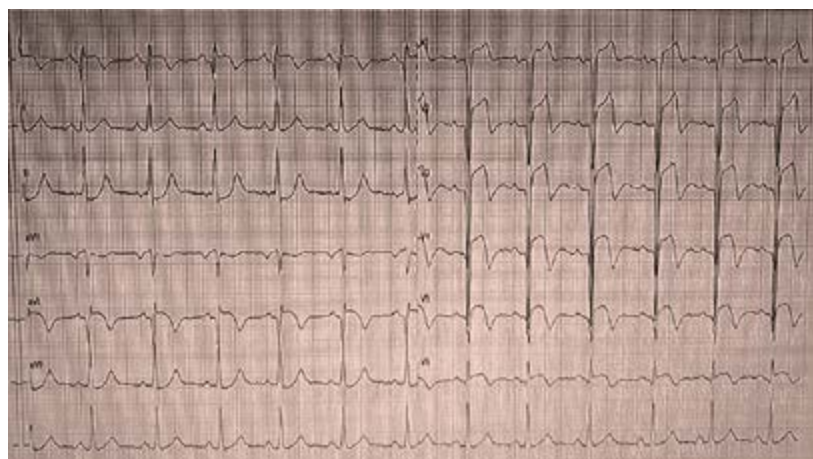
Figure 3. Electrocardiogram. Sinus rhythm, J point elevation of 4 mm, and presence of Q wave in V1 - V6. Q wave with embryonic R in DI and AVL

Table 2. Laboratory values, case 2

Laboratory tests	Values	Laboratory tests	Values
Troponine I	Positive	Platelets	157 x 10³ mm³
Troponine T	Positive	Creatinine	0,82 mg/dL
Leukocytes	9,36 x 10³ mm³	Glucose	100 mg/dL
Neutrophils	74,1 %	Sodium	139,6 mEq/L
Lymphocytes	14,9 %	Potassium	4,1 mEq/L
Hemoglobin	14,2 g/dL	Calcium	9,2 mg/dL
Hematocrit	43 %	PCR	10,54 mg/dL
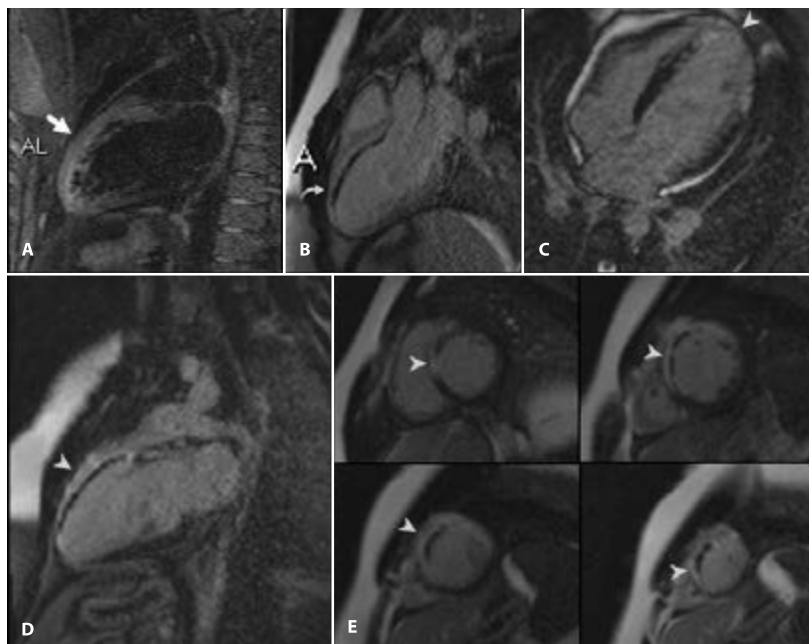
Figure 4. Cardiac MRI. T2-weighted STIR sequence, two-chamber slices (A). T1-IR sequences of early enhancement with Gadolinium three chambers (B); late enhancement four chambers (C), two chambers (D); and short axis series (E). Sequences show hyperintensity in T2/STIR (straight arrow) due to edema of the anterior wall, the left ventricle basal and medial anteroseptal wall, and the apex in all its segments (A). Early enhancement (curved arrow) from the base to the apex of the septum (B) indicates microvascular obstruction. Pathological transmural late enhancement (arrowheads) of ischemic type in the same segments (C-E)
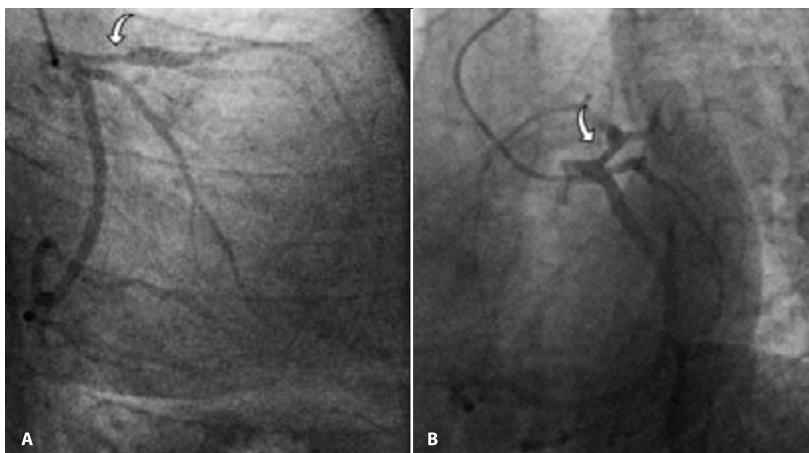
Figure 5. Coronary Angiography. Caudal anteroposterior (A) and caudal left anterior oblique (B) views. Estimated 80 % ostioproximal stenosis (arrows) of the anterior descending artery with subsequent segment ectasia and a sudden transition to an angiographically normal distal segment

socio-cultural causes such as anaerobic exercise, consumption of drugs, carbonated or energy drinks, or it may be idiopathic, the latter resolving spontaneously in 90 % of cases[8].

Of all ED patients with chest pain, 14 % are patients under 40 years of age, yet patients under 40 years of age account for only 4 % to 8 % of AMIs each year[9].

It is important that doctors rule out cardiac problems as pain of cardiovascular origin can be lethal and must be thoroughly ruled out. Serious causes include AMI, ventricular arrhythmias, and aortic aneurysm or dissection[8]. The underlying aetiology is diverse, and the atherogenic cause of ischaemic heart disease is not always implicated in the pathogenesis of the disease, so patients often do not present the epidemiological profile to which the clinician is accustomed[2]. Risk factors in young adults are consequences of changing eating behaviors, loss of healthy lifestyle habits, sedentary lifestyles, and stress[2,10].

Collin *et al.* showed that adults under 40 years of age with chest pain without a known cardiac history and classical cardiac risk factors or with a normal ECG had less than 1 % risk of adverse cardiovascular events at one year[9].

Kawasaki disease should be considered among the coronary artery diseases that occur in young patients with minimal or no risk factors for atherosclerotic coronary artery disease; therefore, it was considered in our clinical case. Furthermore, it must be suspected when marked ectasia or aneurysm of the proximal coronary arteries with or without calcification is observed, followed by a sudden transition to an angiographically normal distal segment[11].

International guidelines recommend the exclusion of AMI, risk stratification, and assessment of coronary artery disease in patients with ACS[1,12,13]. In addition, ACS can manifest as unstable angina or acute myocardial infarction and is diagnosed by clinical assessment, electrocardiography, serum cardiac biomarkers, and invasive and non-invasive imaging. Electrocardiographic findings allow for the classification of AMI into AMI with ST-segment elevation and AMI without non-ST-segment elevation.

It is important to measure cardiac biomarkers in blood serum for diagnosis of ACS, as they often increase in patients with AMI[1]. The presence of elevated cardiac biomarker levels and acute chest pain is not limited to AMI alone. Other cardiac diseases can manifest in similar ways, such as myocarditis, Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA),

Takotsubo cardiomyopathy, cardiac trauma, tachyarrhythmias, among other conditions[6]. In addition, it is of foremost importance to consider Brugada syndrome as part of the differential diagnosis, characterized by ST-segment elevation in the right precordial leads and increment of the risk of sudden cardiac death[14].

Imaging studies allow a better assessment, and their choice depends on the clinical question of importance[7]. These studies can be invasive or non-invasive.

Invasive imaging is recommended in patients with non-ST-segment elevation AMI because of the need for immediate reperfusion therapy by percutaneous coronary intervention or thrombolysis[1]. Non-invasive imaging is usually avoided unless aortic dissection or cardiac tamponade is suspected, for which ultrasound is the first imaging modality used[7].

Non-invasive imaging studies such as CMR may be an option in emergency units to identify patients with non-ST-segment elevation AMI or unstable angina with unobstructed coronary artery disease, especially in those with atypical symptoms or alternative diagnoses, after percutaneous coronary intervention or when the patient's medical history is atypical[6].

The use of CMR allows for excellent tissue characterization, and in the context of acute ACS, it can accurately assess a variety of parameters that determine regional myocardial dysfunction, infarct distribution, infarct size, myocardium at risk, microvascular obstruction and intramyocardial haemorrhage[6,7].

In the case of the patient with acute myocardial infarction, CMR helped identify ventricular wall injury and ischaemia in the affected areas, which allowed confirmation of the diagnosis and thus a more accurate assessment of the severity of the disease.

In addition, CMR has important utility in myocarditis detection[6,7,15], which must be suspected in patients with variable symptoms, including symptoms similar to those of ACS without coronary artery disease and ACS with or without ventricular dysfunction. Myocarditis is the third most common cause of sudden cardiac death and has been associated with 5-12 % of sudden cardiac deaths in young athletes[15]. Although endomyocardial biopsy is the gold standard technique, MRI can diagnose up to 79 % of cases of myocarditis proven by pathology[6]. The Lake Louise criteria are a useful tool for the detection of myocarditis based on the detection of two of three characteristic features: myocardial oedema on T2-weighted MRI, hyperemia on early T1-weighted MRI with

contrast, and fibrosis during late gadolinium enhancement, usually with a non-ischaemic lesion (i.e., in the midwall or subepicardial wall) that does not follow a coronary artery distribution[6].

In the case of the patient with myocarditis, CMR helped identify myocardial inflammation and rule out other possible causes of acute chest pain, so the patient benefited from targeted treatment with a good prognostic outcome.

In conclusion, the focus on the use of CMR for the diagnosis of ACS patients in both young and adult patients is a promising application that could reduce hospital admissions and costs in the emergency department leading to the possibility of better patient classification[16]. However, there is limited access to such studies, in addition to the requirement for trained cardiac imaging staff and the implementation of rapid protocols for unstable patients requiring acute care to be more widely used in the emergency department.

Ethical aspects

The cases presented reflect information obtained from clinical records. Patient confidentiality has been ensured in the data collection and analysis of each case. Informed consent has been obtained from both patients and the data in the publication have been used for academic purposes.

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Case report

Pemphigus foliaceus, seborrheic variety, case report

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Abstract
Case presentation. a 48-year-old male with no known medical history who presented multiple lesions in the form of easily desquamative erythematous and crusted plaques, initially on the anterior thorax, which spread over the face and scalp without affecting the mucous membranes. **Treatment.** In-hospital management was mainly based on topical and systemic steroids, the management of infections superadded to the dermatologic lesions, and psychological support for the patient. A skin biopsy was taken where acantholysis was evidenced, confirming the autoimmune disease diagnosis. **Outcome.** After treatment, the multiple scaly lesions were reduced, the local infection was controlled, and the patient's skin recovered although it still had scars, its functions were restored.

Keywords
Pemphigus, acantholysis, autoimmune disease.

Resumen
Presentación del caso. Se expone el caso de un paciente masculino de 48 años de edad, sin antecedentes médicos conocidos, que presentó múltiples lesiones en forma de placas eritematocostrosas fácilmente descamativas, inicialmente en tórax anterior, que se esparcían sobre el rostro y cuero cabelludo sin afectar las mucosas. **Intervención terapéutica.** El manejo hospitalario se basó fundamentalmente en el uso de esteroides tópicos y sistémicos, así como el manejo de las infecciones sobreagregadas a las lesiones dermatológicas y el apoyo psicológico del paciente. Se tomó biopsia de piel donde se evidenció la presencia de acantólisis, confirmando el diagnóstico de esta enfermedad autoinmunitaria. **Evolución clínica.** Luego del tratamiento se logró una reducción de las múltiples lesiones descamativas, el control de la infección local y la recuperación de la piel del paciente, la cual a pesar de aún presentar cicatrices se encontraba con sus funciones restituidas.

Palabras clave
Pénfigo, acantólisis, enfermedad autoinmune.

Introduction

Pemphigus (from the Greek "pemphix" meaning blister) is a group of autoimmune diseases that produce blisters on the skin and mucous membranes due to the action of autoantibodies on specific proteins of the hemidesmosomes[1]. Likewise, it generates a loss of adhesiveness between epidermal cells, histologically characterized by the formation of intraepidermal blisters, a process known as acantholysis[2,3]. The classic definition of pemphigus describes it as a severe, rare disease with a chronic and aggressive course. Continuous and systematic treatment is essential to avoid its lethal evolution[4].

Three main types are distinguished: pemphigus vulgaris, paraneoplastic pemphigus, and pemphigus foliaceus, according to their clinical and histological manifestations and the type of proteins involved[5,6].

The two most common types are pemphigus vulgaris and pemphigus foliaceus[3]. These two groups differ clinically and histologically, and by their autoantibodies. The former is the more severe form and occurs more frequently in India, southeastern Europe, and the Middle East[7] and is characterized by mucosal involvement. Pemphigus foliaceus manifests mainly on the skin, in the form of well-defined erythematosquamous or erythematous-costly plaques, with a seborrheic appearance and distribution (face, neck, and trunk), where the mucous membranes are generally not affected[6] and in some cases it is characterized by a burning sensation on exposure to the sun, *fogo salvagem* variant[8].

The diagnosis of this type of lesion is based on a combination of clinical and histopathologic findings and is achieved through direct immunofluorescence techniques, mainly performed on perilesional biopsies of affected tissue[3].

Worldwide, the annual incidence is estimated at 21.7 cases per million population. Although it is a rare disease, it is the most frequent form of autoimmune blistering disease. It has been observed in all ages, with a predominance in older adults[1]. Furthermore, although it occurs in both sexes, it has a slight predominance in women. Mortality has been reported at 17.7 %, mainly related to sepsis[9].

Pemphigus has an estimated incidence of two patients per million inhabitants per year in central Europe. In the Americas region, pemphigus is endemic in Colombia and Brazil. However, pemphigus has been reported in young adult patients and children, mainly in El Salvador and other Latin American countries such as Brazil, Colombia, Paraguay, and Peru; thus, the importance and relevance of case documentation[10].

Case presentation

A 48 year old male patient with no known medical history, with a history of one month of observing the appearance of small blisters in the anterior region of the thorax with a progressive increase in number and size until rupture, with serous discharge, moderate pain and crusting, subsequently, the lesions spread to the face and scalp, due to this, he consulted a private physician who indicated treatment with topical neomycin bacitracin.

The patient did not notice any clinical improvement, so he consulted at the emergency unit of San Juan de Dios National Hospital Santa Ana. He denied symptoms such as fever and pruritus. Neither relevant

pathological history was recorded nor contact with people with similar symptoms. He denied having medications, drugs or other substances prior to the clinical record. On physical examination, the patient was alert, oriented and multiple erythematous plaques with irregular, well-defined borders, with melic crusts were observed on the anterior thorax, scalp and mandibular region, without mucosal involvement (Figure 1).

Blood pressure of 120/70 mmHg, heart rate of 76 beats per minute, respiratory rate of 16 per minute, oxygen saturation of 97 %, temperature of 37.1 degrees Celsius.

Laboratory tests showed leukocytosis with a predominance of neutrophils (Table 1). The presumptive diagnosis was over-infected pemphigus vulgaris; therefore, hospital admission was decided, and treatment was started with ciprofloxacin 0.2 grams intravenous every twelve hours and ampicillin plus sulbactam 3 grams intravenous every six hours. After five days, hydrotherapy was started, which after 48 hours, presented sphacelation of the lesions with increased pain and discomfort of the patient (Figure 2). So these signs of clinical deterioration led to the decision to refer the patient to the regional hospital, where they described the patient with multiple dark brown lesions, crust-like with serosanguinolent discharge, erythematous skin-base, easily scaly, on the anterior and posterior thorax, face (beard and eyebrow area) and scalp. The mucous membranes were intact, with no other abnormal findings on physical examination.

Laboratory tests revealed mild leukocytosis, predominantly neutrophils; the rest of the tests were within normal values (Table 1). Chest X-ray and electrocardiogram showed no abnormalities (Figure 3). The patient was admitted to the hospital for suspected pemphigus and started treatment with the following medications: intravenous methylprednisolone, 60 mg every six hours for five days; betamethasone 0.1 % combined with neomycin 0.5 % and bacitracin 0.5 % every day. The patient had completed seven days of double antibiotics in the hospital; therefore, no antibiotics were prescribed.

Treatment

During the patient's hospital stay, a multidisciplinary approach was carried out, including psychological, dermatological, and surgical care; since the presence of dermatological lesions was accompanied by depressive symptoms and anhedonia, it was decided to manage the patient by psychology with non-directive verbal intervention therapies

every 48 hours. A presumptive diagnosis of pemphigus foliaceus was established by dermatology evaluation to rule out seborrheic dermatitis; in addition, daily healing of the lesions was indicated. After three days, the lesions were debrided, and samples were taken for skin biopsy and culture of the secretions (Figure 4). After five days of intra-venous steroids, prednisone 50 mg orally was started for one month.

The culture isolated *Klebsiella pneumoniae ssp. pneumoniae*; for this reason, ten days of antibiotic therapy were completed with meropenem 1 g intravenously every eight hours, according to the result of the antibiogram.

Table 1. Historial de exámenes de laboratorio

	ER LNH*	ER SJDDNHSA**	Within 14 days of entry	Within 28 days of discharge
Leukocytes	12.53 10^3	12.75 10^3	12.34 10^3	10.65 10^3
Neutrophils	69.1 %	83.2 %	68.6 %	85.1 %
Lymphocytes	20.6 %	13.2 %	16.8 %	10.0 %
Platelets	502 10^3	223 10^3	480 10^3	333 10^3
Hemoglobin	13.0 g/dL	13.4 g/dL	12.9 g/dL	12.5 g/dL
Hematocrit	37.3 %	39.7 %	36.0 %	37.2 %
Mean corpuscular volume (MCV)	82.7 fL	87.3 fL	82.9 fL	86.9 fL
Mean corpuscular hemoglobin (MCH)	28.8 pg	29.5 pg	29.7 pg	29.2 pg
C-reactive protein	116.05 mg/dL	-	156.9	-
Albumin	2.8 g/dL	2.8 g/dL	3.1 g/dL	3.3 g/dL
Urea Nitrogen	17 mg/dL	22 mg/dL	22 mg/dL	30 mg/dL
Creatinine	1.26 mg/dL	0.85 mg/dL	0.98 mg/dL	0.84 mg/dL
Corrected calcium	8.3 mg/dL	8.3 mg/dL	8.2 mg/dL	8.9 mg/dL
Phosphorus	2.55 mg/dL	3.33 mg/dL	4.28 mg/dL	2.43 mg/dL
Magnesium	1.7 mg/dL	1.5 mg/dL	2.0 mg/dL	1.9 mg/dL
Sodium	137 mEq/L	136 mEq/L	132 mEq/L	137 mEq/L
Potassium	4.3 mEq/L	4.1 mEq/L	4.3 mEq/L	4.2 mEq/L
Chlorine	98 mEq/L	92 mEq/L	88 mEq/L	100 mEq/L
Prothrombin time	11.1 s	-	-	-
Partial thromboplastin time	28.5 s	-	-	-
Fibrinogen	454.2 mg/dL	-	-	-
International Normalized Ratio (INR)	1.03	-	-	-
HIV	-	-	Non-reactive	-

*ER LNH: Emergency Room Local National Hospital

** ER SJDDNHSA: Emergency Room San Juan de Dios National Hospital Santa Ana

Figure 1. Patient admission status

Outcome

After 28 days of hospital stay, there was a notable improvement in the dermatological lesions (Figure 5), as well as in the patient's mood; consequently, it was decided to discharge him from the hospital with the plan to continue with betamethasone 0.1 % daily and prednisone 5 mg orally every day for three months.

Clinical diagnosis

The diagnosis of pemphigus was confirmed through the result of the skin biopsy, which revealed that the epidermis presented a superficial epidermal blister with inflammatory cells corresponding to neutrophils, acantholysis in the superficial layer and presence of keratinocyte, and due to the clinical features, it was classified as seborrheic pemphigus. In addition to acute stress, diagnosed by psychology.

Discussion

Pemphigus foliaceus, also called superficial pemphigus, is a rare disease of chronic course, characterized by lesions only on the skin[3] and by the presence of anti-desmoglein 1 antibody in the subcorneal area[11]. Pemphigus foliaceus is classified as endemic (*fogo salvagem*) and non-endemic or sporadic[7]. The latter includes a variety known as seborrheic pemphigus, which is identified as localized and is also known as pemphigus erythematosus or Senear-Usher syndrome[8].

Figure 2. Status of Post-hydrotherapy patient
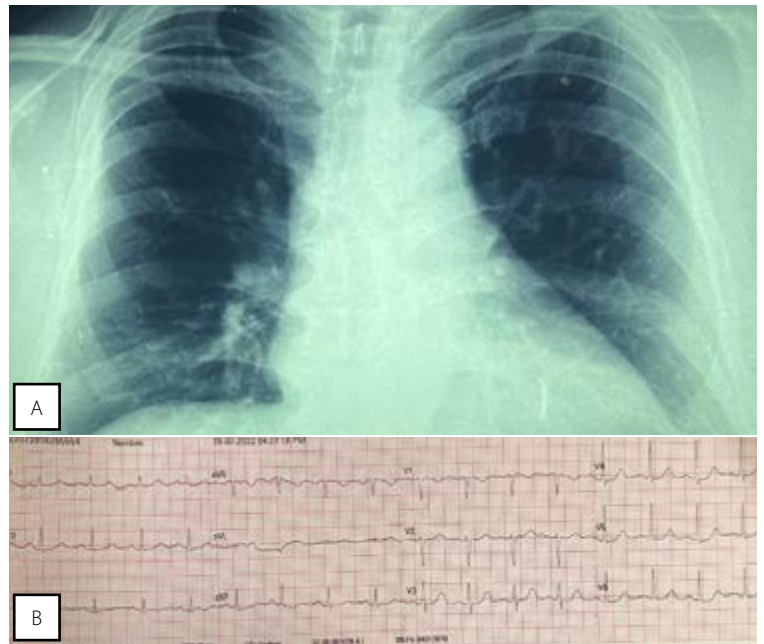
Figure 3. A. Chest X-ray of patient on admission. B. Electrocardiogram from patient on admission

Figure 4. Biopsy site from thoracic skin

Figure 5. Patient status at discharge.

Its etiology is due to the presence of anti-IgG antibodies against the extracellular amino-terminal domain of desmoglein 1 of the keratinocytes of the granular layer[6]. It is important to note that desmoglein 1 is found throughout the epidermis, predominantly in the skin, and is almost absent in the mucosa. However, it is expressed in greater proportion in the more superficial layers[12]. Clinically, the primary lesion is a flaccid vesicle or blister, but due to the location of the epidermal separation, lesions tend to rupture, so intact blisters or vesicles are rarely seen on physical examination[13]. On the contrary, scattered, crusted, well-demarcated, erythematous lesions on the face, scalp and upper trunk are common[6]. Mucosal involvement is infrequent, as presented in the described case, where the initial lesion was in the anterior region of the thorax and spread to the characteristic crusted areas. Skin lesions may cause burning and pain, but the patient does not present severity[3].

On histopathology, pemphigus foliaceus blisters form in the superficial layers of the epidermis, as presented in the biopsy result, while pemphigus vulgaris blisters can form at any epidermal level, but typically, in the lower layers of the epidermis[12]. Diagnosis is based on clinical findings with confirmation of the characteristic histopathological lesion[12].

The main objective of treatment is the control and healing of cutaneous blistering lesions. Pharmacological management aims to cure the blistering eruption, eliminate the functional deterioration associated with the disease, prevent recurrences, reduce the common side effects associated with long-term corticosteroid treatment, and improve the quality of life of patients[4,14].

Depending on the severity, Pemphigus is classified as mild, moderate, or severe to guide treatment[4]. Then, Mild pemphigus foliaceus will be defined as less than 5 % body surface area involvement or a pemphigus disease area index (PDAI) score ≤ 15[14].

For the mild variety, the first-line treatment scheme consists of the use of topical corticosteroids[4]; other authors mention the combination of these with the use of dapsone at starting doses between 50 and 100 mg daily, with an increase of up to 1.5 mg/kg of body weight[4].

As second-line management, treatment with rituximab (two infusions of 1 g two weeks apart) alone or associated with topical corticosteroids or oral corticosteroids is mentioned. Azathioprine and mycophenolate mofetil or mycophenolate sodium have also been described[4,14].

On the other hand, moderate and severe pemphigus foliaceus is that which meets the following clinical criteria: significant pain and an affected body surface area above 5 % or according to the PDAI score (between 15-45 points for moderate, and above 45 points for severe)[4,14]. Its different treatment schemes are based on Rituximab associated with systemic corticosteroids; systemic corticotherapy alone or associated with an immunosuppressive drug as a corticosteroid-sparing agent (azathioprine, mycophenolate mofetil or mycophenolate sodium)[4,14,15].

Ethical aspects

The preparation of this case was based on the Helsinki principles, in which the confidentiality of the patient, who authorized the publication of the clinical case and the images through informed consent, was guaranteed.

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Case report

Epilepsy secondary to encephalitis due to Epstein Barr virus

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Abstract

Case presentation. This case is about a 44 years old woman with a history of occipital headache, incoherent speech and confused thinking. She initially presented ten points on the Glasgow scale and left hemiparesis. Cranial CT scan reported cerebral edema with right thalamic hypodense lesion and progressive neurological deterioration. The electroencephalogram showed unilateral right hemispheric deceleration. The cerebrospinal fluid study showed hyperproteinuria and a predominantly lymphocyte count of 450 cells with preserved glycorrhachia, without the presence of bacteria. **Treatment.** was managed with invasive ventilatory support and antibiotic and antiviral treatment at meningeal doses, in addition to anticonvulsants. Control tomographic findings showed hydrocephalus; a Becker type ventricular shunt was placed. IgM serology was positive for Epstein Barr virus and the viral genome was identified in the cerebrospinal fluid by polymerase chain reaction test. The control brain tomography showed persistent ventriculomegaly and cerebral edema, which led to the diagnosis of encephalitis of viral etiology complicated by epilepsy secondary to a demyelinating structural lesion of the right cerebral hemisphere. **Outcome.** Therapeutic intervention with intravenous immunoglobulin was performed with improvement of the general condition, it was possible to remove the ventricular shunt and pulmonary ventilation ten and 19 days after admission, respectively. The patient is currently in physical therapy with persistence of left hemiparesis, gait disturbances, dysarthria, and controlled convulsive episodes during the last six months.

Keywords
Epilepsy, Brain, Inflammation, Encephalitis.

Resumen

Presentación del caso. Se trata de una mujer de 44 años de edad, con historia de cefalea occipital, lenguaje incoherente y pensamiento confuso. Inicialmente presentaba diez puntos en la escala de Glasgow y una hemiparesia izquierda. La tomografía computarizada de cráneo, reportó edema cerebral con lesión hipodensa talámica derecha y deterioro neurológico progresivo. El electroencefalograma evidenció desaceleración unilateral hemisférica derecha. El estudio del líquido cefalorraquídeo describió hiperproteinorraquia y un recuento a predominio linfocitario de 450 células con glucorraquia conservada, sin presencia de bacterias. **Intervención terapéutica.** se manejó con soporte ventilatorio invasivo y con tratamiento antibiótico y antiviral a dosis meníngeas, además de anticonvulsivantes. Los hallazgos tomográficos de control reportaron una hidrocefalia; se colocó una derivación ventricular tipo Becker. La serología IgM resultó positiva para virus de Epstein Barr y se identificó el genoma viral en el líquido cefalorraquídeo, a través de la prueba de reacción en cadena de polimerasa. La tomografía cerebral de control, evidenció la persistencia de la ventriculomegalia y de edema cerebral, lo que generó el diagnóstico de una encefalitis de etiología viral complicada con epilepsia secundaria por una lesión estructural desmielinizante del hemisferio cerebral derecho. **Evolución clínica.** La intervención terapéutica con inmunoglobulina intravenosa generó una mejoría del estado general. Fue posible retirar la derivación ventricular y la ventilación pulmonar diez y 19 días después del ingreso, respectivamente. La paciente se encuentra actualmente en fisioterapia con persistencia de hemiparesia izquierda, alteraciones de la marcha, disartria y episodios convulsivos controlados durante los últimos seis meses.

Palabras clave
Epilepsia, cerebro, inflamación, encefalitis.

Introduction

Encephalitis is an inflammation of the brain parenchyma[1]. It can occur due to infectious or autoimmune causes[2]. It is characterized by symptoms such as fever, headache, and behavioral or personality alterations; it evolves within 24 to 72 hours with changes in the level of conscious awareness and a stiff neck and may trigger seizures and permanent neurological damage with focal neurological deficits, neurological disability[3], and may cause death if not diagnosed in a timely assessment[1,4].

Worldwide, 1.7 to 12.6 cases per 100 000 populations per year were reported to be diagnosed[4]. In the United States of America (USA), an estimated prevalence rate of 13.7/100 000 was identified, describing that the incidence of viral encephalitis probably increased due to improved detection of the disorders and more widespread diagnostic capabilities and stating that viral causes are very common[5]. In low-income countries, regional reports have recorded a low incidence of viral encephalitis, presenting mainly as recurrent outbreaks[6].

Infection is the most common cause, mainly due to viral pathogens[2,3], which account for about 70 % of confirmed cases of encephalitis[4]. The frequency of viral causes varies according to geographic location, seasonal changes, the patient's immune status, as well as the viral genetic mutations over time[2,4].

In the USA, the most common causes of viral encephalitis are herpes simplex virus (HSV), West Nile virus and enteroviruses[4]. Varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpes virus types 6 and 7, measles virus, mumps virus, rubella virus, St. Louis virus, Eastern equine virus, Western equine virus, dengue virus, rabies virus[5] and recently SARS-CoV-2[7] have been described as the leading agents associated with encephalitis.

In recent years, there has been progress in understanding the clinical and pathobiology of viral encephalitis. However, despite increasing evidence of an underlying inflammatory process, the root cause remains unknown, and targeted therapeutic strategies remain uncertain due to the absence of controlled studies[8].

Although the clinical characteristics of infectious encephalitis are based on neurological symptomatology[9,10], they occur mainly due to inflammation of the brain, even though the exact mechanism that develops them is not understood, among which neurotropic infections that provoke a release of cytokines and lead to cytotoxicity, inflammation, and damage are described. Increased permeability of the blood-brain barrier and perivascular lymphocytic infiltration that can lead to further breakdown of the barrier appear[11-13].

In connection with viral encephalitis, the secondary development of autoantibodies directed to neuronal surface synaptic antigens involves diverse mechanisms[14]. These antigens are often located in the limbic system of the brain, and several *in vitro* and *in vivo* models demonstrate the direct pathogenicity of the antibodies[15]. However, molecular interactions of antibodies with viral antigens can lead to complement deposition, antigen internalization, and direct modulation of antigenic target function. Therefore, the precise potential therapeutic intervention differs significantly, depending on the target antigen. However, at present, there is more clarity from immunogenetic associations and B-cell studies[16].

Although, given the fact that fever, focal neurological deficits, and cerebrospinal fluid lymphocytosis remain as diagnostic criteria for encephalitis, from any cause, cases are likely to be underestimated[2].

Diagnostic confirmation is made by polymerase chain reaction test applied to cerebrospinal fluid, with the detection of various viral agents; however, this test is not available in all countries[17].

Case presentation

It is about a 44 years old woman who consulted with a history of recurrent occipital headache, mild to moderate intensity, radiating to the frontal region, with episodes of vomiting, incoherent speech, and confused thinking.

The patient's history included cytomegalovirus viral encephalitis four years before the consultation. She also stated that two months before, she received diphtheria and tetanus conjugate vaccination with no immediate reaction to the immunization; in addition, she had multiple viral processes in the last two months. There was also a history of two previous pregnancies, both ending in cesarean delivery. She did not present any comorbidity.

In the physical evaluation, the patient presented deficient general condition, hemodynamically stable, with cardiopulmonary status without alterations, and presented with countless projectile vomiting. Initially, she had ten points on the Glasgow scale. The ocular fundus showed discrete bilateral edema of the papilla. In the physical evaluation, she presented blood pressure of 102/54 mmHg, heart rate of 102 beats per minute, and respiratory rate of 28 per minute; pupils were reported as isochoric with decelerated response to light, and there were no signs of cranial nerve involvement. The patient manifested left hemiparesis with a moderate diminished in muscle strength and generalized hyporeflexia, and the Babinski's sign was positive on the left side.

Laboratory tests showed leukocytosis at the expense of segmental, renal, and hepatic function were not altered, and red blood cell and platelet counts were within normal limits (Table 1).

Table 1. Para-clinical at admission

Variables	Values
Hemoglobin	12.3 g/dL
Mean corpuscular volume	89 fL
Mean corpuscular hemoglobin	32
Leukocytes	15990
Neutrophils	89 %
Lymphocytes	10 %
Platelets	320 000
Creatinine	1.02 mg/dL
Urea Nitrogen	20 mg/dL
Total Bilirubin	1 mg/dL
Direct Bilirubin	0.4 mg/dL
Indirect Bilirubin	0.6 mg/dL
Aspartate aminotransferase	32 UI L
Alanine aminotransferase	34 UI L
Cerebrospinal fluid	Lymphocytic cells 450 Protein 59 mg/dL Glucose 98 mg/dL pH 7.2
C-Reactive Protein	125 mg
Protrombin time	14.5 s control 13.8 sec
Partial thromboplastin time	34 s control 36.2 sec

Brain computed tomography performed in the first hours of admission reported cerebral edema with a hypodense lesion in the right thalamus. After 18 hours of hospital permanence, the patient performance evolved with further neurological deterioration; a total of seven points on the Glasgow scale was reported. In addition, there were rales in the right lung base without radiological evidence of a lower respiratory infection, despite the fact that there was clinical suspicion of bronchospiratory pneumonia. At the same time, the patient presented with focal convulsive episodes and motor manifestations in the left hemibody.

The electroencephalogram manifested unilateral right hemispheric deceleration, and mechanical ventilation was started. Lumbar puncture was performed 20 hours after admission; the cerebrospinal fluid study described hyperproteinorrachia and a predominantly lymphocyte count of 450 cells with preserved glycorrhachia, with no presence of bacteria. All viral serologies for neurotropic agents included were found negative on admission, including the HIV test.

Treatment

Based on the suspected neurological infection, intravenous treatment with ceftriaxone, 2 g every 12 hours, vancomycin, 1 g every 12 hours, and acyclovir, 600 mg every eight hours, were indicated.

Control tomographic findings performed on the fifth day of admission reported hydrocephalus. A Becker-type ventricular derivation was implanted immediately. Given the persistence of the neurological manifestations, focal convulsive episodes, and motor manifestations in the left hemisphere that did not subside, treatment was supplemented with phenytoin sodium, 100 mg every eight hours, levetiracetam, one gram every 12 hours, and valproic acid 500 mg every eight hours, all by oral administration.

Outcome

The patient´s clinical condition remained with poor response to stimuli and poor interaction with the environment. After seven days of hospital confinement, a control brain CT scan showed the presence of cerebral edema with ventricular dilatation and alteration of the white matter in the right hemisphere. In addition, IgM serology was positive for the Epstein-Barr virus and negative for the rest of the neurotropic viruses. Subsequently, a polymerase chain reaction test was performed, which identified the presence of a viral genome in cerebrospinal fluid for Epstein-Barr.

The patient relapsed with focal motor seizures in the left hemibody when sedation was interrupted; therefore, sedation was discontinued only after 14 days. At the same time, a new simple brain tomography control was performed, showing the persistence of ventriculomegaly and cerebral edema (Figure 1). Mechanical ventilation continued due to the coma vigil condition. In addition, due to the clinical imaging findings, a diagnosis of viral encephalitis complicated by epilepsy secondary to a demyelinating structural lesion of the right cerebral hemisphere was stablished, and specific management with immunotherapy initiated due to the refractoriness to antivirals.

Five doses of intravenous immunoglobulin treatment were administered and resulted in neurological improvement, evident clinical progress, cessation of motor crises in the left hemisphere, as well as more interaction with the team attending her, compliance with verbal instructions and reaction to stimuli with non-verbal language response. The Becker ventricular derivation was removed 18 days

after its placement, and mechanical ventilation, 19 days after hospital admission. This patient is currently in physical therapy with a stationary evolution since she persisted with evidence of moderate left hemiparesis, gait disturbances, dysarthric language, with controlled seizure episodes during the last six months.
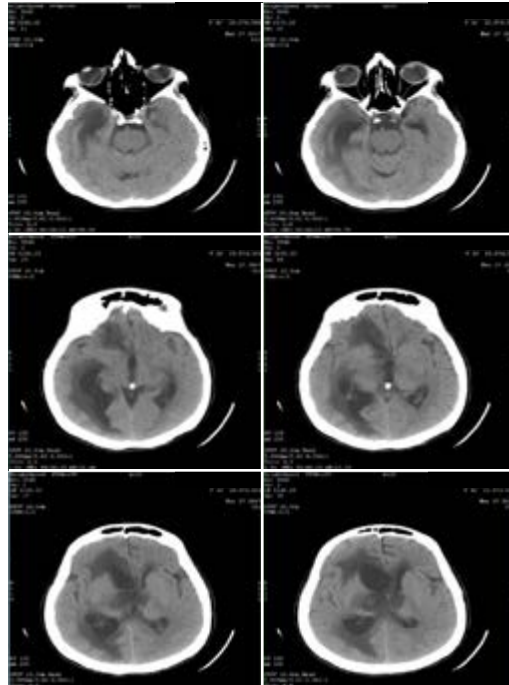
Figure 1. Cranial tomography performed on the patient.

Clinical diagnosis

This case represented a diagnostic challenge due to the clinical manifestations and paraclinical findings that generated the diagnostic suspicion of viral encephalitis complicated with structural epilepsy secondary to an intense right hemispheric demyelination. Confirmation of Epstein-Barr virus infection by serological virus identification tests, such as polymerase chain reaction, emphasized the viral etiology of encephalitis.

Discussion

The diagnostic criteria for encephalitis are based on altered mental state lasting more than 24 hours, with no identified alternative cause, and at least two of the following alterations: quantified fever above 38° C in the last 72 hours before or after presentation, seizure activity unrelated to pre-existing seizure disorders, new focal neurological signs, cerebrospinal fluid pleocytosis with new neuroimaging findings suggestive of encephalitis, and abnormal findings on electroencephalography compatible with encephalitis with other causes having been ruled out[16]. The present case described a patient with seizures, defined as unilateral deceleration of the right hemisphere, considered a common manifestation in viral encephalitis[18]. In addition, a course with progressive neurological deterioration, decreased muscle strength, altered consciousness, and bilateral papillary edema were described.

It is worth noting that approximately one-quarter of patients with confirmed encephalitis will have some symptoms suggestive of an infection outside the central nervous system[16]. The case presented showed neurological changes that progressed to neurological impairment; this may be observed in similar cases where neurological impairment provoked the need to use mechanical ventilation on the patient[19]. Within the clinical exercise, multiple causes of autoimmunity against collagen, metabolic, endocrinologic, oncologic causes, and congenital metabolic defects were ruled out since the patient's age did not support such association and even more, because there were no functional or clinical alterations that would suggest them. Vasculitic causes, immunosuppression, and other primary demyelinating diseases of the central nervous system were also ruled out.

It is clear that an electroencephalogram can be helpful to study encephalitis and evidence of encephalopathy. It would be unusual in primary psychiatric diagnoses or subclinical seizures. Viral encephalitis may be an underlying cause of non-convulsive status epilepticus in some settings. There are electroencephalographic patterns characteristic of viral encephalitis, particularly, the appearance of extreme delta brush, as a pathognomonic sign of encephalitis due to NMDAR12-type[12] antibodies formed by molecular mimicry. Anticonvulsant management needs to be performed and maintained over time, as demonstrated by scientific evidence[18].

Cerebral edema with a hypodense lesion in the right thalamus identified by brain computed tomography in the first hours of admission is consistent with viral encephalitis[17]. Due to the wide range of pathologies with altered mental status, a high index of suspicion is required; furthermore, most patients with encephalitis will not have a severely depressed Glasgow Coma Scale score on initial admission, and may even do well on basic cognitive tests such as the mini-mental test, and many often lack fever or CSF pleocytosis[19].

Regarding the etiology of encephalitis, some studies highlight that the presence of a virus or antigen may suggest a trigger for this entity. The search for the virus or antigen requires continuous efforts, from looking for the presence of Epstein-Barr virus to ruling out HIV and herpes simplex[19]. In this case, the decision to perform the polymerase chain reaction test to detect the viral genome in cerebrospinal fluid, given the positive IgM serology for Epstein-Barr virus, confirmed the presence of the etiologic agent.

Treatment of encephalitis aims to reduce the severity and frequency of sequelae and to improve long-term functional outcomes as measured by motor and cognitive performance. In the case of viral encephalitis, additionally to treatment of the underlying process, it is often necessary to consider management of seizures, movement disorders, behavior, pain, sleep disturbances, and mood disorders. Case reports and series of uncontrolled patients have been reported, in whom the effects of long-term immunotherapy for viral encephalitis have failed to generate any response to antivirals[18]. The findings of these publications show a positive experience with long-term corticosteroids. Moreover, intravenous immunoglobulins and plasmapheresis[18] have been used as strategies to limit the excessive immune response that becomes harmful. In the present case, management with immunoglobulin, as described, substantially improved the clinical progression. Describing new therapies such as hemispherectomy is fundamental because of the sequels that could produce. Surgery has also been reported as a therapeutic option in refractory cases[20].

Most patients with viral encephalitis recover without sequelae. Those who remain symptomatic have difficulty concentrating, speech and behavioral disorders, and or memory loss. In rare cases, patients may persist in a vegetative state. Following viral encephalitis, patients may develop seizures, severe mental retardation, and diverse modes of paralysis[18].

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Original article

Impact of COVID-19 on mental health in Uruguay

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Abstract
Introduction. The history of quarantines has pointed out impacts in the short and long term on mental health. Objective: Within the framework of the measures decreed to reduce the transmissibility of SarS-Cov2, we propose to analyze the repercussions on the mental health of the Uruguayan population. **Methodology.** Analytical design. Application of a self-administered web survey. Absolute and relative percentage frequencies and their confidence intervals (95 %) were analyzed. Binary logistic models were estimated for dichotomous variables and multinomial logistic models for «difficulty falling asleep». **Results.** Regarding anxiety elements, 27.1 % (95 % CI, 24.8-29.3) and 31.0 % (95 % CI, 28-33.3) responded feeling anxious in the first and second cut-off, respectively. 19.9 % (95 % CI, 17.6-21.7) and 31.4 % (95 % CI, 20.06-33.89) reported feeling sad in the first and second cut-off. Medium educational level was associated with the presence of anxiety (p < 0.001), while low educational level was associated with sadness (p = 0.005). A protective effect was observed in households with more than five members for the sadness variable with an OR of 0.41 (95 % CI, 0.22-0.75). Female gender was related to the presence of anxiety and sadness. Medium and high educational levels were related to the presence of anxiety and sadness was associated with unemployment. Sleep disorders were associated with female gender, unemployment and non-communicable diseases. **Conclusion.** The impact on mental health was unequal, especially affecting women from middle socio-educational sectors, between 35 and 59 years of age.
Keywords
COVID-19, Mental health, Anxiety, Depression, Sleep Wake Disorders.

Resumen
Introducción. Los antecedentes de cuarentenas han señalado impactos en el corto y largo plazo en la salud mental. **Objetivo.** Describir las repercusiones generadas en el área de la salud mental en la población uruguaya mayor de 18 años, de las variables ansiedad, tristeza y dificultades para conciliar el sueño, en el periodo comprendido entre el 13 de marzo de 2020 al 10 de junio de 2021. **Metodología.** Estudio transversal analítico. Se aplicó una encuesta web, auto-administrada. Se analizaron las frecuencias absolutas y relativas porcentuales y sus intervalos de confianza (95 %). Se estimaron modelos logísticos binarios para las variables dicotómicas y modelos logísticos multinomiales para «dificultad para conciliar el sueño». **Resultados.** En relación a los elementos de ansiedad, 27,1 % (IC 95 % 24,8-29,3) y 31,0 % (IC 95 % 28-33,3) respondieron sentirse ansiosos en el primer y segundo corte, respectivamente. El 19,9 % (IC 95 % 17,6-21,7) en el primer corte, mientras que el 31,4 % (IC 95 % 20,06-33,89) lo confirmaron en el segundo. El nivel educativo medio se asoció con la presencia de ansiedad (p < 0,001), mientras el bajo se asoció con tristeza (p = 0,005). Se observó un efecto protector en hogares con más de cinco miembros para la variable tristeza con un OR de 0,41 (IC 95 % 0,22-0,75). Se encontró relación entre el género femenino y la presencia de ansiedad y tristeza. Los niveles educativos medio y alto se vieron relacionados con la presencia de ansiedad y la tristeza se asoció con el desempleo. Los trastornos del sueño se asociaron al género femenino, desempleo y enfermedades no transmisibles. **Conclusión.** Los trastornos de ansiedad, la afectación del sueño y los sentimientos de tristeza fueron prevalentes, las familias de mayor número de miembros tuvieron un efecto protector sobre estas manifestaciones.

Palabras clave
COVID-19, Salud mental, ansiedad, depresión, trastornos del sueño.

Introduction

The COVID-19 pandemic brought changes in the behavior of the world population. To prevent contagion, social distancing and quarantine measures were adopted[1]. In Uruguay, on March 13, 2020, the first four cases of SARS CoV-2 infection were confirmed. A sanitary emergency was immediately declared, and to reduce the spread of the virus, measures were adopted, which included the suspension of public events, the isolation of people with probable symptoms or positive COVID-19[2] test results; subsequently, to flatten the epidemic curve, social isolation measures were extended such as the suspension of classes at all levels of education and the promotion of teleworking[3].

Although quarantine was not mandatory for the entire population at the national level, the majority opted for voluntary quarantine. These confinement measures led to profound changes in daily life and in the basic routines of families, which, in addition to uncertainty and an increased workload, had an impact on mental health and socioeconomic aspects[3]. The worsening of mental health problems among adults led to an increase in child maltreatment and the possibility of domestic violence[4].

Previous experiences indicate that these measures tend to trigger different types of repercussions. In relation to the mental health of adults, an increase in psychological symptoms has been described during quarantines, even when these are brief. It is observed that the most affected are women and health personnel[5,6]. In the context of the COVID-19 quarantine, the prevalence of mental health disorders in the population was identified, including post-traumatic stress, anxiety, depression and somatization, which included reactions such as fear and sleep disorders[7,8].

Before the pandemic caused by COVID-19, mental disorders were among the main health problems worldwide. During the year 2020, major depressive disorder presented an increase of approximately 53.2 million cases, which is equivalent to an increment of 27.6 % of cases, and anxiety disorders had an increment of 25.6 %, with a higher prevalence in places where less human mobility was detected[9].

Furthermore, health personnel also presented alterations in their mental health, mainly due to factors related to direct contact with COVID-19 patients, the death of co-workers, and patients' family conflicts. The collaborative research study HEROES, led by the universities of Chile and Columbia, addressed the mental health situation of health personnel in 11 countries in the region: Argentina, Brazil, Chile, Colombia, the Plurinational State of Bolivia, Guatemala, Mexico, Peru, Puerto Rico, the Bolivarian Republic of Venezuela and Uruguay, and revealed the presence of high rates of depressive symptoms, suicidal thinking and psychological distress in health workers[10].

In light of the above, this study describes the repercussions generated in the area of mental health in the Uruguayan population over 18 years old, from a public health perspective, through the variables anxiety, sadness, and difficulties in falling asleep at two different moments during the period from March 13, 2020, to June 10, 2021.

Methodology

An analytical cross-sectional design was developed. The data collection instrument consisted of a survey elaborated on Facebook and disseminated through advertisements on the same social network, given that national data have reported that seven out of ten adults in Uruguay are users of this social network[11]. The population consisted of Internet users over 18 years old, users of the social network Facebook.

The survey was distributed to users of the social network at two time intervals, which were epidemiologically and socially differentiated, so that it was not answered at both times by the same participants.

The first segment took place over a period of nearly nine months, from March 13 to December 21, 2020. It started at the moment when the health emergency was established, with a low number of cases for the region and the world, but with a sense of uncertainty regarding the severity of the pandemic, as well as its duration, and the duration of the measures taken to control the expansion of cases[3].

The second segment was from January 2021 to June 10, 2021, one year after the pandemic was declared (with measures in place since that time). This period was characterized by an exponential increase in cases and deaths due to COVID-19 in Uruguay, as well as by the beginning of vaccination campaigns in the country[3].

The sample comprised a total of 2905 people; 1500 subjects in the first segment and 1405 in the second.

For sample selection, the population was segregated by sex, age, region, and educational level. The presence of quotas for these variables was controlled to ensure a significant number of cases for each category, and weightings were calculated according to the variables used for segmentation.

The sample analysis included five variables: age, gender, current job, non-communicable disease (NCD) status and type of household. Three groups of 18 to 34 years old, 35 to 59 years old and 60 years old or older were defined; educational level were classified into low (less than nine years of formal education), medium (between nine and 12 years of formal education) and high (more than 12 years of formal education); gender categorization divided into male and female; in addition, if the person had a job at the time of the survey, if they suffered from any NCD, and finally, the type of households, which were classified into one-person, two to four members and five or more members. Educational level was considered as a proxy variable for socioeconomic level[12].

Self-perceived symptoms of anxiety or depression in both survey segments were identified through the following block of questions: "I feel anxiety," "I feel sad," "I feel calm and in good spirits," "I feel fear or worry," "I feel more tired than usual." For each of these questions, the options "yes," "no," and "don't know/no answer" were provided. In addition, a question regarding difficulties in falling asleep was included, with the following response options: "no," "yes, sometimes," and "yes, always."

For each segment, the absolute frequency and percentages of the variables were analyzed, as well as their 95 % confidence intervals. Binary logistic models were estimated for the variables "anxiety" and "sadness." For the variable "difficulty falling asleep," multinomial logistic models were estimated. Both statistical and theoretical relevance criteria were used for the multiple model input. The relative quality of the models was assesed using the Akaike criterion, and the adjustment was analyzed through deviation. All estimates were obtained using sampling weights, and an α = 0.05 was used as significance threshold. Data analysis was performed in R software (version 4.1.2)[13].

The project was registered at the General Directorate of Health, Health Evaluation Division of the Ministry of Public Health on August 8, 2020, under number 827113. The research team declares to have complied with the Declaration of Helsinki on ethical principles for medical research involving human subjects.

Results

Table 1 shows the characteristics of the population that participated in the survey at each segment. The sample in both cases was composed of 43 % of the population of Montevideo and 57 % from the rest of the country.

NCD were detected more frequently in respondents in the first segment; at this moment, 61.7 % of respondents stated that they had some NCD (95 % CI, 59.2-64.2) as opposed to 47.4 % in the second segment (95 % CI, 44.8-50.0), with a significant difference in this variable between the two time periods.

In the first segment, 27.1 % (95 % CI, 24.8-29.3) of the respondents answered that they felt anxiety, in contrast to 31 % (95 % CI, 28.0-33.3), in the second segment. Sadness was present in 19.9 % (95 % CI, 17.6-21.7) of respondents in the first segment, in contrast to 31.4 % (95 % CI, 20.1-33.9) who expressed feeling sad in the second segment.

Table 1. General characteristics of the population (first and second segments)

		First segment (n=1500)		Second segment (n=1405)	
		n (%)	95% CI	n (%)	95% CI
Age*	18-34	570 (38.0 %)	35.5-40.4	517 (36.8 %)	34.3-39.4
	35-59	690 (46.0 %)	43.4-48.5	657 (46.8 %)	44.2-49.4
	>=60	241 (16.0 %)	14.2-17.9	231 (16.4 %)	14.6-18.5
Education level*	Low	449 (30.0 %)	27.7-32.3	421 (30.0 %)	27.7-32.4
	Medium	644 (42.9 %)	40.5-45.5	604 (43.0 %)	40.5-45.6
	High	404 (26.9 %)	27.4-29.2	379 (27.0 %)	24.7-29.4
Gender	M	707 (47.1 %)	44.6-49.6	662 (47.2 %)	44.6-49.9
	F	793 (52.9 %)	50.4-55.4	740 (52.8 %)	50.1-55.4
Current Job*	Yes	713 (47.5 %)	45.0-50.0	784 (56.6 %)	53.9-59.2
	No	787 (52.5 %)	49.9-55.0	601 (43.4 %)	40.8-46.1

CI= confidence interval, M=male, F=female.

*: For some of the variables, there were no responses from the total population in both segments.

Therefore, it should be noted that the manifestations of the emotional dimension corresponding to anxiety and depression syndromes were higher in the first segment. On the other hand, difficulties in falling asleep occasionally occurred in 40.8 % (95 % CI, 38.6-43.6), while in the first segment, 11.6 % (95 % CI, 10.0-13.3) reported having them continuously. These sleep disorders did not show significant differences between the two segments time of the survey. Medium educational level was associated with the presence of anxiety (p <0.01)(Table 2). Whereas low educational level was significantly associated with sadness (p <0.01)(Table 3).

It is worth noting the protective effect of households with five or more members for the sadness variable, as observed in the second survey cut-off, with an OR of 0.4 (95 % CI, 0.2-0.8)(Table 3).

On the other hand, female gender related to anxiety and sadness in the second segment of the survey. Those older than 34 presented an OR significantly lower than one for anxiety in both events. For ages older than 59, they were less associated with sadness in the adjusted models for both segments (Tables 2 and 3).

Medium and high levels of education were related to anxiety, and sadness was associated with unemployment. Non-

Table 2. Factors associated with feelings of anxiety during the Covid-19 pandemic in the first and second survey segments, Uruguay (2020 and 2021)

		First segment		Second segment	
		Raw OR (95% CI)	Adjusted OR (95% CI)	Raw OR (95% CI)	Adjusted OR (95% CI)
Gender	M	1		1	
	F	1.09 (0.87-1.38)	1.23 (0.96-1.58)	1.55 (1.23-1.95)	1.32 (1.04-1.68)
Age	18-34	1		1	
	35-59	0.67 (0.52-0.85)	0.59 (0.44-0.78)	0.55 (0.43-0.71)	0.54 (0.41-0.71)
	>=60	0.52 (0.36-0.73)	0.37 (0.24-0.54)	0.42 (0.29-0.59)	0.34 (0.22-0.50)
Education level	Low	1		1	
	Medium	1.61 (1.17.2.24)	1.62 (1.16-2.26)	1.75 (1.31-2.34)	1.59 (1.18-2.16)
	High	2.25 (1.64-3.12)	2.38 (1.66-3.43)	2.75 (2.02-3.77)	2.39 (1.73-3.33)
NCD	No	1		1	
	Yes	1.57 (1.25-1.98)	2.44 (1.86-3.20)	0.66 (0.53-0.83)	0.48 (0.37-0.61)

CI= Confidence interval, M=Male, F=Female, NCD= non communicable diseases.

Table 3. Factors associated with feelings of sadness during the Covid-19 pandemic in the first and second survey segments. Uruguay (2020 and 2021)

		First segment		Second segment	
		Raw OR (95% CI)	Adjusted OR (95% CI)	Raw OR (95% CI)	Adjusted OR (95% CI)
Gender	M	1		1	
	F	1.11 (0.85-1.45)	0.97 (0.73-1.28)	1.55 (1.16-2.07)	1.36 (1.01-1.85)
Age	18-34	1		1	
	35-59	1.10 (0.83-1.48)	0.87 (0.63-1.19)	0.84 (0.62-1.14)	0.64 (0.46-0.90)
	>=60	1.09 (0.74-1.60)	0.65 (0.42-0.99)	0.85 (0.55-1.28)	0.43 (0.26-0.68)
Current job	Si	1		1	
	No	1.47 (1.13-1.91)	1.42 (1.07-1.88)	1.76 (1.32-2.34)	1.80 (1.33-2.44)
NCD	No	1		1	
	Si	1.85 (1.42-2.42)	1.96 (1.45-2.64)	2.30 (1.72-3.09)	2.62 (1.90-3.63)
Household	One-person			1	
	2 a 4 members			0.86 (0.59-1.27)	0.78 (0.53-1.17)
	5 + members			0.55 (0.30-0.97)	0.41 (0.22-0.75)

CI= Confidence interval. M=Male. F=Female. NCD= non communicable diseases.

communicable diseases were associated with the symptom of anxiety in the first cut-off and sadness in both cut-offs. Anxiety in patients with NCDs showed a decrease in the second cut-off (Tables 2 and 3).

Difficulty falling asleep was significantly associated with female gender, unemployment, and the presence of noncommunicable diseases in both survey periods, in both the simple and adjusted models (Table 4).

Discussion

The international literature concerning the impact of quarantines has shown that this type of measure usually generates individual and collective repercussions of different kinds[9].

The prevalence of mental health problems was higher in women for both survey segments. This trend is consistent with the reports of multiple studies affirming that manifestations of anxiety and, or depression are predominantly found in women and, in particular, in young and middle-aged women[14-16].

The survey on children, time use, and gender in the context of the UN Women in Uruguay health emergency reported a higher frequency of symptoms in the area of mental health for the female gender due to a combination of factors; on the one hand, the suspension of attendance at all educational levels and the recommendations to "stay at home" determined an overload in terms of child and adolescent care. This demand generated a higher burden on women, with the consequent widening of gender gaps in domestic chores, increasing the number of hours dedicated to unpaid work. Furthermore, women reported a higher loss of paid employment in terms of jobs and the number of hours per week dedicated to paid work[17]. In addition, domestic violence against women and children rose significantly since the pandemic was declared in Uruguay and other countries[18,19]. These violence has been associated with a higher presence of anxiety and depression, and even more accentuated in those women who do not have a support network[18].

In this study age was identified as a factor associated with lower self-perceived distress. Adults older than 65 years showed to be less stressed, had better psychosocial functioning and were less likely to use avoidant coping behaviors, as was demonstrated by the results of a meta-analysis by Lieneck *et al.* on protective and non-protective factors for mental illness during the COVID-19

Table 4. Factors associated with difficulty falling asleep during the COVID-19 pandemic in first and second survey segments. Uruguay (2020 and 2021)

		Primer corte				Segundo corte			
		Raw OR (95% CI)*		Adjusted OR (95% CI)*		Raw OR (95% CI)*		Adjusted OR (95% CI)*	
		Yes. occasionally	Yes. always	Yes. occasionally	Yes. always	Yes. occasionally	Yes. always	Yes. occasionally	Yes. always
Gender	M	1		1		1		1	
	F	1.77 (1.42-2.21)	3.55 (2.44-5.15)	1.76 (1.39-2.23)	3.26 (2.19-4.84)	1.70 (1.35-2.13)	2.98 (2.07-4.30)	1.46 (1.16-1.85)	2.58 (1.76-3.78
Age	18-34	1		1		1		1	
	35-59	1.23 (0.97-1.57)	1.28 (0.88-1.85)	1.03 (0.78-1.37)	0.72 (0.46-1.12)	0.75 (0.58-0.96)	0.97 (0.66-1.43)	0.70 (0.53-0.92)	0.79 (0.51-1.22)
	>=60	0.85 (0.62-1.18)	0.88 (0.53-1.46)	0.55 (0.38-0.81)	0.41 (0.23-0.72)	0.59 (0.42-0.83)	1.03 (0.63-1.68)	0.40 (0.27-0.60)	0.48 (0.27-0.60)
Educational level	Low	1		1		1		1	
	Medium	1.09 (0.82-1.45)	1.09 (0.72-1.66)	1.23 (0.91-1.65)	1.28 (0.82-1.97)	0.96 (0.74-1.26)	1.37 (0.91-2.06)	0.89 (0.67-1.18)	1.44 (0.93-2.22)
	High	1.05 (0.79-1.41)	0.75 (0.48-1.18)	1.65 (1.17-2.32)	1.38 (0.81-2.33)	1.14 (0.85-1.54)	0.99 (0.61-1.60)	1.10 (0.80-1.52)	1.06 (0.63-1.80)
Current job	Yes	1		1		1		1	
	No	1.32 (1.06-1.65)	1.56 (1.11-2.18)	1.35 (1.05-1.74)	1.34 (0.92-1.96)	1.62 (1.29-2.05)	2.68 (1.89-3.80)	1.73 (1.34-2.23)	2.54 (1.73-3.73)
NCD	No	1		1		1		1	
	Yes	1.80 (1.44-2.25)	3.01 (2.12-4.29)	2.02 (1.57-2.61)	3.42 (2.30-5.08)	1.45 (1.15-1.82)	3.83 (2.65-5.54)	1.67 (1.29-2.15)	4.08 (2.71-6.14)

*Reference: "no difficulty falling asleep". CI=confidence interval. M=male. F=female. NCD=noncommunicable diseases.

pandemic in the United States of America[20]. Despite being consistent with other studies, the apparent protective effect of age is striking. The greater biological vulnerability of older adults to COVID-19 led to specific communication campaigns promotion of social and mental health networks tailored for this population, which probably contributed to its stability, yet, it should not be discarded that the use of a self-administered virtual data collection instrument may have generated some bias in the recruitment of the older adults who finished it.

Another important finding was the significant association of noncommunicable diseases with the three manifestations of the mental health observed (anxiety, sadness, and difficulty falling asleep). This population of people over 65 years old, which was considered at risk from the beginning of the pandemic, was the one that received the recommendation of social isolation emphatically. Moreover, according to a document from the Honorary Scientific Advisory Group (GACH), the initial measures had a heterogeneous impact on care, with repercussions on the quality of care and follow-up of patients with noncommunicable diseases[21]. 21 Multiple studies, including systematic reviews, link the measures taken to control the pandemic with feelings of isolation, loneliness, anxiety and sadness in the population with noncommunicable diseases[22-25]. In addition, it is noteworthy that, between the first and second segments of the survey, the link between the occurrence of NCD and anxiety is inverted. This behavior might be explained by the fact that people with NCD belonged to the priority group for immunization within the vaccination plan launched by the Ministry of Public Health on February 27, 2021. Thus, at the time of the second survey segment, a large part of this group was already immunized with the first dose of the vaccine.

Regarding the link between the type of household and mental health symptoms, it was found that individuals who lived with more than five members had a lower risk of suffering from sadness. Recently published studies have described the availability of strong social networks and connections as a protective factor for all ages against mental health disorders during the pandemic[19-21].

Among the limitations of this study are the factors linked to the data collection method since, although Uruguay presents a broad coverage of social network use, the target audience was limited to the population with the highest use of Facebook, which could be related to economic level or age.

The prioritization of mental health care is present in most public health agendas. However, the mental health of communities has been affected in various ways in the context of the current global health crisis[3,19-21].

The report of the Honorary Scientific Advisory Group informs that, in private healthcare institutions in Uruguay, there was a decrease of 29 % in psychiatric consultations and 58 % in psychotherapeutic consultations compared to 2019. The impact on the mental health of healthcare workers is also highlighted, with a frequency of between 14.7 % and 22 % of symptoms of psychic suffering in the healthcare personnel interviewed in 2020[22]. Similarly, consultations, procedures and population screening strategies for other NCD also showed a decrease, which could lead to a worsening of the main causes of morbidity and mortality in the country in the medium and long term.

Regarding the response of the health system, although remote medical consultations were promoted, they were implemented with certain difficulties. Among the problems mentioned are: the probable decrease in the quality of care, certain limitations in the use of telemedicine resources (enabled by Law 19869 of 04/02/20), the probable abandonment of medication by many patients, multiple coordination difficulties detected, the decrease in the number of care team meetings, difficulties in patient follow-up and in communications between psychiatrists, patients and family members, among others[22].

Conclusion

The COVID-19 pandemic confronted the country with multiple challenges. When evaluating the impact on the different health care areas, from an integral perspective, it was observed that the impact on mental health has been evident. Anxiety disorders, sleep disorders and feelings of sadness were relevant. Households with a greater number of members had a protective effect on emotional alterations. The impact on mental health especially affected women, in general, and particularly women from middle socio-educational sectors within the age range between 35 and 59 years old.

Funding

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Original article

Motives for tobacco, alcohol, and cannabis use in the confinement context due to COVID-19 pandemic

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Abstract
Introduction. Drugs produce significant negative consequences in societies. The prevalence of drug use continues to increase because various reasons lead people to use them. **Objective.** Identify differences in the frequency and amount of tobacco, alcohol, and cannabis use during and after COVID-19 pandemic confinement, the influence of confinement on motives, and risks for developing problematic use. **Methodology.** Analytical cross-sectional study with non-probabilistic sampling at two points in time. Five hundred and twenty young people participated: 246 high school and university students during the confinement in 2020, and 274 in 2022. Sociodemographic data, reasons for consumption, and problematic consumption were evaluated. **Results.** Cannabis use during confinement (41.1 %) was higher than post-confinement (29.6 %; p 0.006). There were differences between the groups of problematic tobacco use during confinement and the social (W 8.178, p 0.017), and coping (W 26.456, p < 0.001) motives; also, between the groups of problematic alcohol consumption and social motives (W 6865.5, p < 0.001); encouragement (W 6768.0, p < 0.001); coping (W 6176.0, p = 0.002) and expansion (W 6774.0, p < 0.001). Among the motives for problematic cannabis use, social (W 6.404, p 0.041); animation (W 9.409, p 0.009); coping (W 9.265, p 0.010), and expansion (W 27.692, p < 0.001) were highlighted. **Conclusion.** Confinement increased the risk of tobacco and cannabis use. Motives for use also increased, except those associated with alcohol use in university students. Problem tobacco use was motivated by social and coping needs; alcohol and cannabis use was motivated by social, entertainment, coping and expansion needs.

Keywords
Alcohol Drinking, Consumption of Tobacco-Derived Products, Recreational Drug Use, Cannabis Smoking, COVID-19.

Resumen
Introducción. Las drogas producen importantes consecuencias negativas en las sociedades. La prevalencia de su consumo sigue aumentando debido a que existen diversos motivos que acercan a las personas a consumirlas. **Objetivo.** Identificar las diferencias en la frecuencia y cantidad del consumo de tabaco, alcohol y cannabis durante y después del confinamiento por la pandemia de COVID-19; así como la influencia del confinamiento en los motivos y los riesgos de desarrollar un consumo problemático. **Metodología.** Estudio transversal analítico con muestreo no probabilístico en dos momentos. Participaron 520 jóvenes: 246 estudiantes de bachillerato y universidad en el año 2020, durante el confinamiento y 274, en 2022. Se evaluaron datos sociodemográficos, motivos de consumo y consumo problemático. **Resultados.** El consumo de cannabis durante el confinamiento (41,1 %) fue mayor que en el posconfinamiento (29,6 %; p 0,006). Hubo diferencias entre los grupos de consumo problemático de tabaco durante el confinamiento y los motivos sociales (W 8,178, p 0,017) y de afrontamiento (W 26,456, p < 0,001); también, entre los grupos de consumo problemático de alcohol y los motivos sociales (W 6865,5, p < 0,001); de animación (W 6768,0, p < 0,001); de afrontamiento (W 6176,0, p = 0,002) y de expansión (W 6774,0, p < 0,001). Entre los motivos del consumo problemático de cannabis se destacan los sociales (W 6,404, p 0,041); de animación (W 9,409, p 0,009); de afrontamiento (W 9,265, p 0,010) y de expansión (W 27,692, p < 0,001). **Conclusión.** El confinamiento incrementó el riesgo de consumir tabaco y cannabis. Los motivos de consumo también aumentaron, excepto las asociadas al consumo de alcohol en universitarios. El consumo problemático de tabaco estuvo motivado por necesidades sociales y de afrontamiento; el de alcohol y cannabis, por necesidades sociales, de animación, de afrontamiento y de expansión.

Palabras clave
Consumo de alcohol, consumo de productos derivados del tabaco, uso recreativo de drogas, fumar cannabis, COVID-19.

Introduction

The COVID-19 pandemic introduced a series of changes in the attitudes and behaviors of the population. One of these was that the Spanish government decreed a state of alarm to deal with the health emergency between March 14 and June 21, 2020. At its end, a "new normality" was declared, which lasted until May 9, 2021. The restriction measures established included social, family, and work limitations that affected relationship habits[1,2] affecting depressive and anxious symptoms that can contribute to the consumption and abuse of substances such as alcohol, tobacco, or cannabis[3], especially in young people[4].

According to Cooper *et al.*, substance use can be understood as a strategic behavior based on the underlying need or desire of individuals, with prior knowledge of the effects, to escape from a negative emotional state or to share with others the experience of the effects produced by the substance[5,6]. Cooper established four motivational categories: 1) self-focused motivations; 2) coping motives; 3) social motives; and 4) social avoidance motives[7], which may have been affected during the pandemic[8], especially in young people[9].

Concerning tobacco, young people are motivated by the desire to experience positive emotions linked to increasing their status or generating an accepted social image, perceiving tobacco consumption as a facilitator of social relations[10].

The influence of confinement and other measures established to deal with the COVID-19 pandemic on the consumption patterns of these substances by students[11] has been highlighted because it is closely linked to social motives[5] and the relationship with peers[11]. However, the results are contradictory. On the one hand, some studies argue that alcohol consumption has decreased due to social restrictions, while others suggest an increase due to the consequences of the pandemic[4,13]. On the other hand, about cannabis, no publications have been found on changes in consumption due to the pandemic, although Schapis *et al.* suggest an increase among students as of COVID-19[4].

Consequently, this study aims to compare the motives for tobacco, alcohol, and cannabis use and the risk of problematic use of tobacco, alcohol, and cannabis among young high school and college students during and after the confinement of the COVID-19 pandemic. Based on the documentation consulted, the hypotheses are: 1) in times of pandemic, young people have used tobacco, alcohol, or cannabis to cope with negative emotions; 2) motivations for tobacco, alcohol, or cannabis use are an influential factor in developing problematic use.

Methodology

A total of 520 individuals were recruited, of whom 266 were high school students from Gavà, a town in the metropolitan area of Barcelona, and 254 university students, all from the province of Barcelona, Spain. Of the total, 246 participated during the COVID-19 pandemic confinement in 2020, and 274 were recruited in 2022. Participants met the selection criteria: 1) they were high school or university students; 2) they had consumed one of the three substances in the last year; and 3) they gave their consent or had the consent of their parents or guardian to participate.

Five instruments were used for data collection, a questionnaire of sociodemographic characteristics: sex, age, and educational level. The Marijuana Motives Measure Short Form (MMM-SF)[14] questionnaire, which was used to address motives for cannabis use, is a shortened version of the Marijuana Motives Measure (MMM)[15], which in turn is an adaptation of the Drinking Motives Questionnaire (DMQ)[7].

The MMM-SF consists of 15 items and evaluates the different motivations for the substance use. It is answered based on a Likert scale from 1 to 5, where 1 corresponds to "almost never" and 5 to "almost always". The psychometric data of the MMM-SF showed good reliability. Cronbach's alpha of 0.820 was in the data analysis of the questionnaire to assess motivation towards smoking. A Cronbach's alpha of 0.873 was in the case of alcohol. Finally, Cronbach's alpha of 0.878 was the motivation for cannabis use.

The Alcohol Use Disorders Identification (AUDIT) questionnaire was used to assess problematic alcohol use. The AUDIT is a self-administered questionnaire consisting of ten questions; three of them are designed to find out the frequency and dependence on alcohol consumption, the next two refer to the attitude towards drinking. The seventh and eighth to adverse reactions, and the last ones are related to problems with its consumption. Therefore, this questionnaire aims to detect problems related to alcohol consumption, i.e., problematic alcohol consumption. The validated version was used in Spain, which showed good psychometric results in terms of reliability, obtaining a Cronbach's alpha of 0.696[16,17].

The Alcohol, Smoking, and Substance involvement Screening Test (ASSIST) was used to assess problematic tobacco use.

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The ASSIST is a screening test for the risk of alcohol, tobacco, and other substance use; however, in this study, it was used only to assess the frequency, dependence, and consequences of tobacco use[18]. Regarding the psychometric data, the items chosen showed good reliability in the data analysis, obtaining a Cronbach's alpha of 0.767.

Problematic cannabis use was assessed using the Cannabis Abuse Screening Test (CAST)[19] questionnaire. The CAST is a questionnaire for estimating problematic cannabis use. Problematic cannabis use was assessed using the Cannabis Abuse Screening Test (CAST)[19] questionnaire. The CAST is a questionnaire for estimating problematic cannabis use. It consists of six items that are answered taking into account the frequency with which one feels identified with the question. The response must be rated from 0 to 4 where 0 corresponds to "never", 1 to "rarely", 2 to "occasionally", 3 to "quite often", and 4 to "very often"[8,19,20]. This questionnaire showed good reliability, obtaining a Cronbach's alpha of 0.832.

The questionnaires were administered through a link to Google Forms in two different moments; the first in 2020 during confinement and the second in 2022. To apply the questionnaires to high school students, face-to-face groups of approximately 30 students were conducted. The university students responded autonomously and personally. In addition, they were asked to forward the survey to acquaintances who met the selection criteria.

The study of the ordinal, nominal and quantitative variables obtained in the questionnaire was carried out by means of different statistical tests using Jeffreys's Amazing Statistics Program (JASP). The Chi-square test was for nominal and ordinal variables. As for quantitative variables, since they did not comply with normality, nonparametric tests were performed: Spearman's correlation and Mann-Whitney U test. The significance level chosen for the results interpretation was $p < 0.05$ for a confidence interval of 95 %.

Both high school and university students were informed of the confidentiality of the responses, the voluntary nature of participation and were not given any reward for their collaboration. For minors, informed consent was obtained from parents or guardians. In the case of adults, to participate in the research, they had to accept the terms and give their consent.

Results

A total of 295 women (56.7 %) and 225 men (43.3 %) participated, with a mean age of 19.94 years (SD 3.365). No statistically significant differences (W 35 868, p 0.108) were between the mean age of females (19.10, SD 3.379) and males (18.74, SD 3.344), nor between the mean age of students who participated during confinement (18.768, SD 2.579) and after confinement (19.10, SD 3.938; W 34 247, p 0.746).

Regarding tobacco (p 0.959) and alcohol use (p 0.096), there were no significant differences between the sexes in the last year. In contrast, cannabis use was in 44.89 % of men compared to 27.46 % of women ($p < 0.001$).

On the other hand, no significant differences were found in the motivations associated with tobacco use between men and women. In contrast with the motives for alcohol consumption, differences were found in the coping motives (p 0.012). In this type of consumption, women obtained higher scores (M 4.531, SD 2.785) than men (M 3.967, SD 2.738). In addition, in the motives for cannabis use, significant differences were found related to social (W 12 754.500, $p < 0.001$), encouragement (W 12 753, $p < 0.001$), coping (W 13 320, $p < 0.001$), conformity (W 13 060.500, $p < 0.001$) and expansion (W 13 393, $p < 0.001$) motives. In all, men's scores were higher than those of women.

Age and educational level were positively correlated with the motives for consumption of the three substances. Thus, the older the age and the higher the level of education, the higher the scores on the motives for consumption. The greatest difference between means (W 14 351.500, $p < 0.001$) was between high school students (M 3.891, SD 5.669) and university students (M 5.497, SD 5.391).

Consumption and risk consumption during and after confinement the pandemic of high school and college students

First, significant differences were observed in cannabis use in the total sample during the last year (p 0.006). During confinement, 41.1 % used cannabis at least once in the last 12 months. In contrast, after confinement, this consumption decreased to 29.6 %. On the other hand, no significant differences were found (p 0.543) between alcohol consumption during (86.2 %) and after confinement (84.3 %). Nor were significant differences found in tobacco consumption (p 0.427) during (48.4 %) and after confinement (44.9 %).

Second, tobacco risk consumption showed significant differences during and after pandemic confinement between the group of high school students ($p < 0.001$)

and the group of university students (p < 0.001) (Table 1). During confinement, 80 % of the high school students were at medium risk; in contrast, after confinement, 76.71 % were at low risk. As for university students, it is worth noting that during confinement, 73.44 % were in medium-risk consumption. This figure dropped to 50 % after confinement.

Likewise, in cannabis use, significant differences were also observed in the risk use of high school students (p < 0.001) and university students (p < 0.001). During confinement, 47.4 % of high school students had risky cannabis use. After confinement, this figure decreased so that 8.1 % of high school students had a risk associated with their use.

On the other hand, 39.7 % of university students had risky consumption during confinement. After confinement, 81.3 % had no risk associated with consumption. Finally, it should be noted that no significant differences were found in the risk of alcohol consumption of high school students (p 0.265) and college students (p 0.352) during and after confinement.

Motives for consumption during and after COVID-19 pandemic confinement

Motives (social, encouragement, coping, conformity, and expansion) for tobacco, alcohol, and cannabis use were higher during the COVID-19 pandemic confinement for both high school and college students, except for alcohol use in college students. All, except cheerleading (W 9096.5, p 0.004) and coping (W 8667, p 0.025) motives, remained the same during and after confinement (Table 2).

Relationship between motives for use and problematic use during and after confinement for the COVID-19 pandemic

The relationship between consumption motives and problematic consumption during and after confinement is shown in Table 3. During confinement, the tobacco risk groups showed significant differences between social (W 8.178, p 0.017) and coping motives (W 26.456, p < 0.001). Those

Table 1. Risk groups before and after confinement for the COVID-19 pandemic as a function of substance and type of studies

-	-	-	During confinement %	After confinement %	χ2	p
Tabacco	High school students	Low risk	18.18	76.71	57.421	< 0.001
		Medium risk	80.00	22.60		
		High risk	1.82	0.69		
	University students	Low risk	20.31	48.44	15.694	< 0.001
		Medium risk	73.44	50.00		
		High risk	6.25	1.56		
Alcohol	High school students	Normal consumption	75.79	69.18	1.242	0.265
		Risk consumption	24.21	30.82		
	University students	Normal consumption	60.68	66.41	0.865	0.352
		Risk consumption	39.32	33.59		
Cannabis	High school students	No risk	39.47	91.10	54.343	< 0.001
		Medium risk	13.16	4.10		
		High risk	47.37	4.80		
	University students	No risk	41.27	81.25	31.224	< 0.001
		Medium risk	19.05	7.03		
		High risk	39.68	11.72		

participants with medium risk in tobacco use showed higher scores in social and coping motives compared to those with low risk.

On the other hand, significant differences were between the alcohol risk drinking groups and the social (W 6865.5, p < 0.001), encouragement (W 6768, p < 0.001), coping (W 6176, p 0.002), and expansion (W 6774, p < 0.001) motivations. Therefore, those with risky alcohol consumption showed higher scores on social motivation, cheerfulness, coping, and expansiveness compared to those with typical consumption.

Finally, significant differences were between the cannabis risk-taking groups and social (W 6.404, p 0.041), encouragement (W 9.409, p= 0.009), coping (W 9.265, p= 0.010), and expansion (W 27.692, p< 0.001) motivations. Thus, participants with higher risk in cannabis use showed higher scores on social motivation, encouragement, coping and expansion than those with low risk.

Similarly, after confinement, a higher risk in tobacco consumption was identified due to higher social (W 192.155, p< 0.001), encouragement (W 200.250, p< 0.001), coping (W 202.619, p< 0.001), conformity (W 187.939, p< 0.001), and expansion (W 187.634, p< 0.001) motivation. The same

is true for risky cannabis use: the higher the risk of use, the higher the social motivation (W 114.964, p < 0.001), encouragement (W 121.506, p < 0.001), coping (W 122.246, p < 0.001), conformity (W 101.426, p < 0.001), and expansion (W 113.729, p < 0.001).

As for alcohol consumption, the trend is the opposite of the other two substances. The results show that risky consumption implies lower social (W 12 003.5, p < 0.001), cheerfulness (W 12 762.5, p < 0.001), coping (W 12 544, p< 0.001), conformity (W 10 718, p < 0.001), and expansion (W 11 861.5, p < 0.001) motivation than normal consumption.

Discussion

The main results of the investigation show that there is no difference in the percentage of young people who have used tobacco and alcohol during and after pandemic confinement and that the percentage of cannabis users has decreased. Furthermore, consistent with other studies[4,13], students' tobacco and cannabis risk use decreased after confinement. Likewise, alcohol risk consumption remained constant during and after confinement. This finding gener-

Table 2. Consumption motives as a function of substance and type of studies during and after COVID-19 pandemic confinement

| | High school students | | | | | | | | | | | |
| | Tabacco | | | | Alcohol | | | | Cannabis | | | |
	COVID-19	Post	W	p	COVID-19	Post	W	p	COVID-19	Post	W	p
Social	6.78	2.562	6493.0	< 0.001	9.642	7.027	8929.0	< 0.001	9.474	1.979	4958.5	< 0.001
Animation	5.909	2.144	6631.0	< 0.001	8.484	5.925	9149.5	< 0.001	10.711	2.116	5000.5	< 0.001
Coping	4.855	1.616	6653.5	< 0.001	4.663	3.630	8630.0	< 0.001	5.737	1.219	5014.5	< 0.001
Compliance	3.309	1.411	6463.0	< 0.001	3.684	2.842	8546.5	< 0.001	3.553	0.774	4968.5	< 0.001
Expansion	3.709	1.418	6494.5	< 0.001	4.547	3.445	8790.0	< 0.001	5.737	1.212	5035.5	< 0.001

| | University students | | | | | | | | | | | |
| | Tabacco | | | | Alcohol | | | | Cannabis | | | |
	COVID-19	Post	W	p	COVID-19	Post	W	p	COVID-19	Post	W	p
Social	7.016	3.930	5833.0	< 0.001	9.974	9.133	8245.0	0.170	6.778	2.914	6334.0	< 0.001
Animation	6.016	3.484	5843.0	< 0.001	9.017	7.477	9096.5	0.004	8.968	3.789	6304.5	< 0.001
Coping	4.891	3.125	5638.5	< 0.001	4.709	4.375	8667.0	0.025	4.794	2.258	6465.0	< 0.001
Compliance	3.625	1.953	6160.5	< 0.001	3.641	3.781	7696.0	0.658	3.317	1.500	6421.5	< 0.001
Expansion	3.266	2.008	5700.0	< 0.001	4.419	4.000	8271.0	0.125	5.905	2.523	6440.5	< 0.001

| | Muestra total | | | | | | | | | | | |
| | Tabacco | | | | Alcohol | | | | Cannabis | | | |
	COVID-19	Post	W	p	COVID-19	Post	W	p	COVID-19	Post	W	p
Social	6.908	3.201	24870.0	< 0.001	9.825	8.011	34926.0	< 0.001	7.792	2.416	23412.0	< 0.001
Animation	5.966	2.770	25243.5	< 0.001	8.778	6.650	36963.0	< 0.001	9.624	2.898	23441.5	< 0.001
Coping	4.874	2.321	24866.5	< 0.001	4.689	3.978	35056.0	< 0.001	5.149	1.704	23680.5	< 0.001
Compliance	3.479	1.664	25422.5	< 0.001	3.660	3.281	33135.0	0.002	3.406	1.113	23500.5	< 0.001
Expansion	3.471	1.693	24681.5	< 0.001	4.476	3.704	34600.5	< 0.001	5.842	1.825	23696.5	< 0.001

ates some controversy. On the one hand, it is consistent with other studies[11,12] that found no differences in alcohol risk consumption before and after confinement in American college students; on the other hand, a recent systematic review points to a decrease in consumption during the pandemic[21] and another points to an increase in alcohol and cannabis[22]. The students who participated in the research were regular users of the different substances.

In addition, a clear decrease was in all motivations (social, encouragement, coping, conformity and expansion) for tobacco, alcohol and cannabis consumption. However, when dividing the sample into high school and university students, the latter maintained the alcohol consumption motivations (social, conformity, and expansion) during and after confinement. It may be due, on the one hand, to the beliefs associated with alcohol consumption in the university population[23] and, on the other hand, to the sociodemographic characteristics of the sample (e.g., living away from home and older age)[24]. The generalized decrease in drinking motives after confinement may be due to decreasing stressors associated with COVID-19 (e.g., social isolation and fear of contagion from their elders)[3] and highlights the key role that the pandemic may have played in young people.

Also, the results show that the main motivations proposed by Cooper et al. and the possibility of developing problematic drug use are related in such a way that the greater the motivation, the greater the risk of drug use[5,8]. It should be noted that during confinement, there were some differences in the motives for consumption compared to risk consumption that were not observed after confinement (Table 3). During confinement and concerning tobacco consumption, the only motives that increased with risky consumption were social and coping motives.

Young people with problematic tobacco use during confinement used tobacco to cope with negative feelings (coping) and reinforce or improve social cohesion. Likewise, with alcohol and cannabis use, all motives for use increased, except compliance. It means that people with problematic consumption during confinement did so to enhance positive feelings (encouragement), reinforce or improve group cohesion (socialization), expansion, and cope with negative feelings (coping).

According to the data found, the social motivations for alcohol consumption obtained higher scores since young people consume alcohol in contexts where there is interaction with others[7,25,26]. On the other hand, Orgaz et al. defend the importance of motivations for encouragement with coping motives and the need of young people to try out experiences with alcohol consumption[27]. It should not be forgotten that during confinement, the domestic consumption of some drugs, such as alcohol, presumably increased[28]. Finally, cannabis showed significant correlations concerning four motivations in confinement participants, with the motivation to expand awareness, self-awareness, and perception (expansion) scoring the highest, followed by encourage-

Table 3. Risk groups about reasons for consumption during and after pandemic confinement

	During confinement													
	Tabacco					Alcohol				Cannabis				
	Riesgo bajo	Riesgo medio	Riesgo alto	W	p	Consumo normal	Consumo de riesgo	W	p	Sin riesgo	Riesgo bajo	Riesgo alto	W	p
Social	5.174	7.352	6.800	8.178	0.017	8.951	11.638	6865.5	< 0.001	7.049	6.824	8.884	6.404	0.041
Animation	5.087	6.121	7.200	3.441	0.179	7.965	10.464	6768.0	< 0.001	8.317	9.765	10.814	9.409	0.009
Coping	3.087	5.242	6.400	26.456	< 0.001	4.329	5.435	6176.0	0.002	4.439	4.706	6.000	9.265	0.010
Compliance	3.652	3.451	3.200	0.018	0.991	3.657	3.667	5229.5	0.368	3.561	3.176	3.349	0.104	0.950
Expansion	3.348	3.473	4.000	1.252	0.535	3.895	5.681	6774.0	< 0.001	4.878	3.941	7.512	27.692	< 0.001

	After confinement													
	Tabacco					Alcohol				Cannabis				
	Riesgo bajo	Riesgo medio	Riesgo alto	W	p	Consumo normal	Consumo de riesgo	W	p	Sin riesgo	Riesgo bajo	Riesgo alto	W	p
Social	0.736	7.433	9.333	192.155	< 0.001	10.727	6.726	12003.5	< 0.001	1.291	10.933	8.727	114.964	< 0.001
Animation	0.632	6.423	8.667	200.250	< 0.001	9.625	5.242	12762.5	< 0.001	1.523	12.533	11.136	121.506	< 0.001
Coping	0.506	5.414	7.667	202.619	< 0.001	5.955	3.043	12544.0	< 0.001	0.785	5.667	8.909	122.246	< 0.001
Compliance	0.489	3.629	6.333	187.939	< 0.001	4.193	2.849	10718.0	< 0.001	0.675	3.000	4.545	101.426	< 0.001
Expansion	0.500	3.732	3.464	187.634	< 0.001	5.125	3.032	11861.5	< 0.001	0.954	5.600	8.636	113.729	< 0.001

ment and coping. On the other hand, post confinement participants obtained significant correlations in all motivations, with higher scores for coping and encouragement motives. These results differ from other studies[8] that reduce the weight of expansion motives versus the likelihood of developing problematic use, despite agreeing with the relevance of coping and animation motives in problematic cannabis use.

It is necessary to comment that the results of this study cannot be generalized to the population to which it refers because the sample is not representative. Despite this limitation, it can be affirmed that the reasons that lead young people to consume alcohol, tobacco, or cannabis are related to the possibility of developing problematic consumption. Therefore, it seems essential to take this factor into account to develop effective prevention strategies and develop personalized treatments that address individual factors in addition to the substance. Similarly, attention to contextual factors is essential to prevent possible consumption in the young population, given that stressful events such as the pandemic and the subsequent confinement motivated by COVID-19, which have physical and psychological repercussions, increase the risk of consuming alcohol, tobacco, and cannabis and, consequently, of developing problematic consumption.

Future research is worth investigating the reasons for increased tobacco and cannabis use after confinement, as COVID-19 may have exacerbated pre-existing risk factors for adolescent drug use[29,30].

Conclusion

COVID-19 confinement increased the risk of tobacco and cannabis use in students, but not alcohol. The motives for using all three substances during confinement were higher, with the exception of college students, who maintained some alcohol use motivations (social, conformity, and expansion). Risky tobacco use during confinement was motivated by social and coping needs; alcohol and cannabis use was by social encouragement, coping, and expansion.

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Motives for tobacco, alcohol, and cannabis use in the confinement context due to COVID-19 pandemic

Multicomponent exercise in the older adult and its effect on frailty syndrome

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Abstract
Aging causes an increase in the vulnerability of older adults. The practice of multicomponent exercise has been proposed to improve the physical and cognitive functionality of the older adult, reduce the frequency of falls and fractures, and prevent sarcopenia. Therefore, this literature review aims to determine the effects of multicomponent exercise in the older adult to prevent the progression of frailty syndrome. A literature search was performed in the Hinari, PubMed, Scopus and Embase databases, using the Boolean operators "AND" and "OR" and as keywords "frailty", "older adult", "falls", "fractures", "sarcopenia" to delimit useful literature for this research. Literature review articles, case-controls, meta-analysis, original articles, systematic reviews less than five years old, published in both English and Spanish were taken into account. Multicomponent exercise causes an improvement in physical functionality, independence, fall prevention, and reduction of sarcopenia, being a useful tool for the regression of frailty syndrome in the elderly.

Keywords
Frail Elderly, Frailty, Exercise, Accidental falls, Fractures, Bone.

Resumen
El envejecimiento ocasiona un aumento en la vulnerabilidad del adulto mayor. El ejercicio multicomponente se ha propuesto como una práctica para mejorar la funcionalidad física y cognitiva del adulto mayor, reducir la frecuencia de caídas y fracturas y prevenir la sarcopenia. Por tanto, en esta revisión bibliográfica se propone determinar los efectos del ejercicio multicomponente en el adulto mayor para evitar la progresión del síndrome de fragilidad. Se realizó una búsqueda bibliográfica en las bases de datos Hinari, PubMed, Scopus y Embase utilizando los operadores booleanos «AND» y «OR» y como palabras clave «fragilidad», «adulto mayor», «caídas», «fracturas», «sarcopenia» para delimitar literatura de utilidad a esta investigación. Se tomaron en cuenta artículos de revisión bibliográfica, casos y controles, metaanálisis, artículos originales, revisiones sistemáticas con vigencia menor a cinco años, en los idiomas inglés y español. El ejercicio multicomponente ocasiona una mejoría en la funcionalidad física, dependencia, prevención de caídas y reducción de la sarcopenia, siendo una herramienta útil para la regresión del síndrome de fragilidad en el adulto mayor.

Palabras clave
Adulto mayor, fragilidad, ejercicio físico, accidentes por caídas, fracturas óseas.

Introduction

Frailty syndrome is a multifactorial clinical condition that alters physiological functions and limits the ability to cope with external stressors, and increases the deterioration of health[1], given that it is associated with age, the biological process of physiological, psychological, and social changes that occur in older adults that increase their vulnerability[1]. Nevertheless, there is still no international consensus on the definition of frailty[2].

In the frail population, alterations in strength, endurance, and physiological functions contribute to a decreased ability to cope with stressors and lead to increased risk of falls, hospitalizations, dependency, and mortality[1].

Currently, there is an increment in the population of older adults. In accordance with the World Health Organization (WHO), between 2020 and 2030, this population will increase by 34 %, and by 2050, it will be close to 65 %[3]. According to Menéndez et al., the worldwide prevalence of frailty syndrome varies widely between 4.0 % and 59.1 % due to the lack of consensus on its definition.[4] In a systematic review published by Siriwardhana et al., the prevalence of frailty syndrome is 17 %, more frequent in women and in low- and middle-income countries[5]. In addition, in Latin America, a prevalence of 7.7 % to 39.3 % is observed, associated with the existence of comorbidities and a higher risk of developing disabilities in the future[6].

Nascimento et al. assert that with aging, people tend to lead a more sedentary life, and only 28 % to 34 % of older adults engage in some physical activity. In addition, it has been described that low-intensity physical exercise improves muscle strength very little, assuring that the incorporation of an exercise program composed of strength and functional training[7], which contains resistance, coordination, balance, and flexibility exercises, increases the physical functionality of the frail older adult; this is known as multicomponent exercise and can be adjusted according to the characteristics or recommendations for those who perform it[8].

According to the study by Llano et al., in a rural area of Brazil, a prevalence of frailty syndrome of 43.4 % was determined, among which physical inactivity and obesity were risk factors[9]. A study conducted by Dent et al. concluded that 94.7 % of all frail older adults should exercise to improve physical functionality, and prevent sarcopenia, falls, and fractures[10]. However, authors Toots et al., in their study conducted in a nursing home during 12 months, found no positive association between the practice of multicomponent exercise and a reduction in the number of falls[11].

Nonetheless, due to the impact that the practice of this exercise has on the quality of life and functionality of older adults, it is essential to continue studying it. This review aims to determine the effects of multicomponent exercise in older adults to prevent the progression of the frailty syndrome through its description, the relationship between this exercise with falls and fractures, and the development of sarcopenia.

For the purpose of this narrative review, a search of international scientific publications using the Hinari, Pub-Med, Scopus, and Embase databases, was undertaken, using terms from the MeSH thesaurus, taking into account the Boolean operators "AND" and "OR." The keywords used were "frailty," "older adult," "falls," "fractures," and "sarcopenia." Original articles, clinical trials, literature review articles, and systematic reviews with a publication period of fewer than five years in English and Spanish were included, and their quality was assessed by analyzing their variability, reliability, and validity.

Discussion

Multicomponent exercise and frailty syndrome in older adults

Frailty in older adults is assessed through different evaluation methods. One of them is Fried's criteria, which evaluates five aspects: unintentional weight loss in the last three years, fatigue sensation in the last four weeks, low physical activity, decrease in walking speed, and muscle weakness. Patients presenting one or two criteria, are classified as pre-fragile, and those meeting three or more are classified as fragile.[12] There are other scales, such as The Clinical Frailty Scale, which evaluates cognitive status, functionality, and comorbidities, with a score between one and nine, where one means that the patient is fit and nine means that the patient is in the terminal stage[13].

Another assessment scale corresponds to the SARC-F (Strength, Assistance with walking, Rising from a chair, Climb stairs, and Falls), which measures the degree of sarcopenia more precisely. It consists of the evaluation of the parameters of strength, ambulation with assistance, standing from a chair, climbing stairs and falls, each measured on a scale of zero to two (zero: not at all and two: very difficult), a score greater than or equal to four points makes the screening results positive for sarcopenia[14]. The lack of a definition of frailty causes difficulties in finding appropriate interventions for its regression and onset[2].

In the last few years, a significant correlation has been identified between physical exercise and the onset of frailty syndrome; it was demonstrated that the greater the physical activity, the lower the risk of mortality, and the greater the improvement in the physical and cognitive function of the older adult. Multicomponent exercise has shown greater benefits in delaying frailty syndrome due to the combination of strength, balance, gait, and endurance, which have a positive impact on the functionality of the older adult, as well as on the performance of basic activities of daily living in patients at home or hospitalized[15-17].

On the other hand, the Short Physical Performance Battery (SPPB) is a test that measures physical functionality and performance through walking speed, balance, and the ability to stand. The test has a maximum score of 12 divided into four points for each of the categories, where the higher the score, the higher the level of physical functionality[18]. Exercise must be adjusted according to age and adapted in intensity and frequency until the program that best suits each patient is found[19].

Hubbard et al. demonstrated that older adults who exercise decrease frailty and mortality risk compared to those sedentary. Frail patients have a mortality risk of 1.21, and those who do not exercise present a risk of death of 1.95 at a 95 % confidence interval of [1.19-1.24] and [1.73-2.28], respectively[20].

According to Casas et al., in a study conducted with a group of 188 older adults with cognitive impairment, the results of one group of members that performed multicomponent exercise were compared with the other group that maintained routine care. Satisfactory results in functional capacity were obtained, measured with the SPPB in the group that performed the exercise program. In this group, the SPPB increased by 0.86 points at the end of the first month and 1.4 points at the end of three months, with $p < 0.01$ and $p < 0.001$, respectively. However, adherence to the program decreased in the second month, and the patients who persisted improved cognitively ($p < 0.05$) at the end of the three-months follow-up[21].

No standard exists regarding the amount of time, frequency, and types of training to be done in multicomponent exercises. According to Monteiro et al., the recommended order for this physical activity consists of starting each session with stretching, then aerobic training, following strength exercises, and ending with stretching and cooling down. Following this model, the authors achieved results, obtaining more benefit in muscle strength, balance, and agility and improve overall physical functionality[22].

The Vivifrail program has been developed in Europe to establish parameters for its implementation. It specifically targets older adults and its purpose is to reduce the incidence and regression of frailty syndrome. The SPPB has been used to diagnose the physical condition, and based on the results, the exercise program suitable for each patient is individualized. The Vivifrail divides into four categories: Category A includes older adults with severe limitations; B, those with mild limitations; C, those who can walk and D, those who are robust[23,24].

The long-term benefits of exercise in older adults were described in the meta-analysis of Souto Barreto et al., which focuses on the existence of a positive association between the practice of exercise for a period longer than one year and the decreasing risk of falls. Furthermore, Oh et al. demonstrated the effectiveness of multicomponent exercise when implemented for a period of between six and 12 months, in addition to the fact that it contributes to the prevention of frailty syndrome and improves the physical condition of patients[25].

Multicomponent exercise and the incidence of falls and fractures in older adults

It is estimated that one in three older adults is at risk of suffering a fall per year and that 30 % of older adults with a history of a previous fall will fall again. In most cases, patients seek medical attention when they suffer some type of injury, such as fractures, head trauma, decreased mobility, hospitalization, or death[26]. Falls occur more frequently in older adults who present musculoskeletal alterations such as weight loss, decreased strength and speed, fatigue, or sensory, cognitive, and nervous system alterations[27].

According to Thomas et al., physical inactivity in older adults is associated with an increment in morbidity and mortality. For this reason, the WHO recommends at least 150 minutes per week of aerobic physical activity accompanied by muscular strength exercises. This study asserts that multicomponent exercise, due to the integration of aerobic and anaerobic components, in addition to balance and resistance exercises, seems to contribute to the reduction of falls and fractures in this population[28].

Multicomponent exercise performed in a 12-week program, with one-hour sessions three times a week, showed results associated with a lower risk of falls[29], and injuries caused by falls were lower in those who practiced exercise[30]; this effect can be extended up to 24 weeks after the intervention[29]. In addition, Hentschke et al. verified that after 24 months, the patients who were not part of the intervention group had an average of 3.11 falls per year[30].

In the study by Puente et al., the control group received three weekly sessions of multicomponent exercise for six months. Despite not finding a significant change in bone mineral density between the control group and the intervention group, the results showed an improvement in balance and gait in the patients who participated in the training, and participation in the exercise

program proved to be a protective intervention against the risk of suffering a fall[31].

Pinheiro et al. identified that combining different types of exercise has a mild effect on the bone mineral density of the femoral neck (standardized effect size 0.09, 95 % CI -0.03-0.21) and the spine (standardized effect size 0.17, 95 % CI 0.04-0.30) as a positive aspect in the prevention of osteoporosis[32].

Alhambra et al. conducted a study that verified a reduction in the risk of falls and fractures and found an improvement in physical performance, balance, and a decrease of 0.4 points in the body mass index in older adults who practiced multicomponent exercise (p = 0.045). In addition, this group presented better self-care skills and a reduced frequency of medical consultations and hospitalization[33].

On the other hand, women have a higher prevalence of falls and fractures, this being related to the loss of bone density and secondary muscle mass due to menopause, as described by Ooi et al.[34] and Alabdullgader et al.[35]. Consequently, increasing the physical functionality of older adults becomes a protective factor that improves balance and flexibility in this population[36].

Postmenopausal women who practiced multicomponent exercise, three sessions per week for 12 months, showed improvement in bone mineral density of the femoral neck and lumbar spine, increased muscle strength, and improved balance. All these factors prevent osteoporosis, falls, and fractures[37]. Along the same line, improvement in posture and the quality of movements in sedentary older women were found after practicing flexibility exercises[38].

Multicomponent exercise and its relationship to sarcopenia

Sarcopenia is a problem of significant importance in older adults because of its association with reduced physical performance, increased risk of fractures, and premature death[39]. According to a study by Barrientos et al., the prevalence of sarcopenia in Costa Rica is 33.2 % between the 70 and 79 years old population, with an increase of 10.3 % in people over 80 years old, with a frequency of 1.7 times higher in women[40].

The factors contributing to muscle mass loss are associated with physical inactivity, inadequate diet, and aging. Genetic factors and endocrine and metabolic alterations are also involved[41]. Multicomponent exercise has shown to be a preventive strategy for sarcopenia and to increase physical performance in older adults[42], although, its effectiveness may depend on the time and frequency of the exercise, whether it is practiced in groups or individually, as well as the comorbidities of each participant[43].

According to a study conducted by Zambrano et al., the patients with comorbidities evolved with improved functionality and independence after practicing multicomponent exercise, with above-average results in the SPPB battery with a p < 0.001. In addition, the patients in the study presented a significant increase in the Barthel scale with a p = 0.0019. Regarding anthropometric measurements, an increase in leg circumference and nutritional status was also observed (with results of p = 0.0014 and 0.0471, respectively)[44].

Hospitalizations increase the vulnerability of older adults to frailty syndrome. Starting the exercise program as soon as possible, in combination with an adequate diet during hospitalization or immediately upon discharge, and limiting bed rest[45,46], significantly reduces frailty syndrome[47,48]. In addition to the supervision by qualified professionals the exercises limit the evolution of sarcopenia and functional decline[47]. In this sense, Sáez de Asteasu et al. showed that multicomponent exercise improved muscle strength in patients who received the usual care during hospital admission, with emphasis on progressive resistance exercise with notable improvement in muscular strength of the extremities[45,46].

It is necessary to promote the use of this exercise program in the older adult population because it is a strategy that reduces the economic impact, is easily replicable, and improves the overall health of both healthy individuals and patients with comorbidities, with a considerable reduction in the incidence of the frailty syndrome and, in those who already suffer from it, allows its regression[49].

Conclusion

Multicomponent exercise intervention program is a strategy that has proven to contribute to the regression of frailty syndrome with the reduction of sarcopenia and the improvement of balance, gait, and bone mineral density that leads to optimizing physical function, reduction of the risk of falls, increment of independency and prevent mortality in older adults.

Although it has not yet been defined how long the benefits of multicomponent exercise on physical functionality can be seen and whether these are mainly in short or long-term, it is necessary that this topic continues to gain momentum and continue to be studied.

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Role of neutrophil extracellular traps in the prognosis of respiratory tract infections

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Abstract

Las trampas extracelulares de neutrófilos (NET, por sus siglas en inglés) han surgido recientemente como un vínculo potencial entre la inmunidad y la inflamación, que podría cumplir un papel clave en la patogénesis de las infecciones de vías respiratorias. El objetivo de esta revisión es determinar su rol como marcador pronóstico en enfermedades infecciosas de vías respiratorias. Para la elaboración de este artículo de revisión narrativa se consultaron las publicaciones disponibles a través de una búsqueda automatizada en las bases de datos de PubMed, Scopus y Embase. Las concentraciones elevadas de trampas extracelulares de neutrófilos (cfADN, complejos de mieloperoxidasas-ADN) en pacientes con cuadro clínico grave por infecciones de vías respiratorias, se relacionan con una estancia hospitalaria más larga, periodo prolongado de administración de antibióticos, aumento del riesgo de ingreso a la UCI, necesidad de ventilación mecánica, disfunción orgánica e incluso la muerte (p ≤ 0,05). A pesar de no contar con un parámetro de medición estandarizado, el exceso de trampas extracelulares de neutrófilos se corresponde con la gravedad del daño tisular observado en pacientes con infecciones de vías respiratorias, esto revela el importante rol pronóstico de la respuesta de los neutrófilos y del proceso de la NETosis en las enfermedades infecciosas pulmonares.

Keywords

Pneumonia, Coronavirus Infections, Neutrophil Extracellular Traps, Prognosis.

Resumen

Neutrophil extracellular traps (NET) have recently emerged as a potential link between immunity and inflammation, which could play a key role in the pathogenesis of respiratory tract infections. This review aims to determine the role of neutrophil extracellular traps as prognostic markers in respiratory tract infectious diseases. For this article a literature review was undertaken, consulting available publications through an automated search in PubMed, Scopus, and Embase databases. High concentrations of neutrophil extracellular traps (cfDNA, Myeloperoxidase-DNA complexes) in patients with severe clinical presentation due to respiratory tract infections are related to a longer length of hospital stay, prolonged period of antibiotic administration and increased risk of admission to the ICU, need for mechanical ventilation, organ dysfunction and even death (p ≤ 0.05). Despite not having a standardized measurement parameter, the excess of neutrophil extracellular traps corresponds to the severity of tissue damage observed in patients with respiratory tract infections, revealing the important prognostic role of the neutrophil response and NETosis process in pulmonary infectious diseases.

Palabras clave

Neumonía, infecciones por coronavirus, trampas extracelulares de neutrófilos, pronóstico.

Introduction

Neutrophil extracellular traps (NET) consist of networks of chromatin granular proteins, and DNA, which are released from the contents of neutrophils as a defense mechanism to trap and destroy microorganisms[1].

Neutrophils are the first line of defense of the immune system, which in response to inflammatory stimuli, uses different mechanisms to eliminate pathogenic microorganisms, including phagocytosis, degranulation[2], and neutrophil extracellular traps composed of extracellular chromatin fibers labeled with antimicrobial proteins that participate in the immune response[3] though, their role in the immune response is clear, the excessive formation can also be detrimental to the host, as they trigger unwanted inflammatory response mechanisms[4,5].

An alternative mechanism developed by neutrophils, which was described by Brinkmann *et al.* in 2004, in which neutrophils carry out a neutrophil defense mechanism where fibrillar DNA structures are released into the extracellular space, and it is evident that one of its particularities, compared to phagocytosis and degranulation, is the efficient elimination of microorganisms[6,7].

Currently, the study of new immunological markers constitutes a relevant area of research with multiple potential applications in the diagnosis, prognosis, and treatment of infectious diseases[8], making it of interest due to the pleiotropic functions of neutrophils, especially in the respiratory tract[9].

On the other hand, respiratory tract infections have been identified as resulting from a varied group of bacterial and viral agents, which cause diseases with similar symptomatology, thus representing one of the leading causes of medical attention worldwide[10]. Recently, the emergence of the SARS-CoV-2 pandemic has highlighted the importance of viral respiratory infections, such as influenza, and other bacterial infections, which are frequently associated with high mortality[11,12].

Respiratory tract infections are a significant cause of morbidity and mortality worldwide[13]. According to the International Forum of Respiratory Societies (FIRS), it is estimated that nearly four million people die from infections each year, 98 % of them due to lower respiratory tract infections[14].

The preparation of this narrative review article included consultation of publications available through an automated search contained in the PubMed, Scopus, and Embase databases. Original articles, cohort studies, and review articles, in Spanish and English, fewer than five years of antiquity,

were included in 81.2 % of the references. Boolean connectors and search expression were used: respiratory tract infections AND neutrophil extracellular traps, pneumonia AND neutrophil extracellular traps, respiratory tract infection AND neutrophil extracellular traps, pneumonia, AND neutrophil extracellular traps.

Therefore, this review aims to describe the role of neutrophil extracellular traps (NET) as a prognostic marker in respiratory tract infectious diseases.

Discussion

Neutrophil extracellular traps in respiratory tract infectious diseases

NETs are a biological phenomenon of rupture of the neutrophil nuclear membrane in response to the presence of microorganisms, which allows the mixing of cellular and nuclear components, ending with the rupture of the cell membrane and the release of the compounds to the extracellular matrix, thus trapping the microorganisms and preventing their proliferation.

Neutrophils are highly effective in eliminating pathogens, with minimal adverse effects on the host; however, these effector mechanisms may not be insufficient to control a massive infection[15].

The role of NET has become of interest for their involvement in infectious diseases of the respiratory tract. Before their release, they are composed of a complex mixture of intracellular compounds assembled by neutrophils within the cytoplasm[16]. Between 20 and 30 proteins that form the extracellular traps are known, including antimicrobial proteins and proteases, as well as cytoskeletal proteins and glycolytic enzymes. NET release may depend on neutrophil elastase, reactive oxygen species (ROS), reactive nitrogen species (RNS), and histone citrullination[17].

When released, NET capture and destroy bacteria, fungi, viruses, and protozoa and participate in the host's immune defenses by forming traps to prevent the spread of pathogens in the organism[18]. Although NET formation is a defense mechanism against microorganisms, recent data suggest that their excessive formation contributes to lung injury by causing epithelial, endothelial, and pulmonary cell death, along with intravascular thrombus formation[19,20].

NET production is a regulated form of cell death called NETosis, different from apoptosis or necrosis[21,22]. Vorobjeva *et al.* have described various mechanisms of NETosis. One of them, the classical or suicidal NETosis

ends with cell death, while vital NETosis is a kind of programmed cell death in which neutrophils maintain their viability and function. In addition, it is characterized by the release of granular components into the cytosol and chromatin decondensation associated with histone modification[23].

Dysregulated formation of neutrophil extracellular traps contributes to the pathogenesis of respiratory tract infections; NETosis is associated with disease severity in patients suffering from multiple organ injuries induced by viral infections such as SARS-CoV-2[24].

Some surviving neutrophils are thought to become anuclear and may cause tissue damage. According to Twaddell et al., the formation of NET produces a cytotoxic effect on the pulmonary epithelium and endothelium. Their excessive production is observed in airway diseases such as pneumonia and other pathologies that cause acute lung injuries, as well as in a varied number of chronic lung diseases[25].

By initiating the release of chemoattractant components and the recruitment of neutrophils, a universal response of the individual to viruses or bacteria is generated. Upon such a stimulus, the neutrophil cell membrane expresses receptors and adhesion molecules for various ligands, including immunoglobulins, membrane molecules on other cells, and cytokines[26].

According to Tomar et al., the progressive infiltration of neutrophils at the site of infection and release of NET produces an immune response by releasing cytokines and chemokines in large quantities resulting in a "cytokine storm" that contributes to the development of acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome and sepsis. Through the release of NET in infectious processes histones, DNA and granular proteins, myeloperoxidase complexes, neutrophil elastase, cathepsin G, and proteinase 3 are dispersed, resulting in severe tissue destruction and establishing the self-amplifying cycle of necroinflammation[27].

Inflammation is crucial for immune defense against pathogens. However, when dysregulated, cytokines that usually mediate protective immunity and promote recovery can cause an overactive immune state, resulting in increased lung tissue damage[28,29].

Although various biomarkers of inflammatory response and infection are currently used, specifically interleukins, C-reactive protein (CRP), or procalcitonin because of their reliability for routine use as diagnostic and prognostic markers, they have several limitations. Some show poor stability and a short half-life, and others have slower kinetics or are not elevated in viral infections, which limits their usefulness[30].

Therefore, the usefulness of new molecules, such as NET and their components, as a new prognostic marker in respiratory infections should be explored.

Identification and quantification of neutrophil extracellular traps in respiratory tract infectious diseases

Pérez et al. report that the procedures for quantifying neutrophil extracellular traps are diverse, and no consensus has been reached among researchers to establish a particular method that is considered the "gold standard"[31]. Similarly, Plana et al. state that, to date, no direct and reliable method to quantify them has been reported; therefore, NETosis measurements are usually based on indirect quantifications of their components separately or in combination[32].

Neutrophil extracellular traps have been studied in great detail, and several components have been described; the most important include decondensed chromatin, nuclear histones, and 30 other granular protein components with bactericidal activity, such as neutrophil elastases (NE), myeloperoxidases (MPO), cathepsin G, and lactoferrin, among others[33,34].

However, not all components are specific to NETosis, but may also be present in other nucleated cells (e.g., eosinophils, macrophages, mast cells) and may be released during other forms of cell death than NETosis[35]. The NET formation is by far best reflected in the release of neutrophil-specific markers, such as histone citrullinated (H3Cit), MPO-DNA complexes, NE, and fragmented circulating DNA (cfDNA), which are the markers measured in most studies[36].

The measurement of total DNA is not NET-specific and also measures DNA from necrotic cells. MPO-DNA complexes are more accurate, because together they measure DNA and MPO specifically from neutrophils[37]. However, quantification of H3Cit by immunohistochemistry is considered the most reliable marker; this process is specific to NETosis[38].

Methods to quantify both NET and their components rely on a wide variety of techniques including enzyme-linked immunoassay absorbance (ELISA), flow cytometry, cell-free DNA-based assays, three-dimensional confocal microscopy and fluorescent microscopy[39,40]. Although each of these techniques and methods has its advantages,

Gupta *et al.* report that there are limitations specific to each of them[22].

Although these measurement methods provide information on changes in neutrophil morphology during infection and in the biochemical processes presented by cells dying from NETosis, they are limited by a series of constraints, such as lack of objectivity, low performance, monotonous, slow and difficult to compare and, or reproduce across laboratories, and high cost[41,42]. However, Rebernick *et al.* state that one of the most commonly used methods to quantify NETs is to make a naked-eye count of the number of decondensed DNA cells and, or NET-associated proteins cells by fluorescence microscopy[43].

Access to tissue samples is generally limited; however, it has been possible to analyze NET in patient samples, which has contributed to the characterization of the role of NET in different diseases and, probably, to outline new lines of biomarkers and therapeutic targets, since blood and plasma parameters of NET formation have been considered as potential prognostic markers[44].

The quantification of NET in plasma and blood allows a better understanding of the pathophysiological processes on human immunity, poorly recapitulating the biology of neutrophils in the lung undergoing inflammatory processes. Inactive neutrophils present in the peripheral circulation to migrate to lung tissue per se, must undergo different maturation processes before reaching an active state. Therefore, bronchioalveolar neutrophils represent a more accurate model for the study of pulmonary pathologies, especially those of infectious origin[45,46].

Given that the existing methods for quantifying NET and their components are not standardized and present some sensitivity and specificity problems, there are no specific values or range to determine "normal" versus "pathological" levels or concentrations of NET and their components in tissue[48].

Usually, in clinical trials, what is known as "cut-off value" is used to establish these values. For this purpose, the levels of NET or its components are determined in plasma, bronchioalveolar lavage, or sputum samples from control patients to obtain a test value and subsequently, compare it with a reference value. The reference value then represents the threshold level of NETs; levels above this indicate risk of mortality, complications, or prolonged hospital stay (Table 1)[49].

Neutrophil extracellular traps in the prognosis of respiratory tract infectious disease

A recent study by Zhu *et al.* carried out among 93 patients hospitalized with influenza A, showed that NET from patients with H7N9 and H1N1 increased epithelial cell permeability and, consequently, cfDNA and MPO-DNA levels correlated positively with the APACHE II scoring system and estimates of mortality (r = 0.4802, p < 0.05) confirming the damaging effect of NET on lung parenchyma. The singular deterioration of pulmo-

Table 1. Comparison of NETosis marker reference values, detection method and type of sample

Reference	Sample	Measurement method	NET	Reference value
Zhu L *et al.*[50]	Blood	ELISA	cfDNA	248.6 ± 38.5 ng/mL
			MOP-DNA complexes	1.1 fold
Mikacenic C *et al.*[51]	Bronchoalveolar lavage fluid	Colorimetric assays	cfDNA	Indetectable
			MOP-DNA complexes	Indetectable
			Peroxidase	Indetectable
Ng H *et al.*[52]	Blood	ELISA	cfDNA	345 (319 - 486) ng/mL
			H3Cit-DNA complexes	84 (64 - 101) ng/mL
			NE	16 (12 - 23) ng/mL
Huckriede J *et al.*[53]	Plasma	Real time CRP	cfDNA	4.1 (2.8 - 5.3) ng/µL
		ELISA	H3 Histones	0.0 (0.0 - 0.0) µg/mL
			NE	0.0 (0.0 - 0.0) ng/mL
			GAS6	14.4 (11.0 - 19.7) ng/mL
			sAXL	17.3 (13.7 - 18.4) ng/mL

cfDNA: circulating fragmented DNA; ELISA: enzyme immune adsorption analysis; GAS6: growth arrest-specific gene 6 detection; H3Cit: citrullinated histones 3; NE: Neutrophil elastases; NET: neutrophil extracellular traps; MPO: myeloperoxidase; PCR: polymerase chain reaction; sAxl: soluble Axl.

nary distensibility suggests that patients with higher serum NETs in the first days after admission are at higher risk of complications, hospital stay, and even death[50].

Similarly, Zho *et al.* mention that when NET are not adequately regulated, they are associated with severe disease, even in the lungs of patients with acute respiratory distress syndromes under mechanical ventilation, as demonstrated in their study comparing samples from patients with severe COVID-19 requiring mechanical ventilation and patients with mild COVID-19 breathing room air, showing that patients requiring mechanical ventilation had significantly higher levels of cfDNA and MPO-DNA ($p = 0.05$)[54].

These studies suggest that severe COVID-19 may be defined by neutrophilia, in the same manner as seen in other diseases caused by pandemic viruses, including H1N1 influenza, SARS-CoV, and Middle East respiratory syndrome coronavirus, which also show neutrophil infiltration at the site of infection, revealing an association between circulating NET markers and inflammation, dysregulation of homeostasis and endothelial damage, with the consequent development of acute respiratory distress syndrome[55].

Recently, Ebrahimi *et al.* also observed that excessive neutrophil activation and subsequent NET production in patients with pneumonia are associated with increased complications, such as impaired alveolar gas exchange, pulmonary dysfunction, and increased risk of death. Their study included 310 patients with community-acquired pneumonia, in which they noted that the time to clinical stabilization of vital signs was longer in patients with higher NET levels with a median of 5.0 (between 2.6 and 9.0 days), compared to those with lower levels, i.e., those in the lower three quartiles (median of 4.0; between 2.0 and 7.9 days) with an adjusted hazard ratio of 0.97; 95 % CI, 0.94 - 0.99; $p < 0.01$), time to discharge was shorter in subjects with lower NET levels (median 7.0; between 5.0 and 11.0 days compared to 9.0; between 5.0 and 14.0 days: HR 0.90; 95 % CI, 0.82 - 0.99; $p < 0.05$) and longer IV antibiotic administration in subjects with higher concentrations (95 % CI, 0.1- 0.94; $p < 0.05$)[56].

Therefore, the authors propose that the systemic and local effect of inflammation provides a way to measure changes in serum NET markers to assess disease prognosis and to establish a new therapeutic targets. Recent evidence shows that high serum NET levels on admission are associated with a worse prognosis.

Conclusions

Based on the literature reviewed, the data show that elevated levels of circulating NET markers in patients with respiratory tract infections can be considered a prognostic marker since they illustrate the severity of the cellular damage observed, precisely among patients with a more severe clinical picture, indicated by severity scales. In addition, they are related to a prolonged hospital stay, a prolonged period of intravenous antibiotic administration, a higher risk of admission to the intensive care unit, the need for mechanical ventilation, organ dysfunction and even death.

Quantification of NET markers is difficult to be implemented in clinical practice due to the challenges that exist because of the lack of standardized methods for their measurement; the findings are significant as they reinforce the fact that NETosis may become a helpful severity prognostic biomarker in infectious airway diseases, especially in COVID-19, influenza, and bacterial pneumonia, which have been the most studied and could be the therapeutic target before the development of acute respiratory distress syndrome.

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Sensitivity of scales as prognostic indicators and palliative needs in elderly patients with non-oncological diseases

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Abstract

Palliative care has a multidisciplinary approach that improves the quality of life. Traditionally, palliative care focused on oncology patients; however, it can be applied to in-patients with advanced chronicity, for whom there is a lack of validated instruments to assess and determine palliative care. This study aims to describe the sensitivity of the NECPAL, PROFUND, and Charlson scales for assessing and determining mortality and palliative care in older adults with chronic non-oncologic disease through a narrative review in the BMJ, Elsevier, PubMed, HINARI, and SciELO databases. Original articles, review articles, and clinical trials in Spanish and English published in the last five years were included. The NECPAL tool identifies patients who are candidates for palliative care and measures the prevalence of palliative care needs. The PROFUND index is a multidimensional prognostic score that estimates the risk for one year mortality in patients with advanced chronicity. As a prognostic tool, it assesses 30-day mortality risk. The Charlson comorbidity index, created to predict one year mortality risk after hospitalization, is an excellent predictor in hospitalized patients, does not require laboratory tests, and is applicable in various clinical scenarios.

Keywords

Palliative Care, Prognosis, Chronic Disease.

Resumen

Los cuidados paliativos tienen un enfoque multidisciplinario que mejora la calidad de vida. Tradicionalmente se centraron en pacientes oncológicos, sin embargo, pueden usarse en pacientes con cronicidad avanzada, en quienes existe falta de instrumentos validados para evaluar y determinar la atención paliativa. El objetivo de este estudio es describir la sensibilidad de las escalas NECPAL, PROFUND y Charlson para evaluar y determinar la mortalidad, y atención paliativa en adultos mayores con enfermedad crónica no oncológica mediante una revisión narrativa en las bases de datos BMJ, Elsevier, PubMed, HINARI y SciELO. Se incluyeron artículos originales, de revisión y ensayos clínicos en español e inglés, publicados en los últimos cinco años. La escala NECPAL permite identificar a los pacientes candidatos a cuidados paliativos y mide la prevalencia de personas con necesidad paliativa. El índice PROFUND es una puntuación pronóstica multidimensional que estima el riesgo de mortalidad a un año en pacientes con cronicidad avanzada. Como herramienta pronóstica evalúa el riesgo de mortalidad a treinta días. El índice de comorbilidad de Charlson, creado para predecir el riesgo de mortalidad a un año posterior a la hospitalización, es un excelente predictor en pacientes hospitalizados, no requiere pruebas de laboratorio y es aplicable en diversos escenarios clínicos.

Palabras clave

Cuidados paliativos, pronóstico, enfermedad crónica.

Introduction

The World Health Organization defines palliative care as a strategy with an "approach that improves the quality of life of patients and families facing problems associated with advanced chronicity through prevention, relief of suffering, assessment and pain management"[1]. It began in the 19th century, with the care of terminal patients by religious communities, using analgesic drugs and technologies that allowed medical advances for the dying process. However, the suffering of these patients was not taken into account.

It was not until the middle of the 20th century that Cicely Saunders, concerned with creating the conditions for the care of these patients, laid the foundations for the modern palliative and hospice care movement based on pain management and other symptoms[2].

The term palliative care was first used in 1975, by the surgeon Balfour Mount, as the currently known definition of comprehensive patient care in the different health services areas, which included in-hospital, outpatient and home support, and in the bereavement stage, combined with teaching and research[2].

Although palliative care alleviates pain, it relieves physical, mental, and spiritual suffering[3] that generates alterations in the patient's quality of life to allow them to maintain an active life, within their possibilities, until the moment of death. In addition, it includes support for the family in coping with the disease and later for bereavement management[4].

The implementation of palliative care is usually in the advanced stages of chronic diseases, and due to misinformation and stigma, the idea of implementing palliative care only before death is widespread[5].

Palliative care in patients involves a social, emotional and physical burden[6] for patients and a high workload for their caregivers[7]; however, integrated palliative care facilitates its provision[8]. Palliative care is adaptive and involves a multidisciplinary team to improve decision-making for patient management[9]. Comprehensive care must be provided to promote quality of life in the phase of deterioration and adaptation to the dying process[10].

Traditionally, the focus has been on oncology patients; nevertheless, palliative care also encompasses patients with advanced chronicity[11] of various diseases, including cardiovascular disease, cancer, major organ failure, drug-resistant tuberculosis, severe burns, chronic terminal illness, acute trauma, extreme prematurity at birth or extreme frailty in old age[12], which constitute a population that requires greater attention to maintain quality of life[13].

Palliative care is not intended to accelerate or delay death but is based on ethical principles, multidisciplinary work, and shared decision-making[4]. They are recognized in the context of the right to health because they contribute to symptom management and reduce healthcare costs[14].

According to Voumard *et al.*, seriously ill older adults are a highly vulnerable group that requires multidimensional, sustainable, and relationally autonomy-oriented care[15]. Patients suffering from three or more chronic diseases increase the risk of mortality. Diseases such as diabetes *mellitus* and ischemic heart disease increase mortality up to eight times and can reduce the patient's life expectancy by 15 years[8].

The aging of the world's population and the increase in noncommunicable diseases have contributed to the growing need for palliative care. It is estimated that about 40 million people require palliative care each year, and only 14 % of patients receive it. Furthermore, approximately 75 % are found in low- and middle-income countries[16]. Generally, in patients with non-cancer chronic diseases, the early initiation of palliative care is delayed because of the overestimation of survival time[17]. This care is similar in patients with and without cancer, treating physical symptoms, psychosocial needs, and family support[18].

In Latin America, 7.6 % of the population has access to palliative care, according to the Latin American Palliative Care Association. In 2020, there were 3.9 healthcare resources (medical, nursing, psychology) per million people in El Salvador[19].

There are multiple ways in which the need for palliative care can be identified, including pain with usual activities, dyspnea at rest, and decreased daily skills. Similarly, the surprise question: "Would you be surprised if your patient died in the next 12 months?" has been implemented for the detection of palliative patients, but its contribution is limited; however, when this question is included in the Palliative Needs Scale (NECPAL)[20], it proves to be a useful tool for detecting patients with advanced chronic disease and palliative needs[21]. However, it is necessary to standardize instruments to identify the need for palliative care, as this is a barrier to its early implementation[22].

Early initiation of palliative care with a holistic approach improves the quality of life and reduces hospitalizations in patients with advanced chronic disease[23].

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This study was conducted to describe the sensitivity of the NECPAL, PROFUND, and Charlson scales as indicators of the need for palliative care and as predictors of mortality risk in older adults with chronic non-oncologic disease.

This narrative review was prepared by searching the BMJ, Elsevier, PubMed, HINARI, and SciELO databases. The terms: "Palliative care AND mortality/prognosis", "Palliative care AND comorbidity", "NECPAL AND Mortality" "PROFUND index AND mortality", "Charlson comorbidity index AND mortality" were used. The selected literature included original articles, review articles, and clinical trials in Spanish and English, published in the last five years.

Discussion

Description of the NECPAL, PRO-FUND, and Charlson scales as tools for establishing palliative care

The increase in the number of patients with advanced chronic diseases has generated the need for palliative care as a priority in health services, and the early initiation of palliative care produces benefits for both the patients and their families[24]. Not only does it consist solely of symptom management, but rather continues curative care in an integrated manner and modifies it as the patient's disease progresses[24].

The importance of timely identification of the need for palliative care has generated the analysis of different instruments that allow prognosis and identify the patients at the last stage of their life. Three tools that have proven significant detection of increased mortality are the NECPAL, PROFUND, and Charlson scales.

The NECPAL (Palliative Needs) tool was developed by the WHO Collaborating Centre for Public Health Palliative Care Programs at the Catalan Institute of Oncology to identify the need for palliative care, especially in the areas of general primary care services and conventional hospital services, measuring its prevalence and allowing the application of palliative care[25]. It is useful in patients with advanced chronicity, highlighting the need for health support, palliative care, symptom control, nutritional, functional, and frailty markers[24].

The PROFUND index (functional prprediction developed for pluripathological patients) was developed by a working group of pluripathological patients. It consists of a score to establish an objective multidimensional prognosis that estimates the risk of mortality in one year in patients with advanced chronicity; however, Méndez et al. demonstrated its usefulness as a prognostic tool through the evaluation of the risk of mortality in 30 days[26].

The Charlson comorbidity index was created to evaluate the risk of death due to comorbidities and is used as a predictor of prognosis and long-term survival. Kuswardhani et al. demonstrated that each point increase in the Charlson index indicates a 16 % increase in the risk of mortality[27], while Fuchs et al. determined that this instrument is an excellent predictor of mortality in hospitalized patients, does not require laboratory tests and is applicable in various clinical scenarios[28].

Timely palliative care ensures that the patient's wishes, needs, and expectations are met because it has a positive impact on the quality of life of those involved, on the response to stress, on the confidence to make informed decisions and on the search for emotional and spiritual satisfaction of the patient and their families[29].

Sensitivity of NECPAL as a predictor of mortality and need for palliative care

The NECPAL tool is applied in patients with advanced chronicity with the aim of detecting palliative needs. First, the professional's perception related to the risk of death must be evaluated; if the surprise question is negative, indicators related to the request for palliative care by the patient or family members, and general clinical indicators of severity and progression. Finally, specific clinical indicators of the severity and progression of the diseases must be evaluated[30].

This instrument has been proven to be helpful for detecting the population with palliative needs among the general population. Also, it shows the predictive capacity for mortality with an area under the curve of 0.81 that allows planning actions aimed at preserving the patient's well-being[30]. In combination with the surprise question, it has better prognostic potential for estimating mortality in patients with advanced chronicity and need for palliative care[31]. The tool used could be extended to patients with a life expectancy of more than one year if the answer to the surprise question focuses on palliative care rather than on the need to establish them[32].

Furthermore, this assessment can be a mortality predictor in patients with advanced chronicity and infection by COVID-19 and patients with two or more

chronic pathologies with poor prognoses[34]. NECPAL is a useful and feasible tool, which adds a prognostic criterion to the palliative approach[35] and considers predictive assessment as a determining factor in identifying patients with these needs[36].

Sensitivity of the PROFUND index as an indicator of onset of palliative needs

The PROFUND index is an objective multi-dimensional prognostic score that predicts one year mortality in patients with multiple pathologies after hospital discharge; it has nine variables, defines the risk of death, and promotes the design of a therapeutic plan according to the characteristics of each patient[37]. Almagro *et al.* highlight the validation of the PROFUND index for predicting one year mortality in patients with advanced chronicity[38]. Martin *et al.* demonstrated that this is a useful tool in the short term, allowing the detection of mortality 30 days, and at three months after hospital discharge[39]. Méndez *et al.* also described its usefulness as a prognostic tool for short-term mortality and its ability to guide decisions in palliative care[40].

The use of this tool with other scales generates a greater association with mortality. It also has a greater predictive capacity than the biomarkers: C-reactive protein, albumin and erythrocyte distribution width, according to Moretti *et al.*[41]. When PROFUND is combined with the Subjective Global Assessment, an increase in its prognostic capacity is obtained, where the area under the curve at 12 months was: 0.747 (95 % CI, 0.65 - 60.83); 0.733 (95 % CI, 0.65 - 0.81) and when combining the two variables: 0.78 (95 % CI, 0.70 - 0.87)[42].

Research by Bernabeu *et al.* has shown that the PROFUND index maintains its accuracy as a predictor of mortality in multi-pathological patients over a four year follow-up period. This index is important in decision-making and therapeutic interventions for multi-pathological patients[43].

Sensitivity of Charlson comorbidity index as a predictor of mortality

The Charlson comorbidity index is characterized by its simplicity. When combined with other predictive scales (such as SOFA and APACHE II), it has been proven to detect mortality in patients with candidemia and advanced chronicity 30 days after hospital discharge[44]. It was created in 1987[45]. There are multiple studies with more than 30 000

patients that validate its usefulness[45]. Hautamäk *et al.* combined this index with the GRACE scale for clinical assessment and prognosis in coronary artery disease, which allowed it to be validated as a support for the management of patients with advanced chronicity[46]. However, Enriquez *et al.* mention that the results may vary due to population diversity among countries[47].

The modified Charlson scale, which includes ten comorbidities, is a functional tool for detecting advanced chronicity in cases of stroke or other pathologies in which access to all data is not possible[48].

The higher the score obtained on this scale, the longer the hospital stay in patients with advanced chronicity[49]. Patients with low Charlson index scores had better survival rates compared to patients with high scores (p-value for the classification test = 0.0265). In contrast, other authors have reported that a score of zero to one is associated with a nearly twofold increased probability of death[50]. It leads to poor post-surgical outcomes in advanced chronicity (r = -0.20)[51] and influences prognostic prediction due to increased risk for comorbidities, which prevent early rehabilitation[52].

Although its use has been limited to studies to detect mortality and survival[52], it is considered one of the most widely used scales to assess survival[53]. Kim *et al.* mention that the variables contained in the Charlson comorbidity index associated with mortality are valid in the short term[54]. Poses *et al.* described a lower reliability related to mortality than with the Apache II scale; however, the latter requires the availability of clinical and laboratory data on the patient during 24 hours of hospitalization, so they deduced that the Charlson index is a feasible method of risk adjustment for the different health services[55]. On the other hand, Bona *et al.* combined the Charlson indices with the surgical risk scale, which allowed the detection of patients at low risk of death. This combination constituted a useful tool for auditing operative outcomes[45].

Conclusion

The NECPAL, PROFUND, and Charlson scales have proven to be extremely effective in determining the need for palliative care in older adults with chronic non-oncologic disease and in predicting the risk of mortality in older adults with chronic non-oncologic disease. The NECPAL tool and the surprise question are valuable instruments, easy to apply, and useful in identifying palliative patients with limited life prognoses. The PROFUND index allows the prediction of

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one year mortality. The Charlson comorbidity index has a prognostic value associated with mortality with an increase of 16 % with each point, and combined with other scales increases its prognostic advantageous. The three instruments investigated are significantly related to mortality and the need for palliative care; therefore, they must be used more frequently to highlight the need for palliative care.

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Sensitivity of scales as prognostic indicators and palliative needs in elderly patients with non-oncological diseases

Probiotics and prebiotics for patients with celiac disease and non-celiac gluten sensitivity

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Abstract

Celiac disease and non-celiac gluten sensitivity are entities that have shown an increase in incidence, making them a topic of interest to provide innovative therapeutic approaches and improve intestinal and extraintestinal symptoms. This review intends to determine the effects of the use of probiotics and prebiotics in celiac disease and non-celiac gluten sensitivity. A narrative review was undertaken by searching for original and review articles no older than five years since publication through databases consulted: HINARI, PubMed and Scopus in Spanish and English. The use of probiotics and prebiotics in celiac disease has shown benefits by restoring the composition of the intestinal microbiota, especially with the use of *Lactobacilli* and *Bifidobacterium* spp.; in non-celiac gluten sensitivity, its use is limited as its pathophysiology is not exactly known, therefore, a gluten-free diet is currently considered to be the best therapeutic guideline. The use of probiotics and prebiotics could alleviate gastrointestinal symptoms and improve dysbiosis in patients with celiac disease and non-celiac gluten sensitivity. However, more studies are needed to demonstrate the benefits of its use as a therapeutic alternative.

Keywords

Celiac disease, Wheat Hypersensitivity, Probiotics, Prebiotics.

Resumen

La enfermedad celíaca y la sensibilidad al gluten no celíaca han tenido un aumento en su incidencia, esto las ha convertido en tema de interés en la búsqueda de enfoques terapéuticos innovadores que ayuden a mejorar los síntomas intestinales y extraintestinales. Esta revisión pretende determinar los efectos del uso de probióticos y prebióticos en la enfermedad celíaca y sensibilidad al gluten no celíaca. Se realizó una búsqueda en bases de datos HINARI, PubMed y Scopus en idioma español e inglés, se incluyeron artículos originales y de revisión con un máximo de cinco años desde su publicación. El uso de probióticos y prebióticos para la enfermedad celíaca ha mostrado beneficios restaurando la composición de la microbiota intestinal, en especial con el uso de *Lactobacilli* y *Bifidobacterium* spp.; en la sensibilidad al gluten no celíaca, el uso se ve limitado al no conocer con exactitud su fisiopatología; no obstante, se propone como mejor pauta terapéutica una dieta libre de gluten. El uso de probióticos y prebióticos podría aliviar los síntomas gastrointestinales y mejorar la disbiosis en pacientes con enfermedad celíaca y sensibilidad al gluten no celíaca. Sin embargo, se necesitan más estudios que evidencien los beneficios de su uso como alternativa terapéutica.

Palabras clave

Enfermedad celíaca, hipersensibilidad al trigo, probióticos, prebióticos.

Introduction

In the last two decades, there has been an increase in the incidence of diseases associated with gluten and wheat intake[1]; these diseases include celiac disease (CD), wheat allergy (WA), and non-celiac gluten sensitivity (NCGS)[2].

The prevalence of CD has increased over the last 50 years; in the general population, it is 0.5 % - 2 %[3]. Every year more than 70 % of newly diagnosed patients are older than 20 years, including patients of 70 years and older, with a male:female ratio of 1:3 to 1.5:1. In Western countries, the histological prevalence is 0.06 % and 1 % in serological screening4. There are no population-based studies of NCGS due to its recent description and the immune response it presents to different proteins from food grains. However, a prevalence of 0.6 % to 6 % has been observed in the general population, mainly in adult women from urban areas in the fourth decade of life[5].

Human food-related conditions are a topic of general interest, with CD and NCGS being among the most common and studied for their pathology, clinical presentation, variants, genetic and environmental factors[6].

For a long time, the primary interest in this condition focused on the genetic factors involved in its presentation and development within childhood and adulthood[7], providing significant findings on the role of the human leukocyte antigen (HLA) complex, also known as the major histocompatibility complex (MHC), and immune complexes within intestinal tissue and CD[8].

The aforementioned has directed the attention of researchers towards the interaction of alterations in the intestinal microbiota, observing that in patients with persistent symptomatology, an alteration of this microbiota was evidenced in comparison with healthy patients[9].

This evidence pointed to the role that the intestinal microbiota and its modifications may play in the pathogenesis, clinical manifestations, and onset of the condition, opening up the possibility of new approaches to treatment and reduced risk of presenting this disease. Current research is looking for new nutritional options to improve the lives of patients with conditions such as CD and NCGS, suggesting innovative therapeutic approaches such as supplements capable of reducing intestinal permeability or suppressing the inflammatory response, such as probiotics and prebiotics.

A narrative bibliographic review of international scientific publications was conducted by consulting HINARI databases through Research4life, Pub-Med, and Scopus. A search was performed using keywords such as "Celiac Disease," "Non-Celiac Gluten Sensitivity," "Gluten," "Probiotics," "Prebiotics," "Microbiota," "Gluten-free diet," together with logical operators "AND" and "OR." Original and review articles related to the topic were included, prioritizing sources with publications less than five years old in Spanish and English. The quality of these articles was evaluated by analyzing their reliability, validity, and variability.

Consequently, this review aims to determine the effects of probiotics and prebiotics in patients with CD and NCGS.

Discussion

During the co-evolution of humans and microorganisms, millions of bacterial species have colonized the human organism. This vast number of microorganisms in the human body is known as the "normal flora," "microflora," or "microbiota." The microbiota consists of bacteria accompanied by fungi, viruses, protozoa, and archaea, colonizing the mouth, ears, respiratory tract, gastrointestinal tract, and skin[10]. They act as regulators of the synthesis of nutrients and metabolites, in addition to preventing the colonization of pathogenic microorganisms and maintaining the integrity of the intestinal epithelium[11].

The CD is an autoimmune enteropathy in which an inappropriate immune response occurs in individuals genetically predisposed to gluten ingestion; It has been shown to occur almost exclusively in patients who present HLA-DQ2 or HLA-DQ8 haplotypes, as well as the presence of the serological markers immunoglobulin A anti-tissue transglutaminase (ATGT) and anti-gliadin deamidated peptide antibodies; it is also characterized at the histopathological level by inflammatory changes in the intestinal mucosa[12,13]. These inflammatory changes are responsible for the intestinal and extraintestinal clinical presentation of the disease[14].

Patients with confirmed CD present an alteration of the microbiota (dysbiosis), being this intestinal microbiota the one responsible for the metabolism of gluten[15]. This is why recent studies support the hypothesis that the intestinal microbiota plays an important role in the pathogenesis, progression, and apposition of the various intestinal or extraintestinal symptoms of CD, mainly abdominal distension, abdominal pain, episodes of diarrhea or constipation, vomiting, fatigue, anemia, loss of muscle mass or weight gain/decrease[16,17].

Some studies have cataloged Firmicutes, *Bacteroides*, and Actinobacteria as the main components of the microbiota of patients with CD18. Several studies have evaluated the salivary, fecal, and duodenal microbiota of patients with CD, observing a decrease in protective species (*Lactobacilli* and *Bifidobacterium* spp, Firmicutes); and an increase in pathogenic species (*Bacteroides*, *Proteobacteria*, *Serratia*, and *E. Coli*) in comparison with healthy subjects[19,20].

On the other hand, there is an imbalance between the presence of Gram (-) and Gram (+) bacteria in patients with CD21. Bascuñán KA *et al.* demonstrated that the total Gram (-) bacteria are significantly higher in patients with active CD, while the *Lactobacilli/Bifidobacterium* ratio compared to *Bacteroides/E. Coli* was significantly lower, the latter being more abundant in patients with active CD than in control subjects[22].

In contrast, non-celiac gluten sensitivity (NCGS) is a syndrome characterized by the presence of intestinal or extra-intestinal symptoms related to the consumption of products made with gluten-containing

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cereals[23,24]. At present, due to the lack of biomarkers to assess NCGS, its diagnosis involves previously ruling out CD and wheat allergy, followed by a gluten-free diet to evaluate the reduction/remission of symptoms[25]. Therefore, the following are considered criteria that can help in the diagnosis of NCGS: gluten intolerance evidenced by the presence of symptoms, negative serology for CD, and no wheat allergyo[26,27].

In NCGS, the response triggered by gluten ingestion leads to an increase in intestinal permeability, and intestinal dysbiosis, followed by a low-intensity inflammatory reaction in the intestinal mucosa and bacterial translocation that finally causes the release of cytokines and gastrointestinal peptides that favor the appearance of intestinal symptoms, the most frequent being abdominal distension, abdominal pain, diarrhea, nausea, gastroesophageal reflux, and, less frequently, extra intestinal symptoms such as headache, fibromyalgia, dermatitis, joint pain and in some cases depression[28,29].

Being a recent entity, the exact role played by the intestinal microbiota in its pathophysiology is not known[30]. Transeth et al. mention studies of duodenal samples showing that there is often an increase in species such as Firmicutes, Actinobacillus, and Rhuminococcaceae and, in turn, a reduction in Bacteroidetes; however, this does not clarify whether the intestinal dysbiosis that occurs in these individuals is the cause or the effect of the disorders associated with gluten intake[31,32].

According to the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are live microorganisms that when administered in adequate amounts have demonstrated beneficial effects on health, restore the composition of the intestinal microbiome, prevent dysbiosis and have demonstrated modulation of the immune system and pro-inflammatory mechanisms; although at the moment, these mechanisms have not been properly defined[33,34]. For this reason, the major risk factor in the safe application of probiotics is the lack of knowledge of their activity. They generally have a beneficial effect on the digestive system, but in some cases, they could predispose to translocation or infections[35].

The intestinal microbiota, through the production of molecules with anti-inflammatory and immunomodulatory functions, is capable of stimulating the immune system, achieving its modulation. These effects occur due to the interaction between probiotics, epithelial cells, dendritic cells, monocytes/macrophages, and lymphocytes[36,37].

Most probiotics belong to the genus Lactobacilli, Bifidobacterium, and Bacillus spp.38; due to their high safety and cost-effectiveness, they are good candidates as therapy for CD. A study by De Angelis et al., reported enzyme formulations, Lactobacilli and Bacillus, called Consortia I: Lactobacilli (Lp.), plantarum (Lc.), paracasei, Bacillus subtilis, Bacillus pumilus, and Consortia II: Lp. Plantarum, Lc. paracasei, Limosi, Lactobacilliireuteri, Bacillus megatherium, B. pumilus, which, under gastrointestinal conditions, have demonstrated gluten hydrolytic activity to non-immunogenic and non-toxic peptides[39].

A study by Marasco G et al. demonstrated that the potential of probiotics for CD management is supported by intestinal dysbiosis, the role attributed to the degradation of toxic components by the microbiota, the maintenance of the intestinal barrier, and the innate and adaptive response of the immune system. Selected strains of Lactobacilli and Bifidobacterium can hydrolyze gliadin fragments produced by digestive proteases into smaller peptides. Probiotics mixed with gliadin fragments can significantly reduce them to being only a source of amino acids[40].

According to the International Scientific Association for Prebiotics, these are a substrate that selectively stimulates one or more groups of microbiota, mostly Bifidobacterium and Lactobacilli. Prebiotics are resistant to the digestive enzymes of the upper digestive tract, which is why they reach the intestine in favorable quantities, stimulating the growth of the microbiota. To achieve the aforementioned benefits, it is necessary to ingest supplements to acquire favorable levels[41].

There are different types of prebiotics, most of them belonging to carbohydrates, mostly oligosaccharides; however, there is evidence that prebiotics are not only carbohydrates. Among these, the following are worth mentioning:

Fructans: these consist of inulin, fructo-oligosaccharides or oligofructose. It has been shown that they can selectively stimulate Lactobacilli. However, recent studies demonstrate that the length of the fructan chain is an important factor in determining which bacteria can ferment therefore, other bacteria can be stimulated directly or indirectly by fructans.

Galacto-oligosaccharides: are the product of the extension of lactose; and they are divided into two groups: those with excess galactose and those manufactured from galactose, through enzymatic transglycosylation.

Starch and glucose-derived oligosaccharides: these are resistant to digestion and promote health by producing high levels of butyrate, which is why it is classified as a prebiotic[41]. Butyrate formation in the intestine occurs mainly from carbohydrate metabolism in glycolysis, but can also form from the metabolism of organic acids and amino acids[42].

The specific consequences of the role of dysbiosis in CD, the exact mechanisms of action, along the mechanisms of action of prebiotics, remain unclear. At the same time, results have been reported in which probiotics and prebiotics have demonstrated an improvement of gastrointestinal symptoms, ameliorating dysbiosis in affected patients. However, further studies are needed to confirm these results and their benefit as a therapeutic alternative[43].

The pathophysiological mechanism leading to NCGS is currently unknown; therefore, the therapeutic targets for this condition are more difficult to identify. Although the gluten-free diet reduces symptoms after its implementation, some patients with NCGS continue to report symptoms despite the strict diet. In a study by Cárdenas-Torres *et al.*, it has been reported that a diet low in fermentable oligo-dimonosaccharides can reduce symptoms in patients with NCGS, but its implementation should be considered with caution due to its association with low absorption of antioxidants and micronutrients[28].

By contrast, oligo-dimonosaccharides, known to have a prebiotic effect on the microbiota, stimulate the growth of *Lactobacilli* and *Bifidobacterium*. Therefore, prebiotic and vitamin supplements are recommended for patients following a diet low in oligo-dimonosaccharides. Few clinical studies have been performed in patients with NCGS investigating the effect of probiotics and prebiotics to reduce the toxic effects of the external precursors, or to improve symptomatology. Hence, there is a need to investigate the pathophysiology, aiming to find more effective interventions apart from the gluten-free diet[44-46].

Gluten-free diet and use of probiotics

Traditionally, when the diagnosis of CD and NCGS is confirmed, the main line of treatment requires the total elimination of foods containing gluten or food that was exposed to gluten during their preparation. On the other hand, another current of thought on the management of patients with CD and NCGS considers that it is impossible to eliminate gluten from the diet of patients due to the patient's already ingrained adherence to their eating habits and cross-contamination in the industrial production of food[46]; therefore, quantitative restriction of the consumption of gluten-containing products is proposed, suggesting the establishment of a limit of up to 10 mg daily as the maximum dose without histological changes that have been observed in the intestinal mucosa of genetically susceptible patients[47].

On the other hand, some studies have shown that, after maintaining a gluten-free diet, children can reverse up to 95 % of the inflammatory alterations of the intestinal mucosa and up to 66 % in adults[48]. In addition, other studies have shown improvement in extraintestinal symptomatology, such as changes in bone mineralization and malabsorption syndrome, after adaptations in the diet of patients. Even so, although the degree of reversibility observed seems to be mainly related to age and early diagnosis of the disease, it should be taken into account that prolonged intake, delayed diagnosis, and the time of initiation of a gluten-free diet are determining factors in the irreversible damage to the intestinal mucosa[49].

One of the main challenges of the gluten-free diet line of treatment is the acquisition of foods that meet the duly certified requirements and provide the assurance that they were not affected by any cross-contamination during processing[50]. Concerning this problem, Silvester J *et al.* stated in their study that the high costs of these products contribute to the difficulty for patients to adhere to a diet strictly free of this protein.

Furthermore, given the proposal for consumption based on quantitative restriction, it is difficult to make a precise quantitative assessment of the gluten contained in the food consumed during the day by a patient and the variability in terms of the cytotoxic dose in each person[51,52]. Because of the various limitations of the traditional form of treatment, there is a need for alternatives, mainly pharmacological, that are accessible, effective, and efficient.

A study by Francavilla R *et al.* showed that the combined use of several strains of bacteria of the *Lactobacilli* and *Bifidobacterium* genus in 104 patients during several weeks significantly improved intestinal symptoms compared to placebo[53]. In a study conducted by Ali B *et al.*, a similar conclusion was reached, regarding the consumption of oral probiotics on gastrointestinal symptoms[54]. Despite the above, there are no studies comparing the endoscopic and histopathological improvement

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of inflammatory processes in the intestinal mucosa with the gluten-free diet and the consumption of probiotics.

The gluten-free diet is traditionally the treatment of choice for the management of CD and NCGS, as it has proven to reverse the inflammatory process. Intestinal and extraintestinal symptoms represent a real challenge for patient adherence, in addition to increased consumption costs and difficulty in acquiring food products duly certified as gluten-free.

Conclusions

The use of probiotics and prebiotics evidenced a significant improvement in intestinal symptoms through the regeneration of the intestinal mucosa, modulation of the immune response and appropriate degradation of gliadin glycoprotein, due to the close relationship between the microbiota and the pathogenesis of CD and NCGS. The use of probiotics and prebiotics to treat CD and NCGS, the *Lactobacillus* and *Bifidobacterium* genera are the ones that show major implication in the improvement of the clinical symptomatology of these conditions, even though there is still little evidence of the effects on the control of the inflammatory processes of the intestinal mucosa and consequently the effects they could have on the histological integrity of the intestine.

Funding

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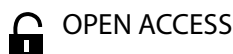# Fast method to determine the cardiac axis with D1 and D3

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Método rápido para determinar el eje cardíaco con D1 y D3

Abstract
The cardiac axis represents the average of the direction of the electrical activation process of the cardiac cells. It is one of the parameters determined in the correct reading and interpretation of the electrocardiogram. Also, not only is it useful as a diagnostic criterion for heart disease but also as a marker of prognosis and mortality in other diseases. Over the years, new formulas have emerged that allow its value to be calculated more accurately. The method using D1 and aVF is one of the most popular. However, it has two unmeasurable points. The first is between 0 and -30 degrees, and the second is between the values of 90 and 110 degrees. Although there are proposals with algorithms that use other leads, an alternative method was explored with D1 and D3 based on the algebraic formula of the inverse tangent and mathematical method for the exact calculation of the cardiac axis. A quick method is proposed that maintains the reliability of the algebraic formula to determine if the cardiac axis is within the normal ranges (-30 to 110 degrees).

Keywords
Electrocardiography, Heart, Heart Conduction System.

Resumen
El eje cardíaco representa el promedio de la dirección del proceso de activación eléctrica de las células cardíacas, es uno de los parámetros que debe determinarse en la correcta lectura e interpretación del electrocardiograma y es útil no solo como criterio diagnóstico de cardiopatías, sino también como marcador de pronóstico y mortalidad de otras enfermedades. Con el paso de los años han surgido nuevas fórmulas que permiten calcular con mayor exactitud su valor. El método que utiliza D1 y aVF es uno de los más populares, sin embargo, presenta dos puntos no medibles. El primero es entre 0 y -30 grados, y el segundo entre los valores de 90 y 110 grados. Aunque existen propuestas con algoritmos que utilizan otras derivaciones, se exploró un método alternativo con D1 y D3 basados en la fórmula algebraica de la tangente inversa y método matemático para el cálculo exacto del eje cardíaco. Se destaca este como una propuesta de método rápido que mantiene la confiabilidad de la fórmula algebraica para determinar si el eje cardíaco se encuentra dentro de los rangos normales (-30 a 110 grados).

Palabras clave
Electrocardiografía, corazón, sistema de conducción cardíaco.

Introduction

The cardiac electrical axis represents the average direction of the electrical activation process, depolarization or repolarization, of the cardiac cells[1], represented in the electrocardiogram; it symbolizes the cardiac ventricular depolarization vector[2].

The identification of the cardiac axis is useful not only as a diagnostic criterion for some diseases, including ischemic heart disease, hypertensive heart disease, and blockages, among others,[3] but also as a prognostic and mortality marker for several diseases[1].

Multiple methods have been described to determine the cardiac axis. One of the most accepted due to its practical way of measuring it, mainly in emergency areas, is that which consists of expressing the voltage of leads D1 and aVF in the Cartesian plane. However, the aforementioned one presents two non-measurable points; the first one is between 0 and -30 degrees, and the second one is between the values of 90 and 110 degrees[3].

Another of the most prominent methods is the three-lead method, so called because it includes leads 1, 2, and aVF, although some authors believe that the aVF lead is not necessary in some cases. The third simple way of assessing the ventricular axis consists of the location of the most isoelectric limb lead[1].

Most authors agree on using mathematical formulas to determine the most accurate way to calculate the cardiac axis[1]. Therefore, this article presents an alternative method with electrocardiogram leads D1 and D3 based on the algebraic formula of the inverse tangent and mathematical method for the exact calculation of the cardiac axis.

Discussion

There are multiple methods and formulas to determine whether the cardiac axis is within normal ranges or presents deviation to the right or left. The most commonly used method makes use of D1 (which represents the angle between 0 degrees and 180 degrees) or X axis and aVF (which represents the angle between -90 and 90 degrees)[4] or Y axis, also known as Two thumbs-up signel[5], this is useful in most scenarios[6]; however, some factors can alter it, among them deep inspiration[7] and some inconveniences identified from the very definition of a normal cardiac axis, since the value considered normal in adults is between -30 to 90 degrees[8-10]. However, several authors consider that the normal value is actually up to 100[11], 105[6,12,13] or 110 degrees[2,14,15] (Figure 1).

The value defined as normal can reach up to 120 degrees in patients between eight and 16 years of age[16,17] or borderline (findings between normal and abnormal values)

in young high-performance athlete patients (caused by physical activity)[18]. The cardiac axis value could vary due to factors such as deep inspirationa[7].

These limits are even more relevant when considering that the diagnosis of pathologies associated with left axis deviation, such as left ventricular hypertrophy, is made based on an angle greater than -30 or even -45 for left bundle branch block[19]. In other disorders, such as the posterior fascicular block, the right deviated axis can be considered from +90 to +180 degrees. However, the axis markedly deviated to the right from +120 degrees[16].

On the other hand, some pulmonary affectations such as pneumothorax, specifically left pneumothorax,[20] COVID-19[21], and pulmonary thromboembolism can also deviate the axis to the right. In the latter case, the axis usually has values from +110 to +140 degrees[22]. Likewise, the axis is representative at +110 and +120 degrees allowing diagnoses such as right bundle branch block accompanied by fascicular block or right ventricular hypertrophy[2,23-25].

Therefore, some authors state that, in practice, the normal value of the cardiac axis is between the range of -30 to +110 degrees[2,14,26] (Figure 1). Then, It is as an axis deviated to the left, presented with a value less than -30 degrees[27] and the axis to the right with a value greater than +110 degrees[14,26].

The disadvantage of the traditional D1 and aVF method is that the range of the cardiac axis is between 0 and +90 degrees[6,28], when both values are positive[6]. It represents at least one blind or unmeasurable point between -30° and 0° within the parameter considered normal (-30 to -90 degrees)[27,29] or two blind points in the extended parameter (-30 to 110 degrees)[1] and includes patients who may be normal within the left or right shift category. The first blind spot of this method lies between -30 and zero degrees which is considered by most authors as normal range[26,27]. The second blind spot is between +90 and +105 degrees[6,26] or even up to +110 degrees[2], a range that can still be considered normal or non-pathological by some authors.

Algebraic formulas for calculating the exact cardiac axis based on a bipolar and a unipolar lead (D1 and aVF) are not exempt from this problem[30].

The fast method using D1 and aVF is popular due to its ease of application and understanding. Other methods as the "six-tap method"[31] or the mathematical or algebraic model for the calculation are not practical, and their application requires more time[3].
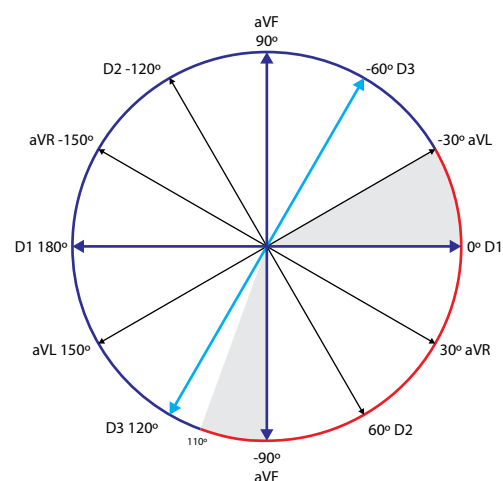
Figure 1. The hexaxial system shows the relationship between the different leads and their axes. The typical range of the cardiac axis is in red (30 to 110 degrees); in blue, lead D1 and aVF; and in light blue, lead D3[3].

However, using the method and the algebraic formula for the calculation of the exact cardiac axis using leads D1 and D3, several scenarios can be extracted that allow a proposal to determine the cardiac axis quickly and reliably without having the spaces or blind spots described above. Therefore, the method using electrocardiogram leads D1 and D3 was explored, based on the algebraic formula of the inverse tangent and mathematical method for calculating the cardiac axis in which two bipolar leads (D1 and D3)[3] are used.

The formula for calculating the cardiac axis proposed by Tarricone[1] using D1 and D3 is: *tan-1 [(D1 + 2D3)/√3 × D1]*[1,19] Where (*tan-1*) is the inverse tangent or arctangent of the result of the algebraic operation of adding the net value of the QRS complex in D1 with the result of multiplying two by the net value of the QRS complex in D3, previously divided by the result of the square root of the product of three by the net value of the QRS in D1[19]. The formula is based on the principle of the Cartesian plane which essentially represents the hexaxial system when calculating the cardiac axis. Like other proposed formulas, this formula adapts the direction of the resulting axes to the Cartesian plane, generating a value in degrees that correlates with the resulting vector, which is what we know as the electrical axis or cardiac axis[1]. The use of the D1 and D3 leads instead of D1 and aVF overcomes the blind spots described above because aVF limits the projection between -90 and +90 degrees, while D3 extends it between -60 and +120 degrees.

From the formula based on D1 and D3, it can be observed that whenever both QRS values on D1 and D3 are positive, and the difference between them is one, the cardiac axis is within normal ranges, specifically between values of +71 and +60 degrees (Table 1), which is also within the mid-range of the cardiac axis (+30 to +75 degrees)[1].

A projection was made showing that when both leads (D1 and D3) are positive, the cardiac axis is between 60 and 71 degrees. A projection was made showing that when both leads (D1 and D3) are positive, the cardiac axis is between 60 and 71 degrees. However, it was identified that to reach values of 60 degrees, the values of D1 and D3 must be 33 and 34 mm respectively. In addition, it can be observed that the closer the values are to 100, the closer the axis will be at +60 degrees (Table 1).

On the other hand, it was identified that the greater the difference between both values, in favor of D3, the result is negative and the angle is closer to 90 degrees, i.e. aVF; whereas, the greater the difference in favor of

D1, it is positive and the angle is closer to 30 degrees, i.e. aVR. Even when the difference between both QRS is notable (x10 or more) and both net values are positive, the axis will be in normal ranges (Table 2). Similarly, if the values are reversed, where D1 is greater than D3, and both parameters are always positive, the axis will remain in normal values.

Alternative methods using the D1, D2, and D3 leads to determine the cardiac axis give values between zero and +90 degrees when all three leads are positive32, which is consistent with the findings of the method using the D1 and D3 values[33].

Therefore, from these data, five important aspects can be derived to simplify the formula:

1. As long as the net QRS values on D1 and D3 are positive, the axis will be in normal ranges.

Table 1. Variation in degrees of the cardiac axis with the algebraic formula D1 and D3 when the difference is 1

Value of D1	Value of D3	Angle in degrees
1	2	71
2	3	67
3	4	65
5	6	63
7	8	62
9	10	62
11	12	61
33	34	60
100	101	60

Table 2. Variation in degrees of the cardiac axis with positive D1 and D3

Value of D1	Value of D3	Difference	Angle in degrees
1	3	-2	76
1	4	-3	79
2	7	-5	78
2	9	-7	80
3	12	-9	79
1	36	-35	89
1	101	-100	90
2	1	1	49
4	3	1	55
6	5	1	57
6	6	0	60
10	1	9	35
20	1	19	32
101	1	100	30

2. The higher both values are and the closer their difference is to one, the closer the cardiac axis value will be to +60 degrees.
3. If the values of D1 and D3 are equal, the cardiac axis will be +60 degrees.
4. The greater the difference between D3 and D1 (with D3 greater than D1) the closer the value will be to +90 degrees.
5. The greater the difference between D1 and D3 (with D1 greater than D3) the closer the value is to +30 degrees.

The formula also allows to determine the scenarios when D1 or D3 are negative. In the case of D1, the distribution behaves as follows. Table 3 shows that when the D1 value is negative, the cardiac axis is almost completely verticalized or deviated to the right. It can be seen that when the difference between the two is negative, the axis is extremely deviated (-169 or +169 degrees), which is observed, for example, in ventricular arrhythmias[34].

When the value of D3 is twice that of D1, the value of net D3 is obtained, represented by +120 degrees in the Hexaxial system, and coincides with that described in the axis findings when D3 is the derivative of greater amplitude[35].

The formula's condition distributes the pattern and generates the need for a value in D3 at least three times greater than the negative net value of D1 for the axis to be over the upper limit (when considering the axis normal to +110 degrees) or a value four times greater to consider the value of +104 (with +105 the maximum value in degrees). However, a value 100 times greater than D1 in D3 is required for the axis to be over +90 degrees.

Likewise, the calculation was performed with negative values of D1 and positive values of D3, and it was verified that the result of the angle remains between 169 and 90 degrees except when the difference between D1 and D3 is less than or equal to -2 (Table 3). Thus, it is possible to establish that when D1 is negative, and D3 does not have a value at least three times greater in absolute values, the axis will have deviated to the right.

The distribution with D3 as the negative value is reflected with a value in degrees as a negative maximum at +71 degrees and as a positive maximum at +30 degrees.

n summary, the interpretation of the cardiac axis according to the projected findings is shown as a quick method to determine the cardiac axis using D1 and D3 by the inverse tangent formula (Table 4).

Therefore, it can be established that whenever the value obtained from the division of D1 by D3 is equal to or less than one, the value of the angle of the cardiac axis will be deviated to the left. However, whenever the product of this division is greater than one, the angle will be above -30 degrees and below or equal to +30 degrees.

From these data four other key aspects can be determined:

1. If D1 is negative and D3 is not three times greater than D1, the axis is deviated to the right (considering the normal axis up to +110 degrees)..
2. If D3 is negative, but the net QRS value on D1 is greater than at least 0.01 at D3, the axis is in normal ranges.
3. If D1 is twice the absolute value of D3, the axis will be at zero degrees.

Table 3. Cardiac axis variation with negative D1 and positive D3

Value of D1	Value of D3	Difference (D3/D1)	Angle in degrees
-3	1	-2	-169
-3	2	-1	169
-3	3	1	150
-3	6	2	120
-3	9	3	109
-3	12	4	104
-3	15	5	101
-3	27	9	96
-3	30	10	95
-3	300	100	90

Table 4. MRapid method to determine the cardiac axis with D1 and D3

D1	D3	axis interpretation
Positive	Positive	Normal
Negative	Positive and 3 times greater than D1	Normal
-	Positive, but not 3 times higher than D1	Desviado a la derecha
Positive and greater than the absolute value of D3	Negative	Normal
Positive, but equal to or less than the absolute value of D3	Negative	Deviated to the left
Negative	Negative	Extremely deviated

4. If D3 is negative and the absolute value of D3 is greater than D1, the axis is deviated to the left.

If both D1 and D3 have a negative absolute value, the cardiac axis will be between -60 and -150 degrees, i.e., extremely deviated. This method changes the value of D3 when it is present with D1 with a negative value. In this case, D3 would have to be four times the absolute value of D1 to be within the normal range (+105 degrees).

From the key aspects that have been extracted from the formula, it is highlighted that the results of the cardiac axis retain the reliability of the algebraic formula to determine if the cardiac axis, given that it is within the normal ranges using D1 and D3, which poses a fast and reliable method to determine the cardiac axis (-30 to +110 degrees); when it is clear that the cardiac axis is within the ranges of -30 to +105 degrees.

When assuming a cardiac axis with the classic values between -30 and +90 degrees, it is possible to establish whether the axis is in normal ranges just by observing the positivity or negativity in D1 and D3. If both values are positive, the axis is in the normal range.

If the derivative of D1 were negative, but the derivative D3 remained positive, and its absolute value is at least three times the value of D1, then the axis will always remain in normal ranges, although borderline (around 109 degrees). If the value of D3 is four times the value of D1, then the axis will be around 104 degrees; otherwise, the axis will be deviated to the right (greater than 105 degrees).

If it is derivative D3 that has a negative value, but D1 is positive, then the axis will be within the normal range as long as D1 is greater than D3 in absolute values. If the value is equal to or less than D3, the axis will be deviated to the left (less than -30 degrees).

It is worth mentioning that since the pathologies that present the axis deviated to the left are representative of axes lower than -30 degrees, most authors consider this as the limit of the left cardiac axis[3,10,11,16].

A similar situation occurs with entities that deviate the axis to the right; the representative value in most scenarios and even in patients with a structurally healthy heart is the limit of +110 degrees,[13,17] which is why several authors consider the normal range of the cardiac axis to be between -30 and +110 degrees. Although there are algebraic formulas that use D1 and aVF to calculate the cardiac axis[3,30] and more advanced methods based on algorithms and the use of one or more leads to determine the cardiac axis,[13] they are not easy to apply or remember in clinical practice.

The inverse tangent formula using D1 and D3 has demonstrated to be a reliable formula for calculating the cardiac axis.[3,30] As a consequence, when this formula is projected, a fast method can be obtained that maintains the same reliability for determining the cardiac axis without the non-measurable points of the traditional method of D1 and aVF.

Conclusions

The fast method highlighted for the calculation of the cardiac axis using D1 and D3 allows obtaining a value extracted from a range that maintains the reliability of the inverse tangent formula without the defects or blind spots presented by the other methods.

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Brief communication

Lidocaine for pain relief in palliative care patients, a case series

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Abstract
Introduction. Neuropathic pain affects 2 % of the population and 15 out of 100 patients who go to a physician suffer from neuropathic pain. This type of pain is common in cancer patients. **Objective.** To determine if the use of lidocaine in intravenous infusion reduces neuropathic pain in palliative care with opioid treatment. **Methodology.** Case series of three patients in palliative care who presented neuropathic pain and underwent multiple infusions of intravenous lidocaine as an adjuvant for pain management; the doses used and the number of infusions were described, pain improvement was evaluated through the visual analog scale and possible side effects were monitored. **Results.** Case 1: visual analogue scale on admission 9/10; 24 hours post lidocaine infusion: 4/10. Case 2: visual analogue scale on admission 6/10; 24 hours post lidocaine infusion 2/10. Case 3: visual analogue scale on admission 8/10; 24 hours post-infusion 2/10. **Conclusion.** Intravenous infusion of 2 % lidocaine reduced neuropathic pain in the three patients of the study, however, the relief is transitory, and the positive effect is lost over time.

Keywords
Pain Management, Lidocaine, Intravenous Infusion, Palliative Care.

Resumen
Introducción. El dolor neuropático afecta al 2 % de la población y 15 de cada 100 pacientes que acuden a consulta médica, sufren de dolor neuropático. Este tipo de dolor es muy común en pacientes con cáncer. **Objetivo.** Determinar si el uso de lidocaína en infusión endovenosa disminuye el dolor neuropático en los cuidados paliativos con tratamiento opioide. **Metodología.** Serie de casos de tres pacientes en cuidados paliativos que presentaron dolor neuropático y se les administraron múltiples infusiones de lidocaína intravenosa como coadyuvante para el manejo del dolor, se describieron las dosis utilizadas, el número de infusiones, se evaluó la mejoría del dolor a través de la escala visual análoga y se monitorizaron los posibles efectos secundarios. **Resultados.** Caso 1: escala visual análoga al ingreso 9/10; 24 horas posinfusión de lidocaína: 4/10. Caso 2: escala visual análoga al ingreso 6/10; 24 horas posinfusión de lidocaína 2/10. Caso 3: escala visual análoga al ingreso 8/10; 24 horas posinfusión 2/10. **Conclusión.** La infusión intravenosa de lidocaína al 2 % disminuyó el dolor neuropático en los tres pacientes del estudio, sin embargo, el alivio fue transitorio y el efecto positivo se perdió con el paso del tiempo.

Palabras clave
Manejo del Dolor, lidocaína, Infusiones Intravenosas, cuidados paliativos.

Introduction

Neuropathic pain (NP) originates as a direct consequence of a lesion or disease that affects the somatosensory system[1]. In this definition, the term "disease" refers to specific pathological processes, such as inflammation, and autoimmune diseases; while "lesion" refers to a macro or microscopically identifiable damage[2].

In oncology, NP is among the most challenging symptoms to alleviate, sometimes presenting as unique affection and at other times mixed with somatic or visceral pain. In non-oncological patients, chronic NP is common in clinical practice and considerably affects the quality of life[3].

Coadjuvant pharmacological treatment includes some medicines with limited effectiveness as tricyclic antidepressants, anticonvulsants, antiarrhythmic drugs, and topical analgesics such as lidocaine; less than 50 % of which bring about an adequate pain control[4].

There are few protocols for the use of intravenous (IV) lidocaine as an adjuvant in the relief of neuropathic pain, such as the pain guidelines of the Latin American Federation of Pain Societies (FEDELAT), which mention that IV lidocaine infusion is used in doses of 5 mg/kg to be administered in 20 minutes, and, if there is improvement in pain, it can be used two to three times a week[5].

Other oncology centers have their schedules, and currently, there is no consensus among them; for instance, at Providence Health Care Hospital in Canada, they use bolus lidocaine, with an optional dose of 1.5 to 2 mg/kg administered three to five minutes in the perioperative period, with a usual loading dose of 100 to 160 mg. Immediately after the bolus, a low-dose IV infusion of lidocaine of 0.5 to 2 mg/kg/hour is given[6]. On the other hand, the San Diego Hospice in the United States of America mentions in their guidelines the initiation of a dose of 1 to 2 mg/kg IV over 30 minutes, and after 30 minutes of starting the dosage, the pain should be measured and documented; if the pain decreases, it must continue at a dose of 0.5 to 3 mg/kg/hour[7].

The most frequent adverse effects include periorbital numbness, dizziness, vertigo, and dysarthria, which usually are due to lidocaine accumulation in the body[1,8]. Among the less frequent are tachycardia, allergic reactions, dry mouth, insomnia, and tremor and metallic taste are occasionally reported[9].

The dosage and duration of intravenous lidocaine infusion remain controversial. The most experience exists in acute postoperative pain as some studies mention that low doses of IV lidocaine (plasma concentrations less than 5 µg/mL) do not interfere with normal nerve conductions and are associated with a lower incidence of adverse effects than other drugs[10].

The objective of this case series is to determine whether the use of IV lidocaine infusion decreases neuropathic pain in palliative care patients who also have opioid treatment.

Methodology

The study is a case series of three patients with NP; each of them receive palliative care and have consulted over ten months for pain that was difficult to control, despite management with opioid analgesics and who were determined to benefit from the use of 2 % lidocaine infusions without adrenaline as supplementary for the management of their pain.

The dose of 2 % lidocaine without adrenaline used in the three patients consisted of 200 mg (200 mg/10 mL vial), diluted in 250 ccs of 0.9 % saline solution to be given intravenously in one hour by continuous infusion pump by the attending physician. In case 1, five infusions were used, in case 2, four, and case 3, two; the time interval between each infusion was determined on an individual basis, with a variable periodicity, between one every week and then one every month.

Three adult patients were included, two men and one woman, who received treatment in a palliative care center in the outpatient or inpatient areas for ten months. The selected cases met the inclusion criteria: acceptance of intravenous lidocaine infusion as an adjuvant for the management of their neuropathic pain, being older than 18 years, having a diagnosis of pain syndromes due to various etiologies, consulting at the palliative care center with basic analgesic treatment (opioids and adjuvants), and having a Visual Analog Scale (VAS) score greater or equal to 4 points.

VAS was measured according to the FEDELAT tools[5] and consisted of a horizontal line of 10 cm. The minimum intensity is the absence of pain; it will be mild up to 4 cm, moderate from 5 to 7 cm, and severe if greater than 7 cm, with an extreme of 10 cm indicating the maximum value of pain[11]. This scale was used for the initial selection of patients to enter the study, before administration of the infusion, and then at 24 and 72 hours.

Two other assessment scales were used; the first was the Karnofsky performance scale, which is a standard way of measuring the ability of cancer or geriatric patients to perform routine tasks. Scores range from 0 to 100, a higher score meaning that the patient is better able to perform daily activities[12]. The second scale used was the Edmonton Symptom Assessment System (ESAS)[13], which consists of visual analog scales to measure the intensity or magnitude of ten symptoms: pain, tiredness, shortness of breath, nausea, depression, anxiety, well-being, sleepiness, appetite, and insomnia[13].

All three patients received the study information sheet, the statement about the adverse effects that could occur, and measures to be taken, and the informed consent forms were handed in and signed prior to lidocaine administration. The nursing staff recorded the vital signs before, during, and after the administration of each infusion and the adverse effects they presented, and the three patients were closely monitored for the length of the study. The research ethics committee of the Universidad Dr. José Matías Delgado approved the Study in Act record number 001-2021.

Case description

Case 1.

It is about a 58 years old man with a Karnofsky index of 60 % who was admitted to the palliative care unit with an oncologic diagnosis of adenocarcinoma of the rectum and sigmoid colon, with mixed pain (neuropathic and bone) of marked intensity located in the right lower limb, an acute compressive fracture in the L1 vertebral body and non-compressive cauda equina syndrome following radiotherapy. On admission, the patient presented a severe pain sensation in the right hip that radiated to the right lower limb with a VAS score of 9/10 and described it as "cramping." In addition, there was a history of diabetes *mellitus* treated with metformin 1000 mg and glimepiride 2mg and a history of arterial hypertension treated with olmesartan 20 mg and amlodipine 5 mg, both diseases were decompensated.

Before admission, the patient was on basic treatment with morphine sulfate, 60 mg every 12 hours, and rescue doses of tramadol 37.5 mg up to every four hours, which he maintained for one year. During the two-day admission, the base treatment was suspended and changed to morphine sulfate 10mg subcutaneously every four hours and pregabalin 75 mg orally every 12 hours, with 6 mg subcutaneous rescue doses up to every hour. He remained hospitalized, with severe pain, requiring rescue medication four times in 24 hours since he presented pain incidental to mobilization, defecation, or ambulation. The indicated dose of morphine was maintained one month after discharge, and he remained in uncontrolled pain before using the first infusion with 200 mg of lidocaine (Figure 1). After the first infusion, the patient had no side effects or significant changes in blood pressure (Table 1).

Case 2.

A 61 years old man with a Karnofsky index of 70 % attended at home with a diagnosis of failed back syndrome secondary to a disc herniation (several L1-L5 segments) and had surgery with segmental and neurological sequelae plus chronic pain syndrome. He received multiple pain management for more than four years, including neuromodulators with no positive results, except for some blocks that generated a slight benefit. He requested medical consultation for neuropathic pain in the lumbar region of high intensity, with a burning sensation that radiated to the inguinal region and both
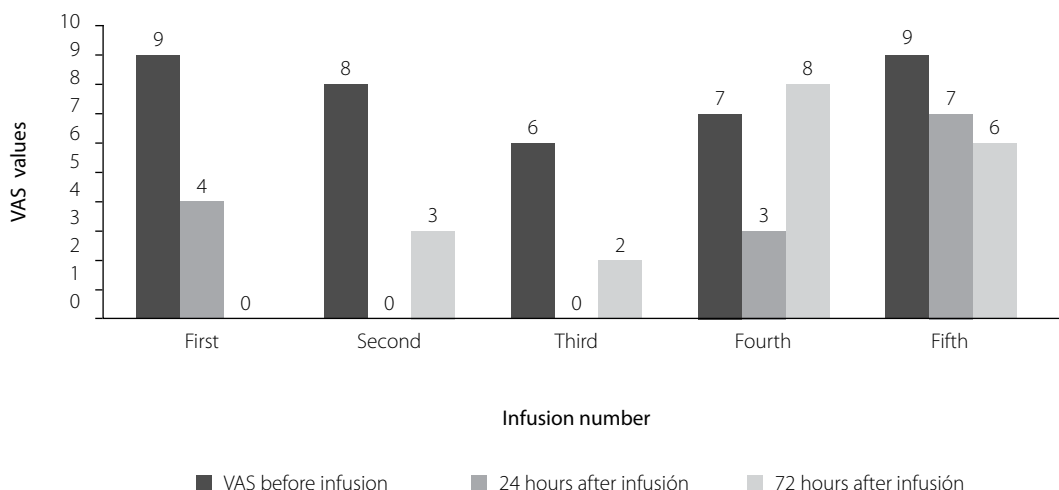

Figure 1. ESAS value, pain before and after lidocaine infusion, case 1

Table 1. Vital sign values of case 1 before, during, and after lidocaine infusion

Infusion number	Arterial Blood Pressure (mmHg)			Heart Rate (bpm)			Oxygen Saturation (%)		
	Before infusion	During infusion	After infusion	Before infusion	During infusion	After infusion	Before infusion	During infusion	After infusion
First	160/80	170/80	150/80	92	89	89	97 %	97 %	97 %
Second	120/70	120/60	120/60	107	106	100	98 %	97 %	97 %
Third	140/80	130/70	130/70	81	80	87	99 %	96 %	96 %
Fourth	140/70	130/70	130/70	97	74	72	98 %	92 %	93 %
Fifth	140/90	140/90	135/88	102	98	96	96 %	95 %	96 %

lower limbs, predominantly on the left, which made it difficult for him to ambulate; he also expressed "feeling like he was walking among stones." Since the first consultation at the hospital center, treatment was started with morphine sulfate 20 mg subcutaneously every four hours, maintaining this therapeutic plan for seven months. It was suspended before the first lidocaine infusion (Figure 2). The patient's vital signs were registered during the lidocaine infusion with 200 mg (Table 2); no significant changes in vital signs or abnormal parameters were reported.

Case 3.

A 78 years old woman, with a Karnofsky index of 60 %, with a non-oncologic diagnostic consulted with a history of progressive posterior thoracic pain due to multiple vertebral fractures secondary to osteoporosis, with exacerbation of neuropathic pain in the last month and a sensation of "tingling" and "pins and needles like electricity" in both lower limbs that was not relieved by any analgesic. The patient reported a history of having undergone vertebroplasty at lumbar levels L1 - L2 and L3 - L4 three months earlier, with slight improvement. She was under treatment with tapentadol 50 mg orally every eight hours and a rescue dose of morphine, 5 mg subcutaneously 3-5 times daily. During the consultation, uncontrolled pain was evaluated, and it was decided to administer lidocaine infusion at a dose of 200mg IV to be given in one hour (Figure 3). No significant changes or out-of-normal parameters in the patient's vital signs were reported (Table 3).

Results

In case 1, during the first infusion, a decrease in pain was reported with a previous VAS of 9/10 points (Table 1), which dropped 4 points at 24 hours, and 0 points at 72 hours. Psychological factors affecting the perception of pain were taken into consideration, and the patient also presented a urinary tract infection during the last infusion. Antibiotic treatment was started, and hypoglycemic treatment was modified to regular subcutaneous insulin according to glycemia.

In case 2, the patient obtained a VAS score of 6 points (Table 2); infusions were administered once a week for two consecutive months. At 24 hours a reduction of 2 points was obtained, and at 72 hours later, in all the infusions a decrease in pain was observed.

In case 3, the patient presented 8 VAS points at the beginning of the process (Table 3), which decreased to 2 points at 24 hours after the administration of the first

infusion and remained on a 3-point scale after 72 hours. The frequency of infusions was one every month, taking into account social factors of distance to the treatment center.

Discussion

There is evidence that supports the effectiveness of lidocaine 2 % IV for the treatment of the different etiologies of neuropathic pain, considering it as complementary treatment[14]. A recent systematic review concludes that lidocaine and other adjuvants are safe in controlled clinical trials for neuropathic pain and were better than placebo and as effective as other analgesics[15]. The doses of lidocaine used in all cases were obtained according to previous studies describing adequate tolerability and safety[16].

Evidence of benefit in terms of pain improvement beyond six hours is scarce17. However, in this study a significant improvement in pain was observed after 24 and 72 hours; this relief subsided over the course of time and required new infusions afterward.

Moulin D et al. agree that the effect of lidocaine is transitory and starts to work 30 to 60 minutes after its IV administration, and its effects can last from two to six hours after the infusion is finished, after which the analgesic effect disappears rapidly[18].

Adverse effects were not recorded in any of the cases; however, most of the time are usually mild and can be managed by decreasing the infusion rate or in some cases, suspending the infusion until the adverse effect subsides; this was not necessary in the patients in the study[9].

Conclusion

Intravenous infusion of lidocaine 2 % decreased neuropathic pain in all three patients in the study; however, the relief was transient, and the positive effect faded over time with no adverse effects to the drug.

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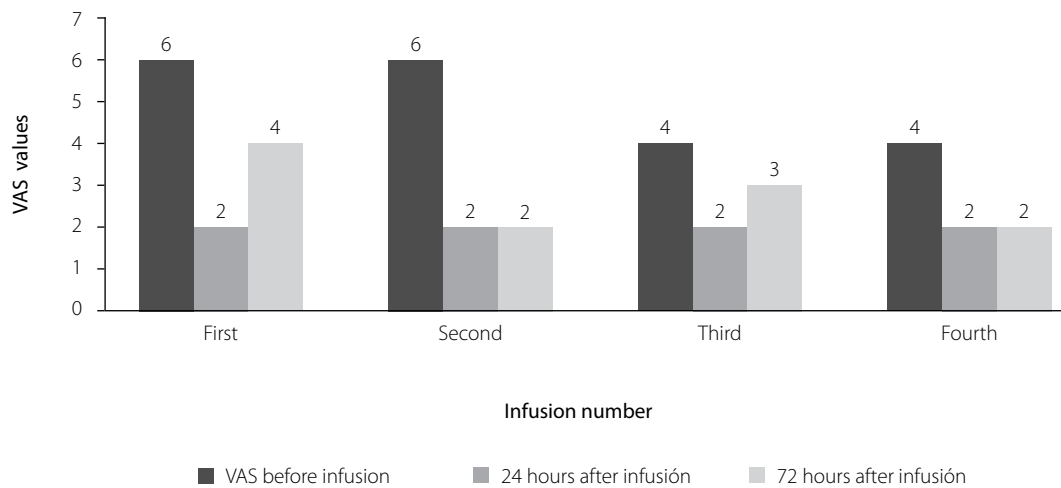
Figure 2. ESAS value, pain before and after lidocaine infusion, case 2

Table 2. Vital sign values of case 2 before, during, and after lidocaine infusion

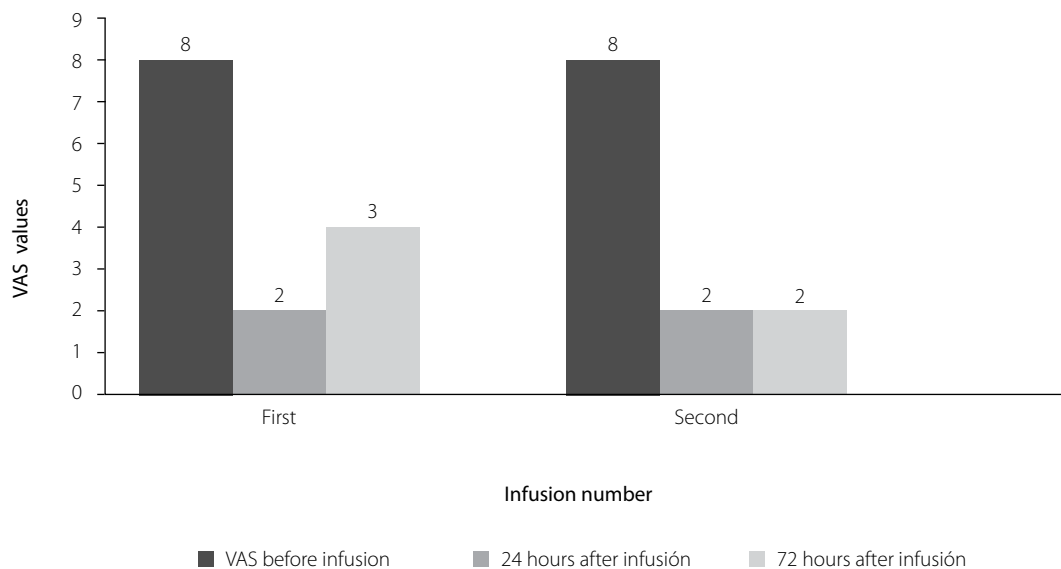| Infusion number	Arterial Blood Pressure (mmHg)			Heart Rate (bpm)			Oxygen Saturation (%)		
	Before infusion	During infusion	After infusion	Before infusion	During infusion	After infusion	Before infusion	During infusion	After infusion
First	112/66	118/76	118/70	72	79	76	97 %	96 %	96 %
Second	99/60	93/61	114/71	71	77	77	96 %	97 %	95 %
Third	97/50	104/67	99/58	68	69	70	94 %	95 %	94 %
Fourth	96/55	102/58	95/51	68	66	63	96 %	93 %	93 %

Figure 3. SAS value, pain before and after lidocaine infusion, case 3

Table 3. Vital sign values of case 3 before, during, and after lidocaine infusion

Infusion number	Arterial Blood Pressure (mmHg)			Heart Rate (bpm)			Oxygen Saturation (%)		
	Before infusion	During infusion	After infusion	Before infusion	During infusion	After infusion	Before infusion	During infusion	After infusion
First	110/70	150/80	140/70	72	63	63	98 %	97 %	97 %
Second	110/70	140/80	140/80	70	63	63	98 %	97 %	97 %

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Mental health of health personnel, an important factor in health care services

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Dear Editor,

Issue number 1 of volume 6 of the journal published the article by Magaña Salazar *et al.* on work stress and mental health of front-line personnel in COVID-19 care in a regional hospital in San Miguel, El Salvador[1]. This article identified a positive correlation, using Spearman's coefficient, between work stress and mental health status, with the use of work stress scales from the International Labor Organization and the abbreviated Goldberg scale. Although the high levels did not reach alarming percentages, health personnel assigned to the first line of care during the COVID-19 pandemic, presented occupational stress and alterations in mental health. A total of 121 workers from the emergency and hospitalization areas of COVID-19 were studied, most of them were women and 44.6 % were nursing personnel; the average age was 33.5 years old. Occupational stress and mental health disorders were found mainly, between the ages of 21 and 40 years old. Nursing, radiology and general services workers presented high levels of mental health disorders[1].

These results coincide with the study conducted at the Jipijapa Basic Hospital on the impact of COVID-19 related to the mental health of nursing personnel, in which several psychological alterations were described, including stress, fear, anxiety, depression, and lack of concentration to fulfill the tasks required by their work, which have increased with the progression of the COVID-19 pandemic. The results showed that the nursing personnel presented psychological alteratio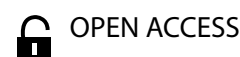ns such as anxiety, depression, anguish, and panic. In addition, somatic problems developed due to the excess of working hours caused by the increased number of patients attended in the Teófilo Dávila Hospital. Similarly, the fear of infecting family members due to the constant risk in the care areas also represented an aspect that affected mental health[2].

During the COVID-19 pandemic, the high demand from critically ill patients, the need for patient isolation, and the consequent use of safety measures such as personal protective equipment increased the anxiety and stress of nursing staff[3].

Muñoz *et al.* emphasize the nursing staff as the health personnel who are responsible for looking after the health condition of patients in hospitalization areas for prolonged periods; this places them in constant exposure to various stressful situations, such as suffering, pain, despair, irritability of patients, the performance of procedures involving painful experiences and death, which generates an emotional burden that often leads them to ignore their self-care and develop feelings such as frustration, fear, anger, or despair, defined as causes of a poorly adaptive stress[4].

Other studies describe that nursing students mainly presented sleep alterations, followed by somatic symptoms and behavioral and interpersonal relationship disturbances. It is striking that 42 % of the participants exhibited exhaustion at a medium level, which constitutes a risk of developing burnout syndrome[5].

On the other hand, it is essential to conduct a diagnosis of the health situation of workers to avoid inadequate work

performances through the implementation of timely interventions, including management processes aimed at improving rest areas and schedules, meal times, recreational meetings for emotional care, continuous staff rotation, as well as the supply of the necessary resources to perform the work, including biosafety equipment[1].

In addition, it is relevant to establish wellness, mental health promotion, and stress reduction programs to foster a healthy work environment for health personnel and a continuous training process for personnel to improve patient care since their working environment plays an essential role in the reintegration of patients to their activities and to society[1].

This necessity leads to the importance of reviewing the experiences and implementing emotional and psychological support interventions in the workplace to strengthen the response of health personnel and health processes, adopting good practices as an excellent opportunity for research and action.

Funding

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Intranasal immunization as a preventive measure against SARS-CoV-2

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Dear Editor,

It is known that the development of intramuscular RNA vaccination has been an effective preventive measure against SARS-CoV-2 infection by producing humoral and cellular immune responses that prevent viremia and systemic manifestations caused by COVID-19. However, Tiboni *et al.* report that the intramuscular route does not provide complete protection against viral replication due to the absence of activation of the mucosal immunity of the upper airways, preserving the risk of transmission[1].

Intranasal vaccination is a novel immunization approach that uses the respiratory lining as an entry point for developing antibodies. Intranasal immunization is a promising option to combat COVID-19 since by using the same route of infection as the virus, it sterilizes the respiratory tract and prevents transmission of the virus; moreover, its administration is easy and convenient for people with trypanophobia[2].

The first nasal vaccine, FluMist, was approved in 2003. It has been effective in reducing the incidence and complications of influenza. At the time being, intranasal vaccines against COVID-19 are under investigation as preclinical and clinical phase I and II clinical trials. Only in China and India intranasal vaccines have been approved, differing in their presentation, since in China, they are used in spray form, while in India, they are as drops[3].

Chavda *et al.* observed how intranasal vaccines have an effect at the mucosal and serum levels, and produce systemic immune responses, as do intramuscular vaccines, which could prevent more severe forms of the disease, and also prevent the virus to reach the lower respiratory tract, which reduces the spread of the virus[2].

Aqu Alu *et al.* explain that inhaled vaccines are attractive as they require no injection needles and no qualified personnel and describe the existence of significant advances in subunit protein vaccines and virus vector vaccines in intranasal SARS-CoV-2 vaccines in preclinical and clinical setting studies[3].

Lei *et al.* used the receptor binding domain to develop an intranasal vaccine, in which they observed superior immunogenicity to intramuscular immunogenicity that maintained long-term for wild-type and novel variables. The use of three doses produced and maintained high levels of neutralizing IgG antibodies in serum for at least one year, which also elicited strong immunity in mucosal IgA antibodies and lung T-cell memory, thus evidencing that this process was due to local lung T-cell proliferation, rather than migration of these cells from lymph nodes, resulting in a promising vaccine due to good local and systemic immunogenicity in mice[4].

Cohen *et al.* determined that anti-S antibodies derive primarily from blood transudation rather than local production in sick and vaccinated persons. Although the intramuscularly administered SARS-CoV-2 vaccine boosted mucosal immune responses in infected persons, the increase in antibody titers was higher in plasma than in mucosa, suggesting the need to develop mucosal-level vaccines to induce potent immune responses at the infection sites[5].

Owing to the benefits of local immunity in the nasal mucosa, researchers at Charité-

Universitätsmedizin-Berlin have developed a live attenuated intranasal vaccine and state that intramuscular vaccines with two doses perform significantly worse in protecting the nasal mucosa because the virus can damage the upper layers of the tissue[6].

Accordingly, Diallo *et al.* determined in their experimental vaccine (IM/IN) that antibodies induced with the ancestral sequence (WT) of the S-protein were less effective in neutralizing Omicron. On this bases, using newer versions of the S-trimer or adding other antigens such as nucleocapsid, ORF, and other proteins that are less mutated than Spike in future formulations is needed. Since viral variants escape antibodies more readily than T cells, a vaccine that induces both T cells and antibodies, particularly in the respiratory tract, may have a significant advantage, suggesting that a nasal protein vaccine formulated with a potent adjuvant may be a suitable approach to provide long-term protection against SARS-CoV-2 in humans[7].

Thus Tang J *et al.* argue that current COVID-19 vaccines are highly effective against the development of severe disease, probably through recruitment of circulating B and T cell responses during reinfection, but offer limited protection against advanced infection, especially for Omicron; with mucosal booster vaccination being necessary to establish robust sterilizing respiratory immunity against SARS-CoV-2[8].

Zhong *et al.* describe how intramuscular vaccine administration creates a global economic burden as low-temperature storage and trained health personnel are required for administration. On the other hand, intranasal administration can be performed through disposable devices with minimal storage requirements for mass vaccination, resulting in a viable option for developing countries[9].

It is the case for El Salvador and the reason why it is crucial to continue research on intranasal inoculation since it is not yet possible to conclude on its clinical effectiveness in humans, nor the safety profile of the intranasal vaccine since it is still in the clinical evaluation phases. Therefore, it is advisable to continue conducting studies to consolidate the effectiveness and safety of the intranasal route, as it is a promising route of administration that needs further studies in humans.

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Simulation-based teaching and education in pediatrics: a paradigm shift

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Dear Editor,

David Gaba described, "Simulation is a technique, not a technology, for replacing or amplifying real experiences with guided experiences that evoke or replicate substantial aspects of the real world in a fully interactive manner[1]."

Medical education has steadily progressed continually, particularly in high-risk specialties such as anesthesia, obstetrics, pediatric emergency-intensive care and neonatal-perinatal medicine. Advances have increased with the implementation of simulation-based training. Clinical simulation changes the traditional view of teaching, which focused on the weaknesses or deficiencies of professionals of health at the time of direct patient care. Based on that experience, they learned how to avoid harm to the next patient[2].

Clinical simulation-based educational programs, such as the American Academy of Pediatrics (AAP) Helping Babies Breathe (HBB), implemented 23 years ago in more than 80 low-resource countries, have taught essential neonatal resuscitation and newborn care skills to support newborns presenting with apnea at birth in low-fidelity simulators, saving many lives[3].

A systematic review measuring the effect of this program was conducted in 2022, using random-effects models to assess heterogeneity using Cochrane Q e 12; it found a decrease in overall mortality, intrapartum stillbirth mortality and first-day mortality[4]. This meta-analysis found high heterogeneity and concluded that implementation of the low-fidelity simulation program in low- and middle-income countries has a significant impact on reducing early neonatal mortality[4].

Simulation as a method of teaching and education with the use of new technologies has allowed the use of high-fidelity mannequins in the neonatology area, which not only approximate the size and weight of term newborns, but also those born prematurely and which also have a realistic airway, skin color and umbilical blood vessels. These advantages also allow the healthcare professional caring for newborns to practice incorporating or improving skills in certain procedures, such as endotracheal intubation, thoracostomy and umbilical catheter placement[5].

In pediatrics, simulation teaching and education was studied by a group from the University of Calgary, Canada, who conducted a meta-analysis using a GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach in the Pediatric Advanced Life Support (PALS) program to compare the effectiveness of high versus low fidelity manikins in the context of advanced life support training to improve knowledge and skills at the end of the course. The meta-analysis demonstrated a moderate benefit for high-fidelity manikins compared to low-fidelity manikins[6].

Simulation-based training provides a safe and secure environment for pediatricians who provide care for newborns and children in special conditions to develop and maintain competency. In addition, simulation-based training is also a valuable tool in teaching behavioral skills such as effective communication, teamwork and leader-

ship, which are essential aspects of health personnel performance in an emergency.

Simulation can be used to develop these non-technical skills that may not otherwise be learned using traditional teaching methods and can be used to improve confidence and knowledge. It is through the various well-designed scenarios, based on real cases presented in hospital assistance, that learners can relate to and trigger cognitive and psychological responses. Simulation is also used to train health care personnel in the cognitive, technical and behavioral skills needed for complex low-frequency, high-risk activities.

The creation and innovation of the modern National Simulation Center at the National Institute of Health is an initiative and product with a vision for the future, grounded on solid scientific and human bases for the teaching and education of pediatricians and health personnel who attend neonatal and pediatric emergencies.

The vision of this form of teaching not only represents a change in education, but also leads to a paradigm shift in order to improve skills and reduce complications in the care of children. As Dr. Perretta, professor of medicine and Clinical Simulation instructor at the SIMMER Center in Buenos Aires, Argentina, says: "Thinking of simulation as a technology is a mistake; clinical simulation is a new educational tool that brings with it a paradigm shift"[7].

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Alerta journal offers authors the opportunity to publish different types of articles. The types of manuscripts allowed are below. Please read the instructions carefully prior to submitting your article.

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 for 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.

Recommended format: CARE guide.

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
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For further information, please refer to the instructions to authors on our website at: www.alerta.salud.gob.sv

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