

# Factors that hinder the diagnosis of postural orthostatic tachycardia syndrome

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## Abstract

Dysautonomias are the result of a malfunction of the autonomic nervous system, among which is the postural orthostatic tachycardia syndrome, a variable and complex health problem that has a considerable prevalence, mainly in adolescents and women. It produces a wide variety of signs and symptoms that are similar to those of other pathologies, which, added to the lack of specific diagnostic tests, often delays diagnosis. Despite the existence of standardized criteria to determine the presence of the syndrome, there is still a gap in knowledge about it. This hinders the approach to the condition and, consequently, its timely treatment. Understanding more about this syndrome and the factors that hinder its early diagnosis would improve patient care and quality of life.

## Keywords

Postural orthostatic tachycardia syndrome, dysautonomia, diagnosis.

## Resumen

Las disautonomías son el resultado de un mal funcionamiento del sistema nervioso autónomo, entre las cuales se encuentra el síndrome de taquicardia ortostática postural, un problema de salud variable y complejo que tiene una prevalencia considerable, principalmente en adolescentes y mujeres. Este produce una amplia variedad de signos y síntomas que son similares a los de otras patologías, lo que sumado a la falta de pruebas diagnósticas específicas, muchas veces retrasa el diagnóstico. A pesar de la existencia de criterios estandarizados para determinar la presencia del síndrome, existe aún una brecha en el conocimiento acerca del mismo. Esto dificulta el abordaje del padecimiento y por consiguiente, su tratamiento oportuno. Conocer más sobre este síndrome y los factores que dificultan su diagnóstico temprano permitiría mejorar la atención de los pacientes y su calidad de vida.

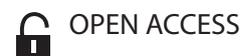
## Palabras clave

Síndrome de taquicardia postural ortostática, disautonomía, diagnóstico.

## Introduction

The autonomic nervous system (ANS) has a cardiovascular domain mediated by its sympathetic and parasympathetic divisions that is responsible for regulating heart rate, blood pressure and homeostasis within the body; alterations in the functioning of one of the branches of this system trigger

dysautonomias<sup>1</sup>. These conditions have acquired relevance in recent years. In addition to the most prevalent, which is high blood pressure, there are others less known but of equal importance, including postural orthostatic tachycardia syndrome (POTS)<sup>1</sup>. Experts have estimated that from 500 000 to 3 000 000 Americans could be affected<sup>2</sup>.



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POTS is a variable and complex health problem, present in adolescents and adults<sup>2</sup> whose symptoms are characterized by palpitations, stunning, generalized weakness, tremors, blurred vision, fatigue and tachycardia, when standing or sitting<sup>3</sup>.

An early diagnosis is important to be able to provide adequate management, otherwise the patient's quality of life tends to decrease due to physical and mental deterioration<sup>4</sup>. Although there is a consensus to clinically define POTS, misdiagnoses are common, due to the similarity of symptoms to other conditions. This causes patients to undergo extensive and unnecessary investigations, receiving fragmented care from multiple specialists<sup>5,6</sup>.

Learning more about POTS can facilitate timely diagnosis and treatment<sup>7</sup>. For this reason, it aims at describing factors that hinder the early assessment of this syndrome through a bibliographic review.

## Discussion

### POTS and the tests used in its diagnosis

The ANS, made up of the sympathetic and parasympathetic nervous system, is responsible for regulating the functioning of the internal environment, heart rate, blood pressure, breathing, among others. Dysautonomias are generated by alterations of ANS with POTS being one of the most common<sup>8</sup>.

POTS is mainly manifested by orthostatic intolerance characterized by an excessive increase in heart rate after sitting or standing and that occurs most often in young people, mainly affecting women. This is one of the disorders observed most regularly in clinics of autonomic dysfunction<sup>9</sup>. It can occur primarily or secondarily to systemic diseases such as paraneoplastic syndrome or diabetes. It is often underdiagnosed, which can eventually compromise the quality of life of those who suffer from POTS<sup>10</sup>.

Federowski states that early clinical observations showed that POTS frequently occurs after an acute, typically viral, infection. However, experts believe that it could be caused by an unidentified implicit factor or be a heterogeneous condition with multiple etiologies<sup>11</sup>. However, Spahic et al. state that the etiology of POTS is still unknown nowadays<sup>12</sup>.

The syndrome is still considered idiopathic with a large number of explanations proposed<sup>13</sup>. Because of this, POTS is often described as a clinical syndrome consisting of multiple heterogeneous disorders often

classified into different subtypes of POTS<sup>14</sup>. The complexity increases because a single patient with POTS can have multiple coexisting diagnoses, the most frequent being autoimmune disorders. There is currently no clear interpretation of how these disorders relate to each other and how each contributes to the symptoms of a single patient<sup>15</sup>.

As has been mentioned, POTS is an autonomic disorder in which a great diversity of signs and symptoms is experienced, including the characteristic presence, according to studies carried out by Kichloo *et al.*, 99 % of stunning, tachycardia in 97 % of tachycardia, 94 % of presyncope, 88 % of dyspnea and 87 % of palpitations<sup>16</sup>. Similarly, Bryarly *et al.* mention that a characteristic that seems to be universally present in all POTS is cardiovascular deconditioning, a specific biological process characterized by atrophy and hypovolemia<sup>17</sup>.

Regarding its epidemiology, Dahan *et al.* estimate that the prevalence was 170:100 000 in 2016<sup>18</sup>. In 2020, Tahirovic adds that the individuals who predominantly present it are the age groups of adolescents and women from 15 to 50 years old<sup>19</sup>.

When evaluating a patient with suspected dysautonomia, laboratory tests are usually performed to establish the diagnosis. Nowadays, there is no laboratory test that indicates its presence or absence in an individual in the case of this syndrome so far. However, the results of these can help to discard other conditions<sup>20</sup>.

The tests to be taken into account are usually as follow: metabolic profile to rule out renal failure, diabetes or metabolic disorders, complete blood count to discard any type of infection or anemia, thyroid stimulating hormone or thyrotropin, thyroxine, cortisol and adrenocorticotrophic hormone to discard thyroid and adrenal dysfunction, serum albumin level to discard malnutrition, among others. From the results, the options for a differential diagnosis are reduced in large numbers and the possibility that the definitive diagnosis of the patient is POTS increases<sup>20</sup>.

Similarly, it is necessary to perform imaging tests and functional tests, although there is no established examination for its detection, but they are executed to carry out a differential diagnosis. Electrocardiograms and echocardiograms are commonly performed<sup>20,21</sup>.

Nevertheless, when there is suspicion of POTS in an individual, the best examination performed is the head-up tilt table test, which allows to observe hemodynamic changes during orthostatic provocation.

Zhao *et al.* describe that this test consists of the patient having to remain in a supine position for ten minutes by measuring his basal blood pressure and heart rate. Subsequently, the patient must remain standing to take the measurements again at intervals of one, three, five and ten minutes<sup>21</sup>.

### **Influence of symptomatic variability and mimicry with other diseases on the diagnostic delay of POTS**

The POTS is regularly identified by a detailed medical history, blood tests and the tilting table test, which serve to ensure that the patient's symptoms are not the result of other medical conditions. This process is rarely simple<sup>22</sup>.

The most common clinical manifestations of an individual with POTS have been mentioned above. However, patients typically show much more complex associated symptoms that cannot be explained physiologically such as orthostatic intolerance. This is interpreted as symptomatic variability<sup>22</sup>.

Although some individuals usually do not meet all the standard criteria, they still suffer POTS since it is a heterogeneous disorder<sup>23</sup>. It is possible to classify POTS according to the pathophysiological mechanisms that occur in the patient, thus existing the subtypes detailed below.

Neuropathic POTS consists of a decrease in norepinephrine (NE) levels in the lower limbs. The problem is not the production of such a hormone, as it remains normal; however, release of hormone is decreased and its reuptake is increased. The reason for this is the peripheral nerves are injured and cannot normally work. Low levels of NE cause loss of autonomous innervation in its sympathetic division of the lower extremities, presenting as a consequence reduced venoconstriction, which affects venous return and causes accumulation of blood in the respective regions, which can be observed clinically as a redness<sup>24</sup>.

In hyperadrenergic POTS, present in approximately 30-60% of patients with POTS, a continuously elevated level of plasma NE ( $\geq 600$  pg/mL) is shown, triggering an increase in sympathetic tone. On physical examination, this manifests as palpitations, tachycardia, hypertension, tremors and anxiety<sup>25</sup>.

Hypovolemic POTS gets its name because 70% of people who suffer from it show a decrease in plasma, red blood cells and total blood volumes. From studies carried out, it is inferred that it may be due to damage to the renin angiotensin aldoste-

rone system related to the decrease in renin and aldosterone levels<sup>26</sup>.

Autoimmune POTS can also be found, whose name is due to the fact that it appears after a viral process, since the antibodies produced and released to combat this infection attack the peripheral nerves and affect the innervation in general, including therefore the sympathetic innervation. Also, it presents characteristics similar to other autoimmune disorders, such as the predominance of the female sex, postviral onset and elevation of autoimmune markers. Studies indicate that in 25% of these patients the triggering disease is Hashimoto's thyroiditis, which has been demonstrated from positive results of antinuclear antibodies for this condition<sup>21</sup>. It was observed that individuals who have developed COVID-19 occasionally present with this subtype of POTS as a result of SARS-CoV-2 infection<sup>27</sup>.

Boris *et al.* establish that the variety of symptomatic combinations of this syndrome causes the delay of the diagnosis of two years on average, since by not observing what is established as determinant symptoms of the syndrome, the manifestations of the patients do not lead to think about POTS in the first instance<sup>28</sup>.

The symptomatology of POTS varies; therefore it can mimic other diseases because some symptoms are absent or others are found in addition to those commonly associated with POTS<sup>29</sup>.

Often the syndrome overlaps with other conditions because there are no established or universally "even" symptoms for it. Those that are common in POTS (headache, fatigue, sleep disturbances and diarrhea) are also present in other diseases<sup>29</sup>, which generates dilemmas when establishing a diagnosis, which is why it is done by discarding diseases that present all or most of the physical indications that the patient shows, usually the POTS being the last to be taken into account<sup>20</sup>.

Blitshteyn states that the psychological diseases with which there is the greatest confusion. Some of the diseases that are frequently misdiagnosed about POTS are panic disorders and chronic anxiety, since they also have characteristic episodes of tachycardia or palpitations, angina, nausea and headache. However, their etiology is different, which helps to differentiate them. In the case of POTS, these are related to cerebral hypoperfusion in response to changes in heart rhythm, while anxiety and panic may be due to the increase in biochemicals mediated by the limbic system<sup>30</sup>.

Another psychological pathology that is usually diagnosed instead of POTS is depression due to the presence of fatigue, headaches, agitation or restlessness. Also, the etiology helps to distinguish them, since in patients with POTS fatigue occurs when performing activities that due to their physical condition trigger fatigue, headaches are due either to hypertension or to the same dyspnea or motion sickness that they present and agitation is related to dyspnea due to the performance of activities that normally do not involve fatigue. In patients with depression, the mental fatigue they possess turns into physical fatigue and remains still at rest, headaches may be due to lack of sleep or poor nutrition and crying and agitation may be due to anxiety<sup>4</sup>.

Although psychological disorders occupy the first place in the diseases that mimic the POTS, these are not the only ones; likewise, there are the gastrointestinal and urinary ones. According to Goodman, the gastrointestinal symptoms that POTS patients may present are dysphagia, early satiety, nausea, vomiting, abdominal pain, constipation and diarrhea, which are related to visceral motility disorder or primary gastrointestinal disorders (celiac disease, gastroesophageal reflux, esophagitis, gastritis, eosinophilic disorders and inflammatory bowel disease)<sup>31</sup>.

Likewise, the presence of urinary symptoms is often observed in patients with POTS, such as frequent urination, difficulty urinating, nocturnal enuresis and incomplete emptying of the bladder. Such ailments lead to misdiagnosis of urinary tract infection, prostate cancer, kidney and bladder stones. Therefore, it is necessary to perform exclusive diagnostic tests and not rule out the possibility that it may be POTS<sup>32</sup>.

For differential diagnosis, imaging tests and functional tests, such as transthoracic echocardiography, electrocardiograms for intraarterial pressure control and extended electrocardiography tests, are necessary, as these usually show normal results in patients with POTS<sup>20</sup>.

### **Impact of widespread knowledge of POTS by health personnel on its late diagnosis**

Due to knowledge gap, the care of patients with POTS is suboptimal since the scope of clinical presentation is not known with certainty, in addition to the lack of information on the pathophysiology of the syndrome<sup>2</sup>.

Although there are standardized criteria for the diagnosis of the syndrome, as there

is no record in the presentation of these, there is not diagnosed by clinicians making the care of patients deficient. Collins *et al.* comment that there is still disagreement between the scientific and medical communities about the definition of POTS and whether it is a condition or a set of related conditions<sup>33</sup>.

Shaw *et al.* state that an online survey conducted by academic institutions and the Dysautonomia International Organization, between 2015 and 2017, 4835 people who were diagnosed with POTS participated and reported prolonged delays in diagnosis with an average waiting time of two years after the first medical consultation. 75 % of them reported being misdiagnosed before the diagnosis of POTS, 67 % of them mentioned that their doctor recognized their symptoms as a physical illness, but they were not sure how to address it; a large number of participants received "psychological and psychiatric problems" as a diagnosis and even had to suggest POTS as a potential diagnosis to their doctor. On average, patients in the study consulted  $7 \pm 11$  doctors before being diagnosed with POTS<sup>7</sup>.

POTS is not the only puzzling condition doctors face every day; however, the symptoms of this are vague and inconsistent, which makes it difficult to approach. Lama establishes the possibility that the diagnosis may be delayed even ten years after the appearance of the first discomfort<sup>34</sup>.

## **Conclusion**

Either different manifestations that can be found in each patient or the superficial knowledge that clinicians have about POTS, make it difficult to detect. Because the usual or common symptoms are not shown, the diagnosis takes a wrong path towards other diseases that the person suffers, which generates delays not only in its detection, but in its treatment. Consequently, those who suffer from it experience a decrease in their quality of life.

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