Polyneuropathy as an initial manifestation of Hereditary Transtyretin Amyloidosis (ATTRV) in a young patient: Case report of a diagnostic challenge

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ABSTRACT: We report the case of a 27-year-old man with transthyretin amyloidosis secondary to the p.Val142Ile mutation with an atypical clinical presentation of predominantly lower limb polyneuropathy without cardiac involvement. p.Val142Ile is mainly associated with cardiopathy, whereas the neuropathic phenotype is mainly associated with p.Val50Met. Our patient belongs to a non-endemic region and due to his lack of support network a possible familial component is unknown. His case represents a diagnostic challenge given the wide heterogeneity of clinical manifestations associated with the disease, with other possible diagnoses of polyneuropathy being reasonably excluded according to prevalence and frequency. The particularly unusual genotype-phenotype association distinguishes this case from the classic description of transthyretin amyloidosis secondary to p.Val142Ile.

KEYWORDS: Amyloidosis, transthyretin, small fiber neuropathy, autonomic nervous system diseases, orphan disease

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Introduction

Hereditary amyloidosis associated with transthyretin (ATTRv) is a genetic orphan disease caused by the progressive accumulation of transthyretin protein due to a mutation in the encoding gene. Its worldwide prevalence has been estimated at up to 38 000 people.[1] It is endemic in Portugal, Sweden, Japan, and sporadically present in the rest of the world. In endemic areas, patients typically have a family history related to the disease, and symptoms usually appear between the third and fourth decade of life.[2] By contrast, the age at disease onset in patients form non-endemic areas is usually more than 50 years, even though they have p.Val50Met (Val30Met) mutation as in those from endemic areas.[3]

The transthyretin mutation results in insufficient protein synthesis, leading to the accumulation of amyloid fibers that cannot be degraded. These fibers mainly accumulate in the heart and peripheral nervous system (PNS), and to a lesser extent in other organs such as the brain, kidney, skin, and muscle.[4] When ATTRv affects the peripheral nerves, it can cause ATTR small fiber neuropathy, a progressive and debilitating condition. This condition is characterized by predominantly pain, marked autonomic dysfunction, and impaired thermoalgesia in its early onset.[2]

The diagnosis of ATTRv with neuropathy remains a challenge for clinicians due to its variable and nonspecific symptoms, despite the severity of the disease. Currently, there are no standardized approaches to assess dysautonomia in ATTRv amyloidosis. Late diagnosis may occur due to the presence of comorbidities and concurrent autonomic symptoms, resulting in delays in treatment and favoring disease progression. This can lead to irreversible and highly disabling changes.[5] This case report presents a young patient with small fiber polyneuropathy as the initial manifestation of ATTRv.

Case Presentation

A previously healthy 27-year-old male metal-mechanic worker presented to the emergency department with myalgia mainly in the lower extremities. He also reported hypoesthesia, subjective weakness of the lower limbs, nocturnal diaphoresis, and involuntary weight loss. The patient reported experiencing similar and intermittent symptoms over the past 2 years. The patient also reported experiencing dysphagia and lumbar pain with mechanical characteristics, without any signs suggesting autoimmunity.

During the neurological physical examination, the patient exhibited decreased strength of 4/5 in all muscle groups, with a predominance in the lower limbs of 3/5, along with variable hypoesthesia in all 4 extremities and pain upon palpation. In previous months, other institutions raised possible differential diagnoses, such as Guillain-Barré syndrome and transverse myelitis which received treatment despite not having diagnostic confirmations and without improvement of the symptomatology.

In the study of the weakness syndrome, initial tests were performed with normal results for hemogram, electrolytes, and renal function. The liver profile showed isolated indirect

hyperbilirubinemia, which prompted further investigation with a hemolysis profile and peripheral blood smear. Both of these tests were within normal limits. The patient's medical evaluation revealed a normal deficiency and metabolic profile. Lumbar puncture was performed and the only finding was mild hyperproteinorrachia. Electromyography and nerve conduction tests were performed and were normal. Creatine phosphokinase levels were negative. Nuclear magnetic resonance of the neuroaxis (cerebral, cervical, thoracic, and lumbosacral) showed findings of sacroiliitis and edema of the lumbosacral fatty plane between L3 and L5. Video swallowing was requested due to the sensation of dysphagia. The test documented alterations in the oropharyngeal functions of swallowing and deconditioning of the orofacial musculature.

An autoimmunity profile was performed due to lumbar pain, sacroiliitis, and lumbar edema reported in the diagnostic image. The profile included negative anti-nuclear antibodies (ANAs), autoantibodies to extractable nuclear antigens (ENAs), and anti-neutrophil cytoplasmic antibody (ANCA), as well as a skin and soft tissue biopsy with negative histopathology and microbiology studies (Gram stain, Ziehl Nielsen, and cultures for common microorganisms and mycobacteria).

The patient's occupational history was reviewed to rule out potential heavy metal intoxications, including lead, arsenic, mercury, chromium, and cobalt. While hospitalized, the patient's neurological clinical manifestations showed high variability, leading to a psychiatric evaluation to consider a possible psychogenic component. The patient was suspected of having borderline intelligence and a possible disorder due to functional neurological symptoms. Treatment was initiated with a serotonin reuptake inhibitor and neuromodulator, but there was no clear improvement.

During hospitalization, the patient experienced pain in the right frontotemporal region. Cerebral magnetic resonance imaging showed evidence of right temporal myositis, accompanied by fever. The patient received antibiotic therapy, including fourth-generation cephalosporin and glycopeptide. A biopsy of the left temporal muscle revealed acute and subacute vasculitis type changes and associated atrophy of neurogenic origin without evidence of reinnervation, Congo red stain was negative. Additional studies were performed to search for other manifestations of vasculitis, these studies included angiotomography of the extremities, thorax, abdomen, and pelvis, as well as ultrasound of the temporal vessels, which did not reveal any abnormalities.

The imaging and laboratory studies did not show any evidence of neurological involvement. However, the presence of dysautonomia, proprioceptive ataxia, lumbar fatty tissue edema, and temporal myositis with atrophy of neurogenic origin raised the suspicion of a possible small fiber neuropathy. Given that previous studies have already excluded the majority of causes of small fiber neuropathy, further investigations were conducted to rule out infiltrative diseases such as sarcoidosis, Fabry's disease, and amyloidosis. The results showed that 1.25 OH vitamin D and ACE were within normal limits, and chest tomography did not reveal any abnormalities. Alpha galactosidase A was also within normal limits. The complete sequencing of the TTR gene resulted in a positive finding for the pathogenic heterozygous variant c.424G>A (p.Val142Ile) missense in the TTR gene, confirming the diagnosis of hereditary amyloidosis associated with transthyretin.

The clinical genetics service evaluated him and reported that this variant is most commonly associated with a cardiac phenotype. However, due to its variable expressivity and incomplete penetrance, it can occasionally manifest with polyneuropathy and explain all the patient's clinical manifestations. The patient underwent electrocardiogram, transthoracic echocardiogram, and cardiac magnetic resonance imaging with gadolinium to evaluate late enhancement. No findings suggestive of cardiac amyloidosis were detected. Based on these results and evidence of exclusively neurological involvement, the neurology service recommended therapy with inotersen to improve the underlying symptoms. Multimodal pain management was indicated, including the use of neuromodulators and weak sustained-release opioids. Due to absent family support and a catastrophic functional decline, the patient was transferred chronic care facility with a physical rehabilitation plan that included physical therapy, speech therapy, and occupational therapy. He has received 2 doses of inotersen so far with no improvement in pain or neurological deficit but without worsening of these symptoms.

Discussion

Transthyretin amyloidosis is a hereditary amyloidosis characterized by the accumulation and deposition of amyloid aggregates of transthyretin protein in peripheral tissues, resulting in dysfunction of the affected organ. This autosomal dominant disorder is highly heterogeneous and has incomplete penetrance. It can be caused by mutations, and depending on the specific mutation, different phenotypes may be observed. More than 120 polymorphisms have been described, some of which are mainly associated with heart disease, while others are associated with neuropathy. The p.Val50Met variant is most commonly associated with neuropathic involvement, while p.Val142Ile is most frequently associated with cardiac involvement.[6] However, Stancanelli et al[7] and Devarapalli et al[8] have described manifestations of dysautonomia and polyneuropathy in patients with this mutation, without cardiac involvement. Likewise, Di Stefano et al[9] document a case of development of mild axonal predominance lenght-dependent sensory-motor polyneuropathy in an Italian patient with the Val142Ile mutation. In early onset ATTRv, there can be clinical manifestations of small nerve fiber involvement but with nerve conduction study that may be normal,[4] as was the case of our patient. It is important to assess small fiber neuropathy using other specific tests that we didn't have available in our institution, so the diagnosis of small fiber neuropathy was made bases on clinical characteristics.

ATTRv is prevalent in certain European and Asian countries and occurs sporadically elsewhere. However, the p.Val142Ile mutation has been reported more frequently in African populations than in European and Asian populations. The highest prevalence of the variant is found in populations derived from East Africa where its prevalence reaches up to 3% of the African-American population.[10] Seventy percent of Africans forced to work as slaves were brought to North America during the Atlantic slave trade between the 16th and 19th centuries, so a global distribution of this allele cannot be ruled out.[11] Although there is no information available about the Hispanic population,[10] there are recent data from Western Sicily that retain an important genetic correlation with the Hispanic population. They highlight that ATTRv is not uncommon in Sicily and the Val122Ile mutation occupies 14% of the data described.[12]

The disease onset is described in the literature as occurring in individuals younger than 50 years old, with clinical manifestations of progressive sensorimotor and autonomic neuropathy. The expected survival rate is approximately 10 to 20 years from onset.[9] Diagnosis in non-endemic regions may take up to 4 to 5 years due to various factors, such as heterogeneity of clinical manifestations and absence of family history, which frequently leads to misdiagnosis,[13] as happened in our patient.

This case presents the challenges encountered in clinical practice when arriving at a diagnosis. The initial symptoms were highly nonspecific, and the lack of a family history made it difficult to establish correlations. The presence of comorbidities and exposure to certain factors further complicated the diagnosis. The diagnosis of ATTRv explained all of his constitutional symptoms, including weight loss, diaphoresis, and intermittent fever, as well as his gastrointestinal symptoms, which alternated between diarrhea and constipation. Additionally, his urinary symptoms, such as loss of sphincter control, and neurological symptoms, including weakness, hypoesthesias, and myalgias, were also explained. A reasonable and systematic differential diagnostic process led to this diagnosis.

The broad spectrum of potential clinical symptoms significantly impacts the quality of life for individuals with ATTRv. In Portuguese patients with the Val30Met variant, a notable change in the Norfolk QOL-DN score was observed in the early stages of the disease, particularly due to autonomic and polyneuropathy symptoms. Autonomic neuropathy is a prominent characteristic of ATTRv and may present as the initial symptom in a significant number of patients. However, assessing dysautonomia in ATTRv amyloidosis is challenging due to the lack of standardized approaches, which makes it difficult to differentiate it from other neuropathies and amyloidoses. The clinical approach remains the most useful tool to identify possible autonomic dysfunction. Therefore, it is essential to systematically examine all the various symptoms to cover the different aspects of autonomic dysfunction.[14]

Strategies should focus on early diagnosis since there are now targeted therapies, such as inotersen and patisiran, that have been proven to enhance survival, quality of life, and disease stability, resulting in better outcomes for those with early-stage disease.[5] Future research is necessary to establish standardized diagnostic methods for assessing dysautonomia in ATTRv amyloidosis and to develop more effective treatment strategies aimed at improving patients' quality of life.

Our case presented with several challenges due to the patient's incomplete and non-specific report of symptoms, as well as absence of family history, which plays a fundamental role in the diagnosis of this pathology. However, an orderly and focused diagnostic process, with a high diagnostic suspicion, allowed us to rule out differential diagnoses and approach the definitive diagnosis based on the patient's clinical history and physical examination.

Conclusions

This report presents a case of ATTRv associated with the p.Val142Ile mutation. The patient's presentation was unusual, with predominantly polyneuropathic involvement. The time to diagnosis was approximately 2 years from the onset of symptoms. Challenges faced before achieving an early diagnosis included the high heterogeneity in symptomatology, the absence of a known family history, and the high number of differential diagnoses that could explain the patient's symptomatology. This case highlights the significance of considering this diagnosis in patients with dysautonomic symptoms and polyneuropathy without an apparent cause. Early diagnosis can prevent fatal outcomes since untreated transthyretin amyloidosis can be lethal.

Author Contributions

JVSP: Study design, writing of the manuscript, review of the final version of the manuscript; SSP: Study design, writing of the manuscript, review of the final version of the manuscript; MCE: Study design, writing of the manuscript, review of the final version of the manuscript; PRT: Study design, writing of the manuscript, review of the final version of the manuscript.

Ethical Responsibilities

Endorsement of the Research and Institutional Ethics Committee of the Faculty of Medicine of the Pontificia Universidad Javeriana and the San Ignacio University Hospital. San Ignacio University Hospital with number 1422-23 on 11 January 2024.

Right to Privacy and Informed Consent

The authors declare that no patient data appear in this article. The authors have obtained the informed consent of the patient who participated in the research, and the confidentiality of the information will be maintained by not disclosing names or identities. This document is held by the corresponding author.

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