

Polineuropatía amiloide familiar: Desafíos diagnósticos en un hombre de 78 años con polineuropatía e insuficiencia cardíaca

Familial Amyloid Polyneuropathy: Diagnostic challenges in a 78-year-old male with polyneuropathy and heart failure

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ABSTRACT

Transthyretin amyloidosis (ATTR) is a rare, progressive disorder caused by the accumulation of misfolded transthyretin (TTR) proteins in various tissues and organs, leading to the formation of amyloid deposits.

In ATTR, genetic mutations (hereditary form) or age-related changes (wild-type form), cause the TTR proteins to become unstable, misfold, and aggregate into amyloid fibrils. These amyloid deposits can affect multiple organs, most commonly the peripheral nerves and the heart.

Symptoms vary depending on the organs involved, being heart failure and/or polyneuropathy the predominant. The treatment aims at stabilizing the TTR, reduce amyloid production, or remove amyloid deposits.

The authors present a case of a 78-year-old man, with a recent onset of polyneuropathy and recurrent episodes of decompensated heart failure, in whom, the diagnosis of Familial Amyloid Polyneuropathy, a subtype of hereditary ATTR was made.

Keywords: Hereditary transthyretin amyloidosis, heart failure, familial amyloid polyneuropathy.

INTRODUCTION

Amyloidosis is a heterogeneous disease, and results from the extracellular tissue deposition of fibrils composed of subunits of a variety of proteins. It can be either acquired or hereditary and may present as either a localized or systemic disease.

Hereditary transthyretin amyloidosis is an adult-onset, autosomal dominant disease produced by mutations in the *TTR* gene, which encodes the transthyretin (TTR) protein¹. The TTR protein, which is normally produced by the liver, pathologically misfolds, aggregates into amyloid fibrils, and deposits in various tissues causing irreversible damage.²

The range of clinical symptoms vary extensively from neurological to cardiac. The phenotypic heterogeneity depends on many factors, such as specific TTR mutation site, geographical distribution, inheritance pattern, timing of onset, and epidemic/non-epidemic aggregation.

A few countries are endemic to the disease, with Portugal being one of them. In fact, Portugal has one of the highest prevalence rates of transthyretin amyloidosis in Europe. The condition is particular-

RESUMEN

La amiloidosis por transtiretina (ATTR) es un trastorno raro y progresivo causado por la acumulación de proteínas transtiretina (TTR) mal plegadas en diversos tejidos y órganos, lo que conduce a la formación de depósitos amiloides.

En la ATTR, las mutaciones genéticas (forma hereditaria) o los cambios relacionados con la edad (forma de tipo salvaje) provocan que las proteínas TTR se vuelvan inestables, se plieguen incorrectamente y se agrupen en fibrillas amiloides. Estos depósitos amiloides pueden afectar a múltiples órganos, siendo los más comunes los nervios periféricos y el corazón.

Los síntomas varían en función de los órganos afectados, siendo la insuficiencia cardíaca y/o la polineuropatía los más predominantes. El tratamiento tiene como objetivo estabilizar la TTR, reducir la producción de amiloide o eliminar los depósitos amiloides.

Los autores presentan el caso de un varón de 78 años, con un inicio reciente de polineuropatía y episodios recurrentes de insuficiencia cardíaca descompensada, en el que se diagnosticó polineuropatía amiloide familiar, un subtipo de ATTR hereditaria.

Palabras clave: Amiloidosis transtiretina hereditaria, insuficiencia cardíaca, polineuropatía amiloide familiar.

ly widespread in northern regions such as Vila do Conde, Póvoa de Varzim, Serra da Estrela, and Figueira da Foz. The Val30Met variant, known as transthyretin familial amyloid polyneuropathy (ATTR-FAP), is the most frequent form of TTR amyloid and in 2016, the prevalence of TTR-FAP was 22.93 per 100,000 adult inhabitants.³

Lack of recognition of the disease, non-specific symptoms, and co-morbidities often leads to delayed diagnosis, which can be fatal, if untreated.

CLINICAL CASE

A 78-year-old male patient with an ECOG of 3, presented to the Emergency Department with a history of shortness of breath and peripheral oedema. The patient had a known history of heart failure with preserved ejection fraction, with prior hospitalizations.

On physical examination, his vitals were: blood pressure of 85/45 mmHg, a heart rate of 62 bpm, and an oxygen saturation of 95%.

He presented with anasarca. Laboratory tests showed mild inflammation, with a C-reactive protein level of 6 mg/dL. There was also evidence of acute-on-chronic kidney disease, indicated by a creatinine level of 1.65 mg/dL, compared to a baseline creatinine of 1-1.1 mg/dL. The urine culture revealed *Klebsiella pneumoniae* ESBL+ (Extended-Spectrum Beta-Lactamase positive), and meropenem was administered for seven days. The patient was admitted to the Internal Medicine Ward for heart failure management.

During his stay, the patient reported progressive loss of strength in both upper and lower limbs, along with recurrent episodes of urinary retention at home. Tetraparesis with gait apraxia was observed. Given the decompensated heart failure and neurological findings, an extensive workup was initiated.

Transthoracic echocardiography revealed heart failure with preserved ejection fraction (LVEF 68%), severe concentric hypertrophy of the left ventricular walls, and images suggestive of myocardial infiltration in the interventricular septum, along with type III diastolic dysfunction. Blood tests, including blood and urine electrophoresis and immunofixation, as well as the serum free light chain assay, were normal. A biopsy of the minor salivary glands showed amyloid deposits. Electromyography of the lower limbs indicated axonal sensorimotor polyneuropathy.

Due to suspicion of ATTR, ^{99m}Tc-DPD scintigraphy and genetic testing were conducted. The scintigraphy revealed abnormal and increased uptake of the tracer in the myocardium (Figures 1 and 2), and the genetic testing identified the p.Val30Met variant in the TTR gene in a heterozygous state. With a diagnosis of Familial Amyloid Polyneuropathy (FAP), the patient was referred to a specialized center, however given the advanced stage of the disease, best supportive care was offered.

DISCUSSION

Familial Amyloid Polyneuropathy remains a challenging diagnosis due to its diverse clinical presentations.

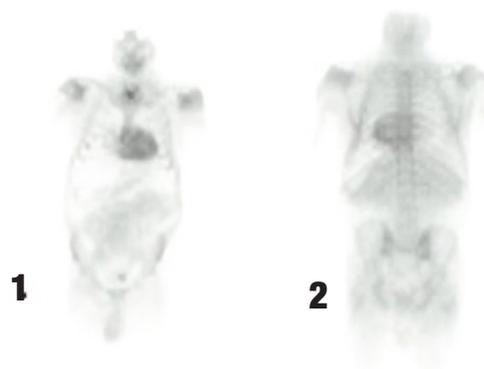
In the last few decades, new mutation types were identified, and to this day, more than 120 TTR gene mutations were described, with the Val30Met being the most common⁵. With the identification of new mutation types, we were able to understand that the presenting symptom, age at onset, type of the neuropathy and additional systemic involvement can be highly variable.

Age at onset is also affected by the geographic area. It is remarkably earlier in patients from endemic regions such as Portugal and Japan, compared to Sweden where late-onset disease predominates.⁷

Length dependent sensory-motor neuropathy with autonomic involvement is the hallmark of the disease. Amyloid typically first affects small nerve fibers altering pain and temperature sensation. Motor deficit appears in the distal lower limbs, and walking becomes increasingly difficult with loss of balance and steppage gait.⁶

In patients with early-onset disease, is not uncommon, for quick deterioration due to autonomic dysfunction and rapid progression of the

Figures 1 (anterior) and 2 (posterior) body views, showing the increased uptake of the tracer (^{99m}Tc-DPD) in the myocardium.



sensory-motor deficit. On the other hand, older patients, the polyneuropathy progresses slowly, often with a cardiac involvement but with less autonomic dysfunction.⁷

Cardiac involvement is the most common extra-neurological manifestation. Heart failure induced by restrictive cardiomyopathy is frequently observed in these patients, together with electrical disturbances. Commonly, findings such as low voltage in electrocardiogram, aortic stenosis and increased ventricular wall thickness in echocardiogram are common.

For its diagnosis genetic testing for TTR is essential. The absence of a pathologic mutation excludes TTR-FAP. The presence of symptoms and documentation of amyloid deposits in tissue, is also important to distinguish symptomatic patients from carriers.

By publishing this clinical case, the authors intend to emphasize the complex presentation with decompensated heart failure, and progressive tetraparesis, coupled with imagiologic and histological findings, that initially pointed to multiple possible diagnoses.

The case highlights several key aspects of FAP, particularly how it mimics more prevalent conditions in older adults. The patient's echocardiogram findings were indicative of restrictive cardiomyopathy, which can be easily mistaken for age-related hypertensive heart disease or hypertrophic cardiomyopathy. This underscores the importance of maintaining a high index of suspicion for systemic amyloidosis in elderly patients with unexplained cardiac or neurological symptoms.

Furthermore, the onset and progression of FAP can vary widely depending on the specific TTR mutation and patient demographics. The p.Val30Met mutation, as seen in this patient, is the most common mutation associated with FAP. It typically presents earlier in endemic regions, but in this case, the late onset of disease and the severe systemic involvement reflects the variability seen in non-endemic areas. The patient's advanced age and the late-stage diagnosis (stage 3) are consistent with the slower disease progression often seen in older patients.

CONCLUSION

In conclusion, this case highlights the importance of considering hereditary ATTR as a potential diagnosis in elderly patients presenting with unexplained polyneuropathy and heart failure. Early recognition and diagnosis are crucial for appropriate management and treatment, as timely intervention can help stabilize the condition and potentially improve patient outcomes.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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This research had no funding sources.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

REFERENCES

1. Vélez-Santamaría V, Nedkova-Hristova V, Morales de la Prida M, Casasnovas C. Hereditary transthyretin amyloidosis with polyneuropathy: monitoring and management. *Int J Gen Med*. 2022;15:8677-8684.
2. Brailovsky Y, Rajapreyar I, Alvarez R. TTR amyloidosis: current state of affairs and promise for the future. *JACC Case Rep*. 2023;10:101759.
3. Inês M, Coelho T, Conceição I, Duarte-Ramos F, de Carvalho M, Costa J. Epidemiology of transthyretin familial amyloid polyneuropathy in Portugal: nationwide study. *Neuroepidemiology*. 2018;51(3-4):177-182.
4. Andrade C. A peculiar form of peripheral neuropathy: familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain*. 1952;75(3):408-427.
5. Kato-Motozaki Y, Ono K, Shima K, Morinaga A, Machiya T, Nozaki I, Shibata-Hamaguchi A, Furukawa Y, Yanase D, Ishida C, Sakajiri K, Yamada M. Epidemiology of familial amyloid polyneuropathy in Japan: identification of a novel endemic focus. *J Neurol Sci*. 2008;270(1-2):133-140.
6. Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol*. 2011;10(12):1086-97.
7. Çakar A, Durmuş-Tekçe H, Parman Y. Familial amyloid polyneuropathy. *Noro Psikiyatir Ars*. 2019;56(2):150-156.
8. Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. *Ther Adv Neurol Disord*. 2013;6(2):129-139.