Case Reports and Reviews

Case Report

A Novel Transthyretin Variant (p.Phe-84-Tyr) for Hereditary Transthyretin Amyloidosis with Polyneuropathy and Early Ocular Findings

Karla Cárdenas-Soto[1], Alechka Arumir-Lira[1], Alejandra Gonzalez-Duarte[1-5], Rivera-De La Parra David[3,4], Pablo Hernandez Reyes[2]

[1]*Department of Neurology, Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[2]*Department of Cardiology, Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[3]*Centro de atención integral del paciente con diabetes. Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[4]*Instituto de Oftalmología Fundación Conde de Valenciana. I.A.P., Mexico City, Mexico*
[5]*Department of Neurology, New York University School of Medicine New York, New York, New York, USA*

Correspondence

Karla Cárdenas Soto

Department of Neurology, Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán Vasco de Quiroga 15, Belisario Domínguez Secc 16, Tlalpan, 14080 Ciudad de México

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Hereditary amyloidosis; Transthyretin familial amyloid polyneuropathy; mutation; visual acuity.

Abbreviations

BASQ: Boston Autonomic Symptom Questionnaire; DLG: global longitudinal strain; hATTR: hereditary transthyretin amyloidosis; LVEF: left ventricular ejection; fraction mBMI: modified Body Mass Index; NIS: Neurological Impairment Scale OCT: Optical coherence tomography PAH: Pulmonary arterial hypertension Phe: Phenylalanine; PPV: Pars Plana Vitrectomy; RVH: Right Ventricular Hypertrophy RWT: Relative wall thickness; TTR: transthyretin Tyr: Tyrosine; VUS: variant of uncertain significance

Abstract

Hereditary transthyretin amyloidosis (hATTR) is a rare disease that affects multiple systems and is triggered by a mutation in the transthyretin (TTR) gene. This report introduces a new pathogenic variant, Phe84Tyr, identified in a patient with no known family history of amyloidosis. The patient exhibited polyneuropathy, cardiomyopathy, and significant ocular involvement, potentially a unique characteristic of this variant.

Introduction

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant disease caused by genetic mutations of the TTR gene on chromosome 18q12.1. The gene's expression results in misfolding of the tetramer due to the protein's destabilization, producing amyloid fibril formation that accumulates systematically [1]. Hereditary transthyretin amyloidosis onset and progression vary according to the mutation and other endemic factors.

The initial symptoms of hATTR amyloidosis are usually related to cardiac, neuropathic, gastrointestinal, and genitourinary symptoms, while other manifestations tend to occur in the later stages of the disease [2].

Transthyretin (TTR) is a transport protein synthesized in the liver and retinal pigment epithelial cells. The eye is a potential target organ for amyloid deposits with proteins like TTR, in which ocular involvement is part of systemic disease. The main sites of ocular amyloid accumulation are in the vitreous process, the iridocorneal angle, and the cornea, causing some complications such as visual loss, glaucoma, retinal vasculopathy, and optic neuropathy [3].

According to the *Mutations in Hereditary Amyloidosis* EURAMY database [4], 146 amyloidogenic mutations have been described. Of these, only 10% present with predominant ocular involvement at the onset. Here, we report a novel mutation with ocular involvement and peripheral neuropathy.

Case presentation

HThe patient is a 55-year-old male, born in Mexico City, but his family originates from Michoacan, Mexico. He first started experiencing symptoms at the age of 48, which included bradycardia as a result of an atrioventricular block that required the placement of a dual-chamber pacemaker in 2016. Subsequently, in 2019, the patient started with erectile dysfunction, followed by loss of visual acuity, corrected with bilateral pars plana vitrectomy (PPV) in both eyes. One year later, he developed neuropathic pain, temperature insensitivity, muscle weakness, and gait impairment without the use of assistance. His echocardiogram showed a left ventricular ejection fraction (LVEF) of 59%, diastolic dysfunction, and right ventricular hypertrophy (RVH). The genetic test with the technique of massive sequencing by amplicons (CENTOGENE, N.V.) resulted in heterozygosity in the TTR gene, proving an amino acid change of phenylalanine (Phe) for tyrosine (Tyr) in position 84 of the chromosome locus 18q12.1 (Figure 1) [5].

Patient with a modified Body Mass Index (mBMI) of 1,315.4 kg g/m2L [6]. The patient had muscle weakness in the upper and lower extremities, with areflexia. His NIS scale

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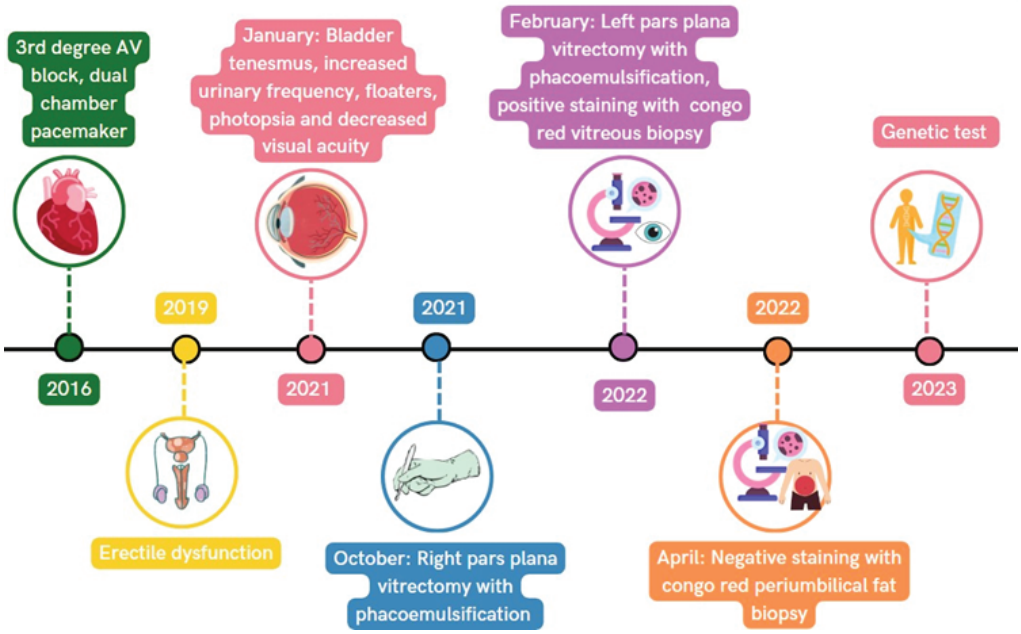

Figure 1. *Timeline of the symptoms.*

scored 41 points [7]. The Norfolk questionnaire scored 53 points showing alterations in his daily life activities, symptoms, small-fiber neuropathy, and autonomic neuropathy [8]. Autonomic dysfunction was prominent, with dizziness during exercise or position change, dyspnea, constipation, nocturia, urinary urgency, and erectile dysfunction. The Boston Autonomic Symptom Questionnaire (BASQ), a quantitative tool to assess the symptoms of systemic dysautonomia, showed a score of 107 points from a max of 410 [9].

Family History

His father and his mother were first-degree cousins. His father was diagnosed at age 64 with multiple sclerosis due to bilateral PPV, and needed a pacemaker. He was in a wheelchair during his last years.

His brother was 53 years old, and had bilateral PPV and glaucoma surgery in the right eye; however, was currently blind, the left eye only perceives shadows, and is bedridden since 2019. Regarding the cardiologic assessment, the patient has undergone a 3rd-grade complete block atrioventricular block being necessary for a pacemaker. Furthermore, the autonomic questionnaire resulted in genitourinary and gastrointestinal manifestations in addition to the sensory-motor signs previously described. The deceased reason was a heart attack during the half of 2024.

His 51-year-old brother had visual acuity of light perception after bilateral PPV and implantation of Ahmed's valve in the left eye. In the right eye, the cornea is vascularized with grade 4 atalamia and an intraocular pressure of 40 mmHg. The left eye had a normal anterior segment, and the posterior pole exhibited whitish tissue with grade 4 vitreous hemorrhage. He presented constipation, neuropathy, paresthesias, postural hypotension, palpitations, urinary retention and incontinence, muscular weakness that requires assistance with a walking stick, axonal demyelinating polyneuropathy, temperature insensitivity, and a positive genetic test for hATTR.

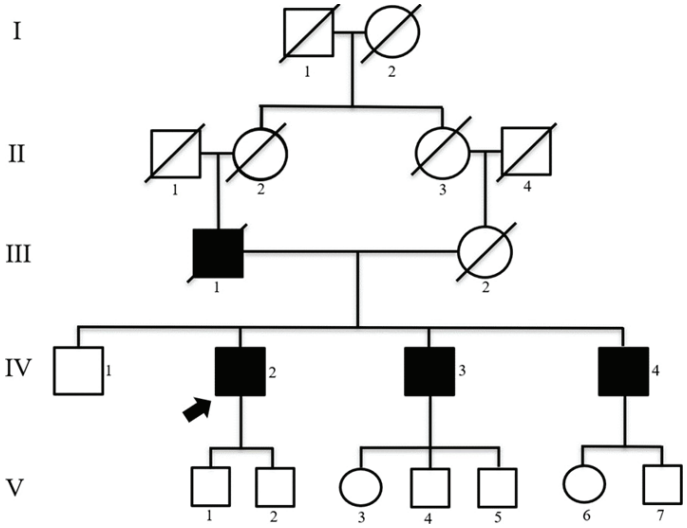

Figure 2. *Pedigree of the family. III-1(proband father): At age 64, he was diagnosed with multiple sclerosis, had bilateral PPV, and needed a pacemaker. He was in a wheelchair during his last years; III-1 (father) and III-2 (mother) were cousins; IV-2: Proband with Phe84Tyr mutation; IV-3 (brother): 53 years old, bedridden with bilateral PPV; IV-4 (brother): 51 years old, bilateral PPV and weakness.*

Ophthalmologic assessments

The eye exam showed severe amyloid deposits in the vitreous cavity that required surgical management with vitrectomy. The pathological findings in the retina were dot and blot hemorrhages, vascular loops, intermittent arterial perivascular gray deposits of amyloid, and pigmentary atrophic areas (Image 2). The optical coherence tomography (OCT) two years after the last surgery showed epiretinal amyloid deposits above the internal limiting membrane, atrophy of the inner nuclear layers, particularly the retinal nerve fiber layer, the ganglion cell layer, inner plexiform layer, and bipolar cell layers (Image

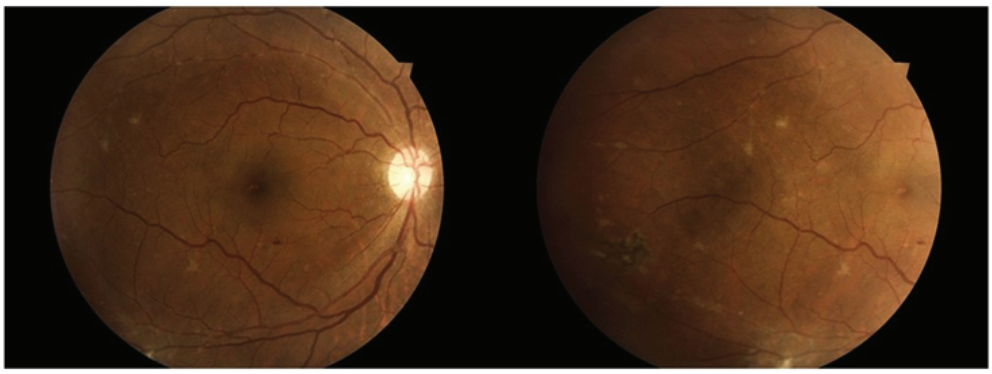

Image 1. *Clinical retina photography of the right eye with amyloid-associated retinopathy.*

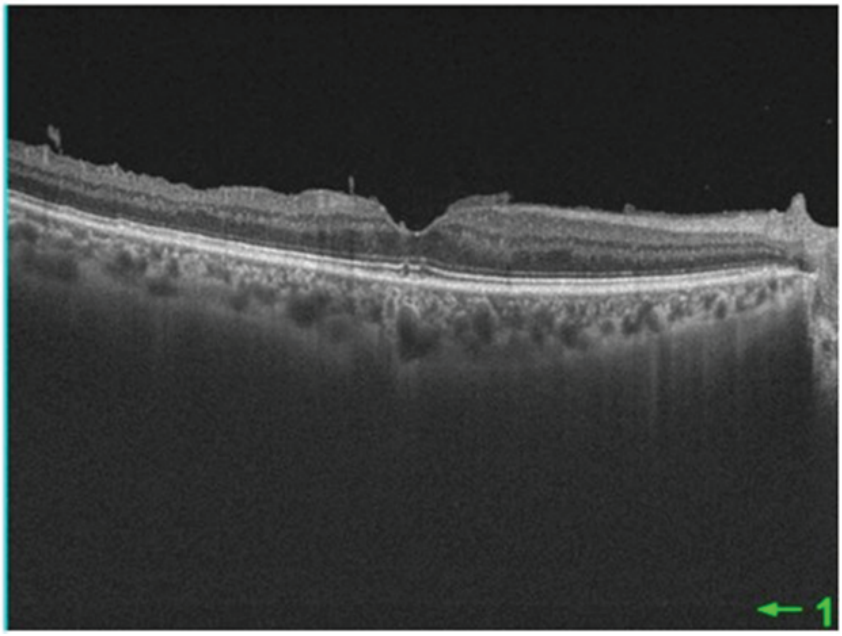

Image 2. *Optical coherence tomography with findings compatible with amyloid-associated retinopathy.*

1 OCT). These atrophic areas were randomly found in the parafovea and perifovea. Minimal photoreceptor damage was also found, measured by the discontinuity of the ellipsoid layer in the fovea. The best corrected visual acuity was 20/20 in the right eye and 20/30 in the left eye. Interestingly, there were no significant changes in the anterior segment, and the intraocular eye pressure was normal (14mmHg in both eyes).

Echocardiogram

In March 2022, the cardiologist led an echocardiogram that showed a mass of 86 g/m2 and, a relative wall thickness (RWT) of 0.45, compatible with concentric remodeling, the interventricular septal thickness of 13 mm, LVEF 3D of 59%, DLG -19.2%, the apical gradient was 0.63, and the FE/global longitudinal strain ratio was 3.0. He was diagnosed with grade 1 diastolic dysfunction with a low probability of PAH. The test did not observe other clinical data, such as myocardial granulate patterns.

Small Nerve Fiber Function

Quantitative Sensory Testing (QST) showed hypoesthesia to cold and warm temperatures, hypoalgesia for cold pain, and anesthesia for hot pain in the dorsomedial left foot (L5) and palmar aspect of the left hand (C7).

Sudomotor Function

SUDOSCAN® showed decreased conductance of 24 µS in hands and 52 µS hypohidrosis in feet.

Conclusions

This report illustrates a clinical case of ATTRv amyloidosis with the v Phe-84-Tyr, categorized as a variant of uncertain significance (VUS). The patient was the proband however, in hindsight, his family history is consistent with at least three antecessors compatible with symptoms and at least seven more suspicious cases in the next generation. Although peripheral neuropathy and cardiomyopathy were the initial manifestations, there was notable severe ocular involvement and recurrent amyloid deposition two and three years after PPV.

Only a few TTR mutations have been reported with this clinical picture. At the same time, surgical removal of the amyloid is the treatment of choice for those with significant visual loss secondary to amyloid deposits in the vitreous cavity. After the first pars plana vitrectomy (PPV), the intraocular production of mutant TTR protein is uninterrupted, resulting in continuous amyloid deposition [10], which may prompt a second ocular intervention in the following years [11].

Conflict of Interest

No interests are declared.

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