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BRIEF COMMUNICATION

Late-onset and fast progressive neuropathy and cardiomyopathy in Val32Ala transthyretin gene mutation

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Abstract

More than 100 mutations of the transthyretin gene have been reported in autosomal dominant familial amyloid polyneuropathy. This rare disease causes severe motor and sensory disability, dysautonomia, and in some patients also cardiomyopathy. The diagnosis can be challenging mainly in sporadic adult patients showing clinical, laboratory, and neurophysiological findings overlapping other forms of chronic neuropathy. We describe the clinical features and course of a patient harboring the rare p.V32A (c.155T>C) variant that was previously described in only two patients and whose pathogenicity was unclear.

Keywords Transthyretin · Neuropathy · Cardiomyopathy · Val32Ala

A 60-year-old Caucasian man was referred about 2 years after the onset of progressive weakness and cramps in the lower limbs and later impairment of the distal upper limbs. He carried the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) based on the clinical report of sensorimotor demyelinating neuropathy with temporal dispersion and high cerebrospinal fluid (CSF) protein level (124 mg/dl; normal value < 45 mg/dl; cells 4/mm^3). He was on prednisone 50 mg daily for 2 months, with no evidence of functional improvement, and on angiotensin-converting enzyme inhibitor and beta-blocker for hypertension and cardiac extrasystole.

At the time of our examination, the patient needed a cane to walk and complained of functional impairment in finger movements. He also reported reduced sweating, surges of arterial pressure, impotence, episodes of incontinence, and weight loss of 15 kg occurred over the last 6 months. The neurological evaluation showed diffuse muscle wasting, weakness of distal upper limb muscles and of both proximal and distal lower limb muscles, loss of deep tendon reflexes, reduced light touch and pinprick sensation with a stocking-glove distribution, and vibratory sensation at the distal sites of the lower limbs. He did not complain of pain. The neurologic Impairment Score in the Lower Limbs (NIS-LL) was 69.5. His body mass index (BMI) was 21.2. He did not complain of cardiac failure symptoms and had no dyspnea during daily physical activity (NYHA I).

At nerve conduction study, compound motor action potential (CMAP) of tibial and peroneal nerves and sensory nerve action potential (SNAP) of median, radial, and sural nerves were not excitable, while the median CMAP amplitudes were 2.9 mV and 2.6 mV with the conduction velocities of 31 m/s and 50 m/s, respectively. Needle electromyography showed active denervation of distal limb muscles and diffuse chronic neurogenic muscular abnormalities. Serum electrophoresis and immunofixation ruled out monoclonal gammopathy. CSF analysis confirmed the albumin-cytological dissociation (protein 181 mg/dl, cells 3/mm^3). Lumbosacral magnetic resonance imaging did not show spinal nerve root enhancement. Transthoracic echocardiogram revealed hypertrophic concentric cardiomyopathy, valvular thickening with mild mitral insufficiency, atrial enlargement, and mild pericardial effusion. Scintigraphy with technetium-99m-3,3-diphosphono-1,2

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propanodicarboxylic acid (^{99m}Tc-DPD) showed intense myocardial capture suggestive of amyloid deposition. Slit lamp examination did not show vitreous floaters.

The patient underwent subcutaneous abdominal fat tissue examination that did not find amyloid deposition, which was eventually revealed at sural nerve biopsy (Fig. 1). *TTR* sequencing demonstrated the heterozygous p.V32A (c.155T>C) mutation. Sequencing of his asymptomatic sister and sons was negative (Fig. 1).

Off-label treatment with tafamidis 20 mg daily was started. At 8-month follow-up, he showed a satisfactory functional recovery with the improvement of proximal muscle strength, balance, and trunk control, allowing him resuming the work although walking with an aid. NIS-LL reduced to 54.5 and BMI increased to 22.8.

Discussion

The p.V32A (c.155T>C) mutation was first described in 2005 in a Chinese man with autosomal dominant pattern of inheritance and uncertain pathogenicity because two siblings and three sons harboring the same mutation were asymptomatic [1]. One further Iranian-Jewish patient with late-onset progressive neuropathy was described in 2007 [2]. In two further patients whose clinical picture was not described, mass spectrometry–based proteomic analysis of sural nerve reported the unspecific deposition of serum amyloid P component and apolipoprotein E besides TTR [3].

Our clinical report strengthens the pathogenicity of p.V32A mutation, which is located in a well-established function domain of the protein and close to the commonly mutated

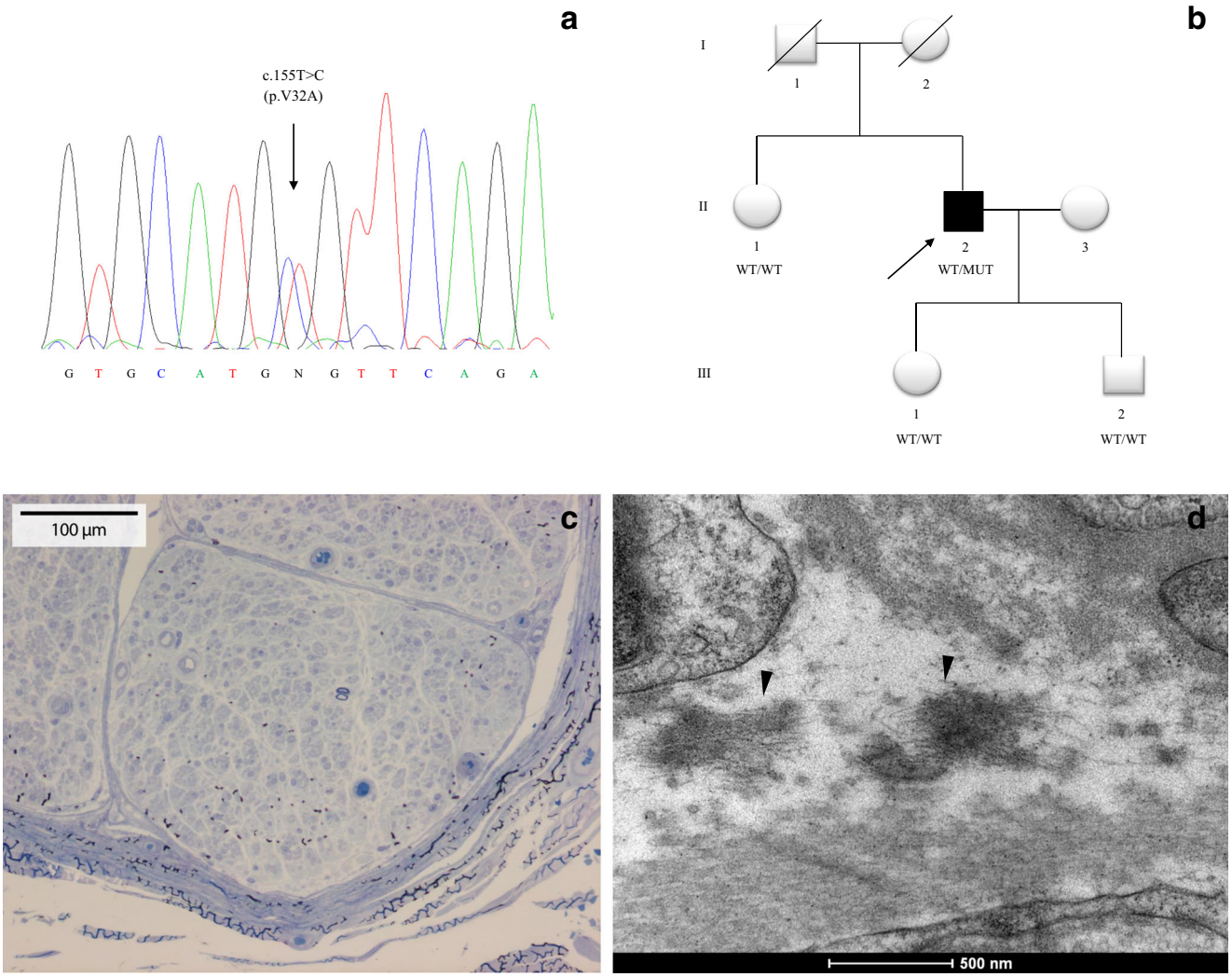

Fig. 1 **a** Electropherogram showing the heterozygous transthyretin p.V32A (c.155T>C) mutation identified in an index case. **b** Family pedigree with transthyretin gene analysis in asymptomatic sister and sons. **c** Semi-thin sections of sural nerve showing severe myelinated nerve fiber loss and **d** electron microscopy of sural nerve revealing fibrillar amyloid deposits (arrows)

codon 30 (V30 M), as a rare cause of inherited amyloidosis with possible late-onset and fast progressive course. Our patient showed a remarkably high level of CSF protein that likely led to the misdiagnosis of CIDP [4] along with the fast progression to disability, the lack of other affected family members, and the misleading interpretation of the neurophysiological examination [5]. Moreover, the patient did not complain of pain, which is common in familiar amyloid polyneuropathy. Loss of body weight, dysautonomia, and hypertrophic cardiomyopathy addressed the work-up toward the final diagnosis of TTR-related disease. Treatment with tafamidis improved the clinical picture and allowed the partial functional recovery of the patient.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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