A sporadic case of late-onset familial amyloid polyneuropathy
with a monoclonal gammopathy

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Abstract

A 77-year-old Portuguese woman reported gradual worsening of burning and numbness in the feet and hands, fatigue, anorexia, weight loss, diarrhoea and decreased visual acuity. She had a medical history of atrial fibrillation and recent episodes of dizziness and blood pressure fluctuations. There was no relevant family history. The diagnostic workup documented a severe axonal sensorimotor peripheral neuropathy, a monoclonal IgG kappa protein on serum, a severe left ventricular hypertrophy on the echocardiogram and probable vitreous deposits of amyloid on ophthalmologic examination. Pain and dysautonomia with an axonal neuropathy and multisystemic involvement raised the possibility of amyloidosis. The presence of a detectable monoclonal protein, older age at disease onset and absence of family history of disease usually suggest immunoglobulin light-chain amyloidosis. However, in this case, both the genetic testing and the biopsy of the salivary glands confirmed transthyretin amyloidosis. In those patients with a monoclonal protein, particularly in sporadic and late-onset cases, the diagnosis of transthyretin amyloidosis can be challenging, mimicking immunoglobulin light-chain amyloidosis.

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1. Introduction

Transthyretin amyloidosis (ATTR) is an autosomal dominant disease that may present with a length-dependent small-fibre sensory-motor and autonomic neuropathy, cardiomyopathy, nephropathy and ocular involvement. The most common mutation is TTR Val30Met (substitution of methionine for valine at position 30 of transthyretin) and the largest focus may be found in Portugal [1,2]. Although this mutation has incomplete penetrance, 80% of the carriers of the mutated gene develop the disease at the age of 50 in Portugal [1].

We describe a sporadic case of late-onset ATTR with a monoclonal gammopathy.

2. Case report

A 77-year-old Portuguese woman reported gradual worsening of burning and pain starting in the feet and progressing proximally, since the age of 65. Some years after symptom onset, she also developed pain in the hands and numbness in the same areas. Her medical condition slowly deteriorated with fatigue, anorexia, weight loss and diarrhoea.

She had a medical history of hypertension, atrial fibrillation and recent episodes of dizziness and blood pressure fluctuations along with decreased visual acuity on her right eye of unknown aetiology during the last years. There was no family history of neurological disease.

She was first observed at the age of 77 in our Neurology department. The neurological examination revealed mild distal limb weakness, generalized hyporeflexia, sensory loss in a stocking–glove distribution and sensory ataxia of gait.

We conducted a diagnostic workup for suspected polyneuropathy. Nerve conduction study and electromyographic testing documented a severe axonal sensorimotor peripheral neuropathy. The laboratory investigation identified a monoclonal IgG kappa protein on serum, slight increase of free light chains (kappa 42 mg/L, normal 6.7–22.4 mg/L; and lambda 30.6 mg/L, normal 8.3–27.0 mg/L) and β2 microglobulin (3.45 mg/L, normal 1.09–2.53 mg/L), slight decrease of creatinine clearance (66 mL/min) and raised NT-proBNP levels (1800 pg/mL, normal <450 pg/mL), with normal haemoglobin, sedimentation rate, calcium, urea, creatinine and free kappa/free lambda ratio. The

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Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related amyloidosis. This disorder, which is characterized by depositions of insoluble monoclonal immunoglobulin light chain fragments in various tissues, may present with a neuropathy in 20% of cases [4]. Clinically and electrophysiologically, the neuropathy associated with AL amyloidosis resembles ATTR. Additionally, some characteristic patterns of organ involvement in AL amyloidosis are indistinguishable from those in ATTR [1,2,4]. However, the presence of a detectable monoclonal protein, older age at disease onset and absence of family history of disease usually suggest AL amyloidosis rather than ATTR [1,2,4].

Nevertheless, among the general population 3.2% of patients older than 50 years may present a monoclonal gammopathy [5] and therefore a coincidental association of a monoclonal protein can occur in a small proportion of patients with ATTR [6–8]. Previous studies showed that some patients evaluated for AL amyloidosis actually had hereditary amyloidosis [6,7].

Despite the clinical similarities, the misdiagnosis of hereditary amyloidosis as AL amyloidosis may have severe implications because of different treatments, prognoses and familial implications. Definitive differentiation of AL amyloidosis and ATTR requires sequence analysis of TTR gene and/or analysis of the subunit protein comprising amyloid tissue deposits [1]. While nerve biopsy was classically used to diagnose amyloid polyneuropathy, it is an invasive procedure and there is a risk of a false-negative result due to the discontinuous distribution of amyloid deposits along the nerve axis [8]. Amyloid can also be visualized in the abdominal fat but negative biopsy findings do not rule out ATTR. On the other hand, salivary gland biopsy is a sensitive and minimal invasive method to detect amyloid deposition [9,10].

In the case of our patient, the detection of TTR Val30Met mutation and the presence of transthyretin amyloid deposits in the salivary glands allowed us to confirm the diagnosis of ATTR. Diagnosis of ATTR can be challenging, particularly of late-onset cases with no family history. Our report highlights monoclonal gammapathy as a potential diagnostic pitfall in ATTR. Therefore, a high index of suspicion is the key to an early, accurate diagnosis.

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References


