

## Diagnostic challenges in hereditary transthyretin amyloidosis with polyneuropathy: avoiding misdiagnosis of a treatable hereditary neuropathy

Hereditary transthyretin (ATTR) amyloidosis is a debilitating highly penetrant autosomal dominant disease leading to motor disability within 5 years and generally fatal within a decade without treatment.

In Italy, hereditary ATTR amyloidosis shows broad genetic and phenotypic variability.<sup>1</sup> Peripheral nerve damage can be isolated, in the absence of cardiac and autonomic involvement. Such a presentation makes it often difficult to distinguish ATTR amyloidosis-related peripheral neuropathy from other acquired peripheral neuropathies of adulthood.

Nowadays, avoiding misdiagnosis of ATTR amyloidosis is of vital importance because diverse treatment options are available, including liver transplantation and anti-amyloidogenic therapies with tafamidis or diflunisal, which all appear to be particularly effective in early disease stages.

In this study, we aimed to assess frequency, type and causes of misdiagnosis of ATTR amyloidosis in Italy.

We reviewed the medical records of 150 patients with ATTR diagnosed at the Amyloid Research and Treatment Centre between 1999 and 2013. Hundred-four (73%) were male with an average age of onset of 61 years (31–86). Most frequent mutations were Val30Met (p.Val50Met) (39; 26%), Glu89Gln (p.Glu109Gln) (28; 19%), Phe64Leu (p.Phe84Leu) (20; 13%), Ile68Leu (p.Ile88Leu) (14; 9%), Thr49Ala (p.Thr69Ala) (2; 5%). We reviewed electrodiagnostic (EDx) studies

of 19 patients misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and we assessed fulfilment of European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) EDx criteria for demyelination. We excluded from the analysis distal motor latency prolongation and distal compound motor action potential (CMAP) duration in the median nerve because of frequent median neuropathy at the wrist from carpal tunnel syndrome and conduction block in the tibial nerve for technical reasons.

ATTR amyloidosis had been misdiagnosed in 49/150 (32%) cases. Most frequently considered alternative diagnoses were CIDP, lumbar and sacral radiculopathy and lumbar canal stenosis, paraproteinaemic peripheral neuropathy, AL amyloidosis and other causes of acquired neuropathy (table 1).

Thirty (61%) patients received immune therapy, including intravenous immunoglobulins (22 patients, 45%), steroids (25 patients, 51%) and immune suppressors (6, 12%) or a combination of them (22 cases, 45%) without clinical improvement. Moreover, 11 patients (22%) previously diagnosed with lumbar spinal stenosis and radiculopathy secondary to degenerative spine disorder underwent spine surgery with no or only transient clinical improvement of symptoms.

Delay from disease onset to correct diagnosis was significantly longer in misdiagnosed patients compared with those not misdiagnosed ( $46.4 \pm 25.4$  months vs  $34.7 \pm 26$  months;  $p=0.01$ ).

In a multivariate logistic regression model, late onset after 55 years, absence of family history, male gender and absence of symptomatic heart involvement were independently associated with misdiagnosis (table 1) but not autonomic dysfunction, small fibre neuropathy symptoms and mutation type (Val30Met vs non-Val30Met).

Seventy-six patients underwent a tissue biopsy before being referred to our centre. The tissue biopsy failed to show amyloid deposit in 9/35 (25%) nerve biopsies, 15/32 (47%) fat pad biopsies, 7/16 (43%) biopsies performed in other sites, but in none of heart biopsies. A negative tissue biopsy was more frequent in misdiagnosed versus non-misdiagnosed cases (40% vs 20%), although this difference did not reach statistical significance. In nine patients with a previously negative result, fat pad biopsy was repeated in our centre and showed the presence of amyloid deposits.

EDx study at time of misdiagnosis was available for review in 19 cases. Seven of them fulfilled EFNS/PNS criteria for definite demyelinating polyneuropathy. Reduced conduction velocities were observed in 11 of them, as low as to 33 m/s at the upper limbs and 30 m/s at the lower limbs. Slow conduction velocities were invariably associated with reduced CMAP amplitudes.

Lumbar puncture was performed in 7/30 patients diagnosed with CIDP and showed cytoalbuminological dissociation with mild elevation of proteins in five cases ( $70 \pm 21.5$  mg/dL, range 49–96).

Finally, the contemporary presence of M-protein was misleading in six cases diagnosed as AL amyloidosis or paraproteinaemic peripheral neuropathy.

Our study shows that ATTR amyloidosis is still misdiagnosed in a high proportion of cases, with significant increase, up to 1.5-fold and 4 years, in diagnostic delay. Lack of family history, late onset of the neuropathy and absence of cardiac involvement were significantly more frequent in misdiagnosed patient and often misled practitioners into suspecting a different cause of acquired neuropathy. Moreover, our study identified male gender as another risk factor for ATTR misdiagnosis, although this could be due to the high proportion of patients misdiagnosed with degenerative disorders of the spine, which is more common in the male gender.

CIDP was the most frequent misdiagnosis of ATTR amyloidosis in Italy and, as suggested by previous studies,<sup>2–6</sup> demyelinating features on nerve conduction study and a mild raise of CSF proteins were found to be a relevant factor leading to disease misdiagnosis. However, it is not fully understood whether reduced conduction velocity changes represent true demyelination or are mainly secondary to loss of fast conduction large diameter fibres. There is also no obvious explanation for presence of cytoalbuminological dissociation in CSF. We speculate that a disruption of the integrity of blood–nerve barrier at the level nerve roots may occur, possibly due to amyloid deposition at this level. Interestingly, loss of tight junctions and the fenestration of endothelial cells, as well as other changes in endothelial cell morphology and number, were recently identified as common pathological finding by electron microscopy in sural nerve biopsies from patients with ATTR amyloidosis.<sup>7</sup>

Of note, spondilogenic radiculopathies and lumbar canal stenosis were also frequently suspected before the diagnosis of

**Table 1** Alternative diagnosis for patients with hereditary ATTR amyloidosis and variables associated with misdiagnosis of hereditary ATTR amyloidosis

Misdiagnoses	n=49 (%)			
Chronic inflammatory demyelinating polyneuropathy	30 (61)			
Lumbar and sacral radiculopathy and lumbar canal stenosis	11 (22)			
Paraproteinaemic peripheral neuropathy	3 (6)			
AL amyloidosis	3 (6)			
Wild-type ATTR amyloidosis	1 (2)			
Toxic peripheral neuropathy	4 (8)			
Vasculitic peripheral neuropathy	1 (2)			
Motor neuron disease	1 (2)			
Fibromyalgia	2 (4)			
Other diagnosis	2 (4)			
Multiple misdiagnosis	9 (18)			

  

Variables associated with misdiagnosis of ATTR amyloidosis	Misdiagnosed patients (n=49) (%)	Not misdiagnosed patients (n=101) (%)	OR (95% CI)*, p value	OR (95% CI)†, p value
Late onset (after 50 years)	46 (94)	74 (73)	5.59 (1.60 to 19.49), p=0.007	3.89 (1.02 to 14.81), p=0.046
Absence of family history	28 (58)	36 (36)	2.4 (1.19 to 4.83), p=0.01	2.19 (1.01 to 4.89), p=0.049
Male gender	42 (86)	69 (68)	2.78 (1.12 to 6.86), p=0.02	2.67 (1.02 to 6.98), p=0.044
Absence of heart involvement (NYHA<2)	31 (63)	46 (46)	2.05 (1.02 to 4.14), p=0.04	2.60 (1.19 to 5.66), p=0.016
Negative tissue biopsy	14/36 (39)	8/40 (20)	2.5 (0.9 to 7), p=0.08	-

\*Univariate logistic regression.

†Variables significantly associated with misdiagnosis in the univariate model were tested in a multivariate logistic regression model.

NYHA, New York Heart Association.

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ATTR amyloidosis and a not negligible proportion of these patients underwent spine surgery with partial or no benefit. These data should encourage to raise awareness in neurosurgeons and orthopaedic surgeons about the possibility of ATTR amyloidosis in patients with sensory disturbances and progressive motor deficit at lower limbs, particularly in association with bilateral carpal tunnel syndrome.

It is worth noting that, even when the diagnosis of amyloid neuropathy was suspected and a tissue biopsy performed, the absence of amyloid deposits drove clinicians to reject the diagnosis of amyloid neuropathy in 40% of them and do not perform further genetic testing. In this regard, it is well known that diagnostic sensitivity of biopsy varies greatly across different tissues and various stages of the disease and negative biopsy result does not rule out the disease, particularly in patients with typical signs and symptom. Altogether this observation emphasises the need for performance of these tests in well-equipped and experienced centres.

ATTR amyloidosis should be timely considered and TTR gene testing performed in the differential diagnosis of

unexplained late-onset sporadic progressive axonal and axonal-demyelinating polyneuropathies.

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