INVITED EDITORIAL

This Invited Editorial accompanies a Research Paper, see page 552

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 6, pages: 486–487
DOI: 10.5603/PJNNS.a2020.0102

ISSN 0028–3843

# Unravelling the colourful tapestry of hereditary transthyretin amyloid polyneuropathy in Poland

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(*Neurol Neurochir Pol 2020; 54 (6): 486–487*)

Peripheral neuropathies are common and have many potential aetiologies. Hereditary transthyretin amyloidosis (hATTRv) has received much media attention in recent years because it is a treatable cause of neuropathy, and one for which disease-modifying therapies are now available.

While the characteristics of hATTRv neuropathy are not unique, it is a multisystem disease often manifesting with additional organ involvement such as the heart, gastrointestinal tract, and autonomic nervous system. The disease is relentlessly progressive and, if left untreated, fatal [1].

The global prevalence of hATTRv related polyneuropathy is estimated to be between 5,000 and 10,000 people. Unlike Portugal, Sweden and Japan, the disease is not endemic to Poland, where the extrapolated prevalence has been estimated to be between 12 and 286 people affected, out of the country's nearly 38 million inhabitants [2]. However, these numbers are likely to be underestimates as many patients with this disease go undiagnosed or are misdiagnosed [3]. In an Italian series of 150 patients diagnosed with hATTRv at the Amyloid Research and Treatment Centre between 1999 and 2013, 32% had been misdiagnosed [4]. Furthermore, there is often a significant delay in diagnosis. In one French series of 90 patients without a known family history of the disease, the mean time to diagnosis was four years [5].

Delays in diagnosing hATTRv are most pronounced in non-endemic regions, particularly in patients lacking a clear family history of the disease. Having a high clinical suspicion for this multisystem disease and its various phenotypes is necessary to achieve an earlier diagnosis [6]. While the specific genetic mutation in the transthyretin (TTR) gene certainly impacts upon disease manifestations, the time of onset and severity, even in those with the same mutation, can differ to a striking extent, further adding to the diagnostic challenge.

To date, more than 150 TTR mutations have been described. The most common TTR mutation in Europe and Latin America is Val30Met, while Val122Ile is the most frequent in the United States [1].

Marta Lipowska and her team have now shed some light on the clinical and genetic characteristics of patients with hATTRv polyneuropathy in Poland [7].

Lipowska et al. describe 16 Polish patients with five different TTR mutations causing hATTRv polyneuropathy. The most common mutation which was identified in four unrelated families was Phe33Leu, which often presents as a mixed phenotype with both polyneuropathy and cardiomyopathy [7]. A recently published series of 10 Polish patients with hATTRv cardiomyopathy also found the Phe33Leu mutation to be the most common, suggesting that this variant may be endemic in Poland and the Baltic region [8].

Despite growing awareness of this potentially disabling and fatal disease, there are undoubtedly many patients around the world with hATTRv amyloidosis who remain undiagnosed. Lipowska's case series nicely illustrates the variety of ways in which Polish patients have manifested this disease, and the rollercoaster ride many have experienced before finally reaching an accurate diagnosis.

We must consider amyloidosis when neuropathy is accompanied by other clues such as bilateral carpal tunnel syndrome, autonomic dysfunction, gastrointestinal distress, unexplained weight loss, cardiomyopathy, renal disease, and even blindness.

With the evolution of disease-modifying therapies which can potentially halt disease progression, the early recognition and treatment of hATTRv amyloidosis remains paramount.

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