Treating TTR amyloidosis – early diagnosis is essential

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In the JNPP paper by Beauvais et al., the authors address the important question of diagnosis of early neuropathy and/or cardiomyopathy in ATTR variant carriers. ATTRv amyloidosis is an autosomal dominant systemic disorder associated with more than 120 TTR variants which particularly affect the peripheral and autonomic nervous system and the heart but can affect multiple other tissues. The treatment of this fatal disease has been revolutionised by disease-modifying therapies (DMTs) especially the TTR gene silencers (the small interfering RNAs, patisiran and vutrisiran and the antisense oligonucleotide, inotersen) which dramatically reduce the production of TTR by the liver. Currently, TTR gene silencing therapies are licensed for ATTRv neuropathy and are known to be more effective if started early in the disease course. As age of onset and penetrance varies with different ATTR variants, it is increasingly important to have accurate markers of neuropathy disease onset.

In this retrospective study, the authors studied a large cohort of 130 ATTRv carriers with normal nerve conduction studies. They used a wide range of neurological and cardiac assessments including questionnaires, physical examination, intraepidermal nerve fibre density assessment, autonomic assessment with heart rate variability, Sudoscan and mIBG scintigraphy, BNP, NT-pro BNP, troponin, echocardiogram, cardiac MRI, and bone scintigraphy and skin biopsies to search for amyloid. Using this comprehensive assessment, they diagnosed amyloid in 16.9% (22) of carriers (6.9% with overt disease and 10% with asymptomatic disease). This enabled treatment in affected patients.

In the past, there was a tendency to think of ATTRv neuropathy (previously called familial amyloid polyneuropathy) and ATTRv cardiomyopathy (previously called familial amyloid cardiomyopathy) separately and many of the therapy trials in the last decade had either a neuropathy or cardiomyopathy outcome measure as the primary outcome measure. This has delayed access to effective therapies for ATTRv, for example, gene silencers are not licensed for ATTRv cardiomyopathy alone yet. ATTRv is increasingly recognised as a systemic disease and this paper is an excellent example of comprehensively assessing the earliest manifestations of the peripheral and autonomic neuropathy as well as the cardiomyopathy in ATTRv carriers. As the authors discuss there are other novel biomarkers of early nerve involvement being explored including imaging (MRI and ultrasound), neurophysiological (QST) assessments and plasma neurofilament light chain levels. Future prospective studies will determine the optimal assessment package for ATTRv carriers and whether certain assessments are more sensitive for early diagnosis in specific variants but in the meantime the authors suggest a minimum of a skin punch biopsy and DPD scintigraphy for the detection of amyloid deposits to enable early treatment with DMTs.

Current diagnostic strategies concentrate on the diagnosis of the neuropathy or cardiomyopathy but it is notable that in both ATTRv and ATTRwt (wild type) amyloidosis, amyloid is often deposited in connective tissues especially the carpal tunnel causing carpal tunnel syndrome (CTS) as the first clinical disease manifestation. The diagnosis of isolated CTS even with histological confirmation of TTR amyloid deposition does not qualify a patient to receive any DMTs currently and it will be interesting to see if this changes in the future with better understanding of the natural history and the increasing development of effective, safe and easily delivered therapies.