Clinical phenomenology of TTR Neuropathy

J. Finsteter
Kar Messeri-Institute, Austria

Transthyretin-related (TTR) familial amyloid polyneuropathy (FAP), also known as hereditary amyloid TTR-FAP (ATTR-FAP), is an autosomal-dominant, adult-onset, rare; either isolated hereditary neuropathy or associated with multisystem involvement. TTR-FAP is characterized by irreversible, progressive, and persistent peripheral nerve damage. TTR-FAP is due to mutations in the TTR gene, of which the most frequent is p.Val30Met. Mutations in the TTR gene lead to destabilization and dissociation of TTR tetramers into variant TTR monomers, resulting in the formation of amyloid fibrils, which are consecutively deposited in various tissues including the peripheral nerves. Deposition of amyloid in the peripheral nerves leads to sensory-motor and autonomic neuropathy and several non-neuropathy specific abnormalities. Types of TTR variants, age at onset, penetrance, and clinical presentation attributable to a specific mutation may vary between countries. Phenotypic and genetic variability and non-disease-specific symptoms often delay diagnosis and lead to misdiagnosis. Suggestive of a TTR-FAP are the polyneuropathy, the positive family history, and autonomic dysfunction with gastrointestinal disturbances, cardiac involvement, carpal tunnel syndrome, unexplained weight loss, and resistance to immunotherapy. If only sensory A-delta or C-fibers are affected, small fiber neuropathy ensues and may represent a diagnostic challenge. Diagnostic tests for small fiber neuropathy include determination of epidermal nerve fiber density, laser-evoked potentials, heat- and cold-detection thresholds, and measurement of the electrochemical skin conductance. Pharmacotherapy with tafamidis, a TTR-stabilizing agent, can be highly effective if started early in the disease course. Another therapeutic option, particularly in countries where tafamidis is not yet approved is liver transplantation.