Objective markers for onset of transthyretin familial amyloid polyneuropathy in asymptomatic ser77tyr mutation carriers

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Transthyretin familial amyloid polyneuropathy (TTR-FAP) in Israel is commonly due to a Ser77Tyr mutation in the TTR gene, identified among Jewish Yemenite descents. Disease onset due to this mutation is usually after the age of 50, with penetrance of approximately 70% at the age of 70 years, progressively affecting multiple organs, and fatal within a few years. Early treatment delays disease progression but current therapies are not approved for healthy carriers. Timely diagnosis of disease onset is therefore imperative to provide effective treatment. However, disease onset criteria for asymptomatic patients or those with common, non-specific sensory symptoms are not well defined. Congo-red staining of amyloid deposits is the most objective evidence for active disease. This is effectively tested in skin punch biopsy, which is also used to diagnose small fiber neuropathy (SFN) by quantifying the intra-epidermal nerve fiber density (IENFD). However, while low IENFD may mark the pre-symptomatic phase of TTR-FAP, it is non-specific, occurring in SFN due to a variety of etiologies. We assessed for objective disease hallmarks in asymptomatic TTR Ser77Tyr mutation carriers that have active disease per Congo-red staining. Eleven carriers were identified, which were asymptomatic or had non-specific, intermittent neuropathic symptoms with normal IENFD. Two asymptomatic carriers showed presence of amyloid in skin, accompanied by moderately low IENFD and showed a median neuropathy at the wrist. An additional asymptomatic carrier with a median neuropathy at the wrist attributed to recurrent symptomatic carpal tunnel syndrome during pregnancies that clinically resolved had no amyloid deposits and normal IENFD. Eight carriers showed no median neuropathy at the wrist, two had low IENFD but no amyloid and in three, a skin biopsy was not obtained due to young age. We conclude that presence of a median neuropathy accompanied by denervation of skin in asymptomatic mutation carriers suggests active TTR-FAP disease.