Clinical and Epidemiological Characteristics of Patients With *TTR* Mutations and Polyneuropathy Manifestations of Hereditary Transthyretin Amyloidosis: Insights from A Genetic Testing Program

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Objective:
To characterize the clinical profile of patients suspected of having hereditary transthyretin amyloidosis (hATTR or ATTRv [variant]) with polyneuropathy .

Background:
hATTR is a rapidly progressive and fatal disease caused by mutations in the transthyretin gene (*TTR*) that result in the deposition of misfolded TTR protein in major organs and systems, leading to multisystem dysfunction. Patients often experience a mixed phenotype of both cardiomyopathy and polyneuropathy. Early diagnosis, which can be facilitated with genetic testing, is key to achieve optimal patient outcomes.

Design/Methods:
This study analyzed data from patients enrolled in the hATTR Compass program, a confidential genetic testing program offered in the United States (including Puerto Rico) and Canada for patients with possible hATTR with polyneuropathy symptoms or with a family history of hATTR.

Results:
Of 718 patients with a confirmed pathogenic *TTR* mutation, 345 had ≥1 polyneuropathy symptom. The mean age of symptomatic patients was 69 years, most were male (59%) and African American (70%). Few patients reported a family history of hATTR (18%). Cardiologists and neurologists referred 65% and 8% of symptomatic patients, respectively. Patients who reported on pre-diagnosis experience (10%) saw an average of 2.4 doctors before their genetic diagnosis visit. Patients presented with a variety of symptoms including heart disease (53%), sensory dysfunction (44%), bilateral carpal tunnel syndrome (26%), autonomic dysfunction (24%), and motor dysfunction (26%). Of note, patients with the p.53L mutation, generally considered a predominantly neurologic phenotype mutation, presented with heart disease.

Conclusion:
Diagnosis of hATTR amyloidosis is challenging, as many patients see multiple doctors before being diagnosed and most do not have a known family history of hATTR. Patients with hATTR often present with polyneuropathy and cardiomyopathy symptoms. Recognition of hATTR symptoms and performing genetic testing facilitates diagnosis of this debilitating and fatal disease.