

## Analysis of characteristics and prognostic impact of phenotypes in hereditary ATTR

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**Background:** Hereditary transthyretin-related amyloidosis (h-ATTR) is a systemic infiltrative disease caused by a single amino acid mutation on the transthyretin (TTR) gene, which destabilizes the protein and can determine its deposition on multiple organs, including heart and peripheral nervous system.

**Purpose:** We aimed to characterize and compare clinical, instrumental, and prognostic features of patients affected by h-ATTR by dividing the population into the disease's main phenotypes (unaffected carriers, cardiac, neurological or mixed phenotype).

**Methods:** Two hundred and eighty-five subjects of a single-centre cohort with a recognized pathogenic mutation on TTR gene were retrospectively included in the analysis. Phenotypes of disease were defined at baseline. Neurological phenotype (NP) was defined according to sensorimotor and/or autonomic dysfunction, while cardiac phenotype (CP) was defined in the presence of unexplained maximum wall thickness >12 mm and other typical echocardiographic findings. Unaffected carriers (UC) and mixed phenotypes (MP) presented none or both of the above-mentioned features, respectively.

**Results:** Two hundred and ten patients showed clinical signs of the disease, 37 (13%) with CP, 65 (23%) with NP and 108 (38%) with MP, while

75 subjects (26%) were UC. Ile68Leu was the most represented mutation (96 subjects, 34%), followed by Val30Met (21%) and Glu89Gln (13%). NP patients (mostly Val30Met) had mPND score >1 in 45% of patients, were younger at diagnosis (mean 47 years,  $p<0.001$  vs CP/MP), and sex was equally distributed. In contrast, CP patients were older at diagnosis (mean 70 years,  $p<0.001$  vs CP/MP), predominantly male (as well as in MP) with a higher incidence of tunnel carpal syndrome and a shorter time interval between onset of symptoms and diagnosis (mean 17 months,  $p<0.001$  vs CP/MP). NYHA class, ECG findings, left ventricular wall thickness and ejection fraction did not significantly differ between CP and MP. After a mean follow-up of 59 months, 98 (34%) patients died. On a Kaplan-Meier survival analysis, mean survival times were 208, 123, 150 and 95 months for UC, CP, NP and MP, respectively, with a statistically significant difference in affected patients between NP and MP ( $p=0.012$ ).

**Conclusions:** H-ATTR is a rare systemic disorder whose natural history, including age of onset, clinical characteristics and instrumental findings, is strongly influenced by primary phenotypes, ranging from the excellent prognosis of unaffected carriers to the inauspicious outcome of mixed phenotypes.

