Hereditary ATTR amyloidosis in the Netherlands: cardiac disease and age at the time of diagnosis

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Introduction

Different amyloidogenic ATTR genotypes are present in the Netherlands. The presenting symptoms usually determine the first medical specialty contact. This often results in a mono-disciplinary approach for clinical assessment and during follow-up. ATTR amyloidosis presents most often as a neuropathy, therefore patients are regularly under the supervision of only a neurologist.

The aim of this study was to investigate the degree of cardiac symptoms in patients with hereditary ATTR amyloidosis irrespective of the presentation to support the concept that a multi-disciplinary approach is necessary for disease management.

Methods

The University Medical Center Groningen (UMCG) is the national referral center for amyloidosis. In this study all 71 patients of the UMCG were included that fulfilled the criteria of a genetically and histologically proven hereditary ATTR amyloidosis (10 different genotypes).

Clinical and laboratory baseline measurements were set at the time of a first positive biopsy. For statistical analysis, two subdivisions were made. The first division was based on the prevalence of the most frequently occurring ATTR variants and the second was based on age. A neuropathy was defined on clinical findings, cardiac involvement was defined as elevated NT-proBNP levels (> 125 ng/l).

Statistics were performed using the chi-square test when a variable was dichotomous. For continuous data the Kruskal-Wallis equality-of-populations rank test, the One-way ANOVA or the Student T test were used, when appropriate. Pearson's r was used for the correlation between age at onset and NT-proBNP plasma levels.

Results

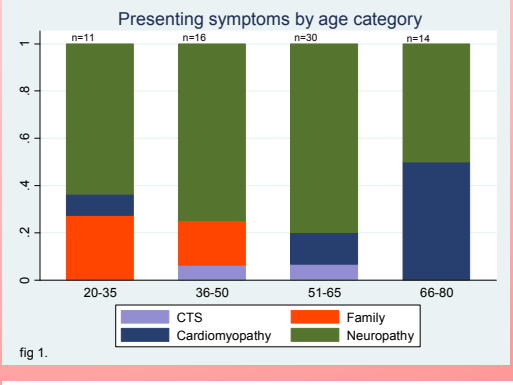

fig 1.

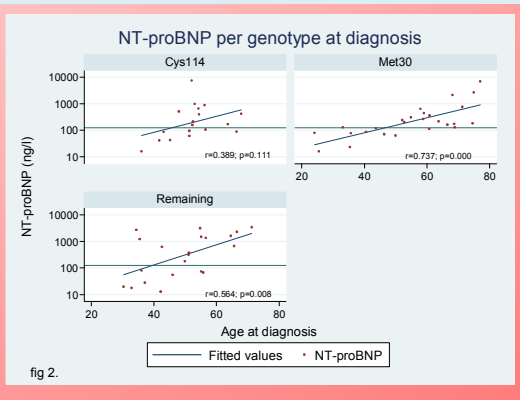

fig 2.

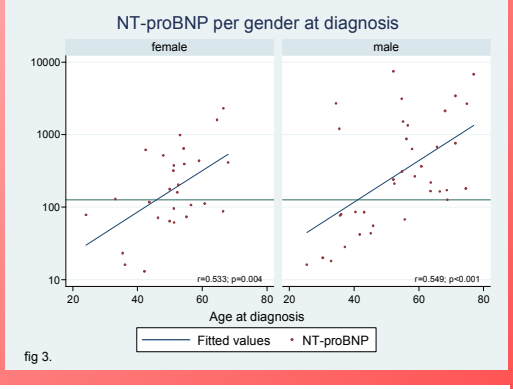

fig 3.

Based on genotype three groups with more than 20 subjects could be distinguished: Tyr114Cys (n=21), Val30Met (n=26) and a group comprising all other genotypes (n=24). Based on age four groups were distinguished : 20-35 y (n=11), 36-50 y (n=16), 51-65 y (n=30) and 66-80 y (n=14), *fig 1*. Slightly more males than females were present (55%) and the mean (SD) age at diagnosis was 52 (13) years. Mean age among the different genotype groups did not differ (p=0.359). Per age category most often a neuropathy was the presenting symptom: 20-35 y (64%), 36-50 y (75%), 51-65 y (80%) and 66-80 y (50%). The age at disease onset differed among the presentations (fig 2): neuropathy 52 $\pm$ 12 y, cardiomyopathy 64 $\pm$ 12 y, family 37 $\pm$ 8 y and CTS 49 $\pm$ 3 y (p<0.001). In all patients a correlation was found between age and the NT-proBNP plasma levels (r=0.552, p<0.001). In both the Met30 genotype group (r=0.737, p<0.001) and in the remaining group (r=0.564, p=0.007) the correlation between age and NT-proBNP levels was present, in the Cys114 group no correlation was observed (r=0.389, p=0.111), *fig 2*. The correlation between age at onset and NT-proBNP was present in males (r=0.549, p<0.001) and females (r=0.533, p=0.004), *fig 3*.

Conclusion

The older the ATTR patients are at the time of diagnosis, the more frequent cardiac involvement is present, irrespective of the initial presentation. Therefore, a multidisciplinary approach is the obvious way to manage and treat this systemic disease.