HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: EXPERIENCE FROM THE GRONINGEN AMYLOIDOSIS CENTER OF EXPERTISE

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INTRODUCTION

Pathogenic variants in the gene encoding transthyretin (*TTR*) result in hereditary ATTR (ATTRv) amyloidosis, a clinically heterogeneous multisystem disorder. The Amyloidosis Center of Expertise of the University Medical Center Groningen (UMCG) in the Netherlands, was established in the 1960s as a national referral center for diagnosis and treatment of patients with all types of amyloidosis.

OBJECTIVE

To provide an overview of the different *TTR* variants, number of families, disease characteristics, and genotype-phenotype correlations of patients and presymptomatic carriers who presented to the UMCG Amyloidosis Center of Expertise for genetic and/or clinical evaluation.

METHODS

This study retrospectively analyzed patients and presymptomatic carriers with a pathogenic TTR variant who presented to the UMCG Amyloidosis Center of Expertise for genetic and/or clinical evaluation from 1985 to 31 August 2019.

RESULTS

We identified 231 carriers of a pathogenic *TTR* variant.

Of them 71 (31%) are symptomatic ATTRv patients who are currently being treated at the UMCG. 47 carriers are asymptomatic and undergo periodical screening. A total of 96 patients (42%) are deceased, including 27 obligate carriers identified through pedigree analysis. A total of 17 carriers were either awaiting their first visit or were evaluated elsewhere (**Table 1**).

The most common pathogenic variant was TTRV30M (p.Val50Met) in 112 patients (48%). The largest single family carried the pathogenic TTRY114C p.(Tyr134Cys) variant (34 carriers). The six most common variants were TTRV30M, TTRY114C, TTRV122I p.(Val142Ile), TTRV71A p.(Val91Ala), TTRG47E p.(Gly67Glu), and TTRE89K p.(Glu109Lys) (**Table 2**).

Median age of onset for all ATTRv patients was 51.8 years.

Genotype-phenotype correlation studies are ongoing; of the 72 symptomatic TTRV30M patients (deceased and alive), 90% showed polyneuropathy, 68% autonomic neuropathy and a diagnosis of cardiomyopathy was made in 65%. Of eleven TTRV122I carriers, six (54%) had polyneuropathy (**Figure 1**).

Table 1. *Distribution of pathogenic TTR variant carriers.*

Distribution of patient status (n=231)	
Asymptomatic TTR mutation carriers	47 (20)
Symptomatic ATTRv amyloidosis	71 (31)
Deceased	69 (30)
Genotyped but not evaluated at GrACE	17 (7)
Obligate carriers	27 (12)

RESULTS

Table 2. *Distribution of TTR mutations in The Netherlands (patients alive and deceased).*

Distribution of TTR-mutations in the Netherlands (data of the Amyloidosis Center of Expertise) (n=231)		
Mutation		**N (%)**
TTRV30M	p.(Val50Met)	113 (49)
TTRY114C	p.(Tyr134Cys)	34 (15)
TTRV122I	p.(Val142Ile)	18 (8)
TTRV71A	p.(Val91Ala)	16 (7)
TTRV94A	p.(Val114Ala)	11 (5)
TTRG47E	p.(Gly67Glu)	10 (4)
TTRE89K	p.(Glu109Lys)	8 (3)
TTRS23N	p.(Ser43Asn)	3 (1)
TTRH88R	p.(His108Arg)	3 (1)
TTRA45G	p.(Ala65Gly)	3 (1)
TTRA36P	p.(Ala56Pro)	2
TTRD74H	p.(Asp94His)	2
TTRA97D	p.(Ala117Asp)	1
TTRD99N	p.(Asp119Asn)	1
TTRI107V	p.(Ile127Val)	1
TTRR103H	p.(Arg123His)	1
TTRS23R	p.(Ser43Arg)	1
TTRT119M	p.(Thr139Met)	1
TTRV122del	P.(Val142del)	1
TTRP125L	p.(Pro145Leu)	1

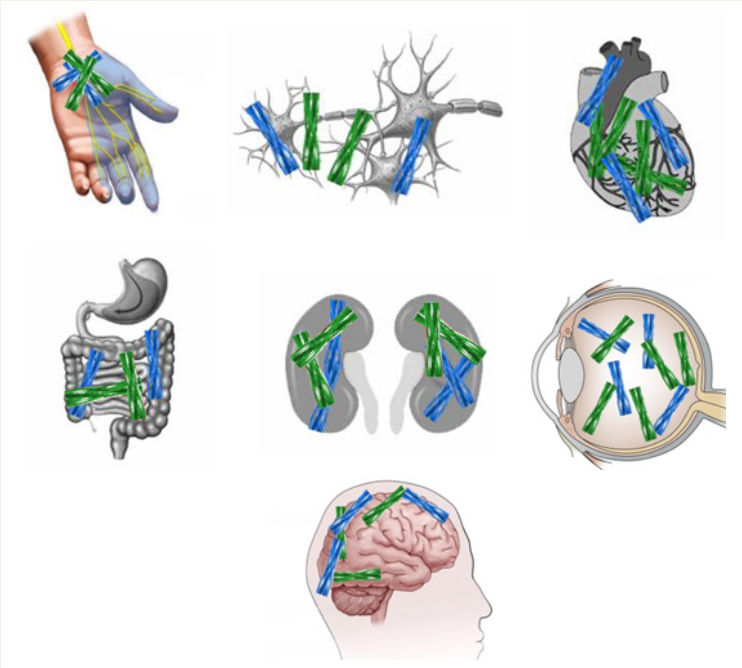

Figure 1. *Genotype - phenotype correlation studies are ongoing.*

CONCLUSIONS

Our data illustrate the phenotypical heterogeneity of ATTRv amyloidosis in a large national cohort. Variant- and organ-specific analyses of disease penetrance and prognosis are ongoing. Since ATTRv amyloidosis is a rare disorder, the size of our cohort demonstrates the importance of a Center of Expertise for a large referral area. This enables us to perform this study and to continuously improve the management of ATTRv amyloidosis patients and their presymptomatic family members.

https://www.amyloid.nl

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