Diagnostic yield of multigene panel testing in patients with suspected cardiac amyloidosis

Milou Berends[a,b], Hendrea S.A. Tingen[a,c], Alwin Tubben[a,d], Johan Bijzet[a,e], Henny H. Lemmink[a,f], Friso L.H. Muntinghe[a,b], Ewout J. Houwerzijl[a,b], Peter van der Meer[a,d], Riemer H.J.A. Slart[a,c], Reinold O.B. Gans[a,b], Bouke P.C. Hazenberg[a,g], Hans L.A. Nienhuis[a,b] and Paul A. van der Zwaag[a,f]

[a]Groningen Amyloidosis Center of Expertise, Depts of [b]Internal Medicine, [c]Nuclear Medicine and Molecular Imaging, [d]Cardiology, [e]Laboratory Medicine, [f]Genetics, [g]Rheumatology & Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

INTRODUCTION

A diagnostic algorithm for the diagnosis of cardiac amyloidosis has been established[1]. According to this algorithm, when encountering strong cardiac tracer uptake on bone scintigraphy and if immunoglobulin light chain (AL) amyloidosis is excluded, cardiac transthyretin amyloidosis (ATTR-CM) can be diagnosed.[1] Only *TTR* genotyping remains to be performed to distinguish between hereditary and wildtype ATTR-CM. However, several cases of other rare hereditary types of amyloidosis with cardiac tracer uptake on bone scintigraphy have been reported.[2-5] It is possible that these cases may be misdiagnosed as wildtype transthyretin amyloidosis (ATTRwt) if the diagnostic algorithm is followed (Figure 1).

OBJECTIVE

This study aims to determine the diagnostic yield of multigene panel analysis in patients with suspected cardiac amyloidosis. It seeks to identify other rare hereditary types of amyloidosis that might otherwise be misdiagnosed as ATTRwt amyloidosis with only *TTR* genotyping.

METHODS

All consecutive patients with suspected cardiac amyloidosis without a known family history of hereditary amyloidosis referred to the University Medical Center Groningen between 2017 and 2023 were enrolled.
All patients underwent genetic analysis using the multigene panel Amyloidosis*. The results of genetic analysis were related to the findings on bone scintigraphy (Figure 2). Strong cardiac tracer uptake was defined as Perugini grade 2-3.

*Multigene panel Amyloidosis: *APOAI, APOAII, APOCII, APOCIII, B2M, CST, FGA, GSN, IL31RA, LYZ, OSMR,* and *TTR*.

RESULTS

In total 245 unrelated patients were included, of whom fourteen had a pathogenic variant. In the group of patients with Perugini grade 2-3, ten patients had a pathogenic variant in the *TTR*-gene consistent with a diagnosis of ATTRv-CM. Two other patients with Perugini grade 2-3 had a pathogenic variant in the *APOCII*- or *GSN*-gene. However, the amyloid was mass spectrometrically typed as transthyretin, and the variants could not be related to the cardiomyopathy. In the group of patients with Perugini grade 0-1, one patient had a pathogenic variant in the *APOAI*-gene consistent with AApoAI-amyloid in fat tissue biopsy. Another patient had a likely pathogenic variant in the *OSMR*-gene, which could not be related to the cardiomyopathy (Table 1 and Figure 3).

CONCLUSIONS

- **The yield of multigene panel analysis in patients with suspected cardiac amyloidosis is 4.5%.**
- **Multigene panel analysis has no added value compared to *TTR* genotyping only in patients with suspected cardiac amyloidosis with Perugini grade 2-3.**
- **Multigene panel analysis can provide added value in patients with suspected cardiac amyloidosis and Perugini grade 0-1 in our population.**

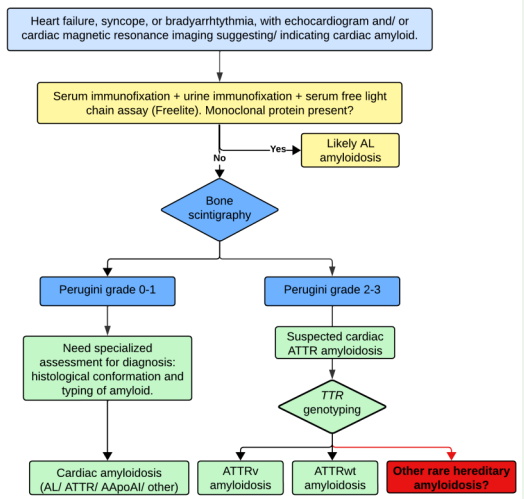

Figure 1. *Diagnostic algorithm for suspected cardiac amyloidosis, modified from Gillmore et al.[1]*

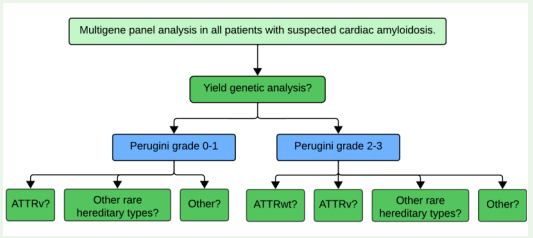

Figure 2. *Experimental diagnostic algorithm for suspected cardiac amyloidosis with multigene panel testing in all patients.*

Abbreviations

AApoAI: apolipoprotein A I amyloidosis; AApoAIV: apolipoprotein A IV amyloidosis; AL: immunoglobulin light chain amyloidosis; ATTRv: hereditary transthyretin amyloid; ATTRwt: wildtype transthyretin amyloid; CM: cardiomyopathy; GLS: global longitudinal strain; IVS: intraventricular septum thickness; IQR: interquartile range; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; TTR: transthyretin.
Multigene panel Amyloidosis: *APOAI, APOAII, APOCII, APOCIII, B2M, CST, FGA, GSN, IL31RA, LYZ, OSMR,* and *TTR*.

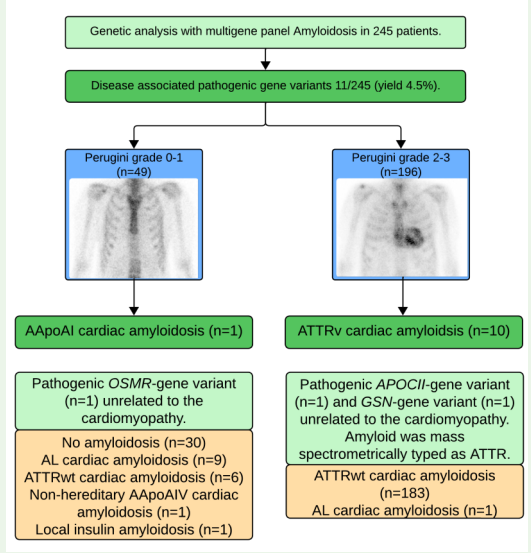

Figure 3. *Yield of multigene panel analysis (in relation to bone scintigraphy).*

Table 1. *Patient characteristics.*

	ATTRv (n=10)	ATTRwt (n=191)	Other* (n=44)
Bone scintigraphy, n (%)			
Perugini grade 0-1	0	6	43
Perugini grade 2-3	10	185	1
Gender (male/ female)	9/1	168/23	33/11
Age (years)	71±9	78±6	65±14
Gene variants	**10**	**2**	**2**
APOAI	0	0	1
APOCII	0	1	0
GSN	0	1	0
OSMR	0	0	1
TTR	10	0	0
Cardiac characteristics (median [IQR])			
NT-pro-BNP (ng/L)	2344 [1122 - 4300]	2645 [1513 - 4289]	1435 [313 - 3281]
Troponin T (ng/L)	79 [55 - 162]	48 [36 - 67]	28 [16 - 50]
GLS (%)	12 [-13 - -8]	-9 [-12 - -8]	-11 [-14 - -9]
IVS (mm)	16 [15 - 17]	17 [15 - 19]	14 [11 - 15]

Other*: no ATTRv or ATTRwt amyloidosis.

REFERENCES

1. Gillmore et al. 2016. *Circulation*; 2. Vonberg et al. 2015. *Amyloid*; 3. Yazaki et al. 2003. *Kidney Int*; 4. Quarta et al. 2013. *Amyloid*; 5. Haslett et al. 2023. *Eur Heart J Case Rep*.

University Medical Center Groningen — *G*roningen *A*myloidosis *C*enter of *E*xpertise — university of groningen

Contact: scan QR-code or email m.berends@umcg.nl