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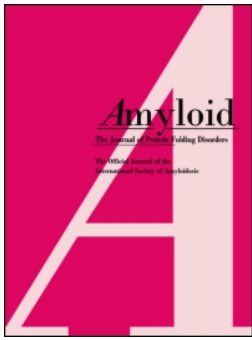
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Neurofilament light chain, a biomarker for polyneuropathy in systemic amyloidosis

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ABSTRACT

Objective: To study serum neurofilament light chain (sNfL) in amyloid light chain (AL) amyloidosis patients with and without polyneuropathy (PNP) and to corroborate previous observations that sNfL is increased in hereditary transthyretin-related (ATTRv) amyloidosis patients with PNP.

Methods: sNfL levels were assessed retrospectively in patients with AL amyloidosis with and without PNP (AL/PNP+ and AL/PNP-, respectively), patients with ATTRv amyloidosis and PNP (ATTRv/PNP+), asymptomatic transthyretin (*TTR*) gene mutation carriers (*TTR* carriers) and healthy controls. Healthy controls (HC) were age- and sex-matched to both AL/PNP- (HC/AL) and *TTR* carriers (HC/*TTR*). The single-molecule array (Simoa) assay was used to assess sNfL levels.

Results: sNfL levels were increased both in 10 AL/PNP+ patients ($p < .001$) and in 10 AL/PNP- patients ($p < .005$) compared to 10 HC/AL individuals. sNfL levels were higher in AL/PNP+ patients than in AL/PNP- patients ($p < .005$). sNfL levels were also increased in 15 ATTRv/PNP+ patients, compared to both 15 HC/*TTR* ($p < .0001$) and 15 *TTR* carriers ($p < .0001$). ATTRv/PNP+ patients with progressive PNP (PND-score > 1) had the highest sNfL levels compared to patients with early PNP (PND-score 1) ($p = .05$). sNfL levels did not differ between *TTR* carriers and HC/*TTR* individuals. In the group comprising all healthy controls and in the group of *TTR* carriers, sNfL levels correlated with age.

Conclusion: sNfL levels are increased in patients with PNP in both AL and ATTRv amyloidosis and are related to severity of PNP in ATTRv amyloidosis. sNfL is a promising biomarker to detect PNP, not only in ATTRv but also in AL amyloidosis.

Abbreviations: AL: amyloid light chain; AL/PNP+: amyloid light chain amyloidosis with polyneuropathy; AL/PNP-: amyloid light chain amyloidosis without polyneuropathy; ATTRv: hereditary transthyretin-related amyloid; ATTRv/PNP+: hereditary transthyretin-related amyloidosis with polyneuropathy; CMAP: compound muscle action potentials; EMG: electromyography; FLC: immunoglobulin free light chain; HC/AL: age- and sex-matched healthy controls for patients with amyloid light chain amyloidosis; HC/Total: all healthy controls; HC/*TTR*: age- and sex-matched healthy controls for asymptomatic *TTR* mutation carriers; NCS: nerve conduction studies; NfL: neurofilament light chain; PND: polyneuropathy disability; Simoa: single-molecule array; SNAP: sensory nerve action potential; sNfL: serum neurofilament light chain; *TTR*: transthyretin; *TTR* carrier: asymptomatic carrier of a pathogenic *TTR* mutation.

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Neurofilament light chain; systemic amyloidosis; polyneuropathy; biomarker; AL amyloidosis; ATTRv amyloidosis

Introduction

Amyloid light chain (AL) amyloidosis and hereditary transthyretin-related (ATTRv) amyloidosis are two of the main types of systemic amyloidosis [1]. In both AL and ATTRv amyloidosis the peripheral motor and sensory nerves are frequently affected, leading to a progressive axonal sensorimotor polyneuropathy (PNP) [2,3]. Detecting PNP at an early stage is important for

diagnosing new patients and is crucial for prognosis and choice of treatment in patients.

This is particularly relevant because there are several drugs available that delay or even halt disease progression of ATTRv amyloidosis. Importantly, these treatments have greater benefit when started early in the course of the disease [4–7]. In patients with AL amyloidosis, PNP is the presenting manifestation in about 10% of patients [8,9]. However, if specifically looked for, PNP can be found in

25–39% of patients [8,10,11]. The emergence or progression of PNP during follow-up should raise suspicion of disease progression. In this respect, detecting PNP is helpful in diagnosing and monitoring patients.

In patients with proven systemic amyloidosis, PNP is a clinical diagnosis for which EMG examination (often referring to nerve conduction studies and needle electromyography) is commonly used to confirm axonal degeneration [12,13]. However, this method is to some degree burdensome for patients, does not detect small fibre neuropathy, has limited sensitivity for axonal damage in early disease stages and is only part of a composite method to evaluate gradual progression of the PNP [14,15]. There is a clear clinical need for an easily applicable serum biomarker for both the early detection and follow-up of PNP in systemic amyloidosis.

Neurofilament light chain (NfL), a major cytoskeletal protein of neurons, is released into the blood and cerebrospinal fluid after axonal damage. Serum NfL (sNfL) has been shown to be a promising biomarker for PNP in several diseases affecting the peripheral nervous system [16,17]. However, the diagnostic value of sNfL as a biomarker for PNP in systemic amyloidosis has not been studied in detail. Two recent reports suggest that sNfL is increased in patients with ATTRv amyloidosis and PNP [18,19].

The objective of this study is to investigate the relationship between sNfL and PNP in patients with AL amyloidosis and to corroborate previous observations that sNfL is increased in patients with ATTRv amyloidosis and PNP.

Methods

Study participants

Patients with AL and ATTRv amyloidosis were diagnosed according to current guidelines [20,21]. Patients who visited the University Medical Center Groningen (UMCG) between January 2010 and December 2018 were assessed for eligibility based on information available in their electronic patient records in this retrospective study.

Two groups of patients with AL amyloidosis were selected: one group with PNP (AL/PNP+) ($N=10$), and a second group without PNP (AL/PNP-) ($N=10$). PNP was defined as symmetrical distal neuropathic symptoms or signs of sensory loss. The absence of PNP was defined as no neuropathic symptoms or signs of sensory loss. As peripheral neuropathy is primarily a clinical diagnosis in AL amyloidosis [22], EMGs were not routinely performed and were, therefore, not available for most of the patients. AL amyloidosis patients were treatment naïve at the time of serum sample collection. In patients with AL amyloidosis, the severity of PNP was graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grading scale [22].

Patients with ATTRv amyloidosis were included if they had PNP (ATTRv/PNP+) ($N=15$). PNP was defined as symmetrical distal neuropathic symptoms, or signs of sensory loss and had to be confirmed by EMG examination. In patients with ATTRv amyloidosis, disease severity was

assessed using the Polyneuropathy Disability Score (PND) [20]. Individuals with a pathogenic mutation in the *TTR* gene, but without any sign or symptom of disease (neurological, cardiac, gastro-intestinal and ocular), normal EMG results and the absence of amyloid in subcutaneous adipose tissue and in other available tissues, were included as asymptomatic carriers (*TTRv* carriers) ($N=15$).

Healthy controls without any signs or symptoms of PNP were age- and sex-matched for both the AL/PNP- group (HC/AL) ($N=10$) and the *TTRv* carriers (HC/*TTRv*) ($N=15$).

All procedures were in compliance with the Declaration of Helsinki. The study was approved by the institutional review board of the UMCG Registration number: 201900860.

Blood sample collection and NfL measurement

Blood samples were drawn at the outpatient clinic of the UMCG, centrifuged at 2700 rpm for 10 min at room temperature and stored within 1 h at -20°C . Samples were coded and sent blinded for clinical details to the University Hospital Basel for analysis of sNfL levels. Serum NfL was measured using the ultrasensitive single-molecule array assay (Simoa; NF-light Advantage Kit) using a HD-X platform (Quanterix).

Statistical analysis

Data were analysed at the UMCG. sNfL levels were compared using a two-sided Mann-Whitney *U* test. Correlations between sNfL and age, creatinine, Troponin T and NT-proBNP were determined using Spearman's correlation coefficient. A p value $\leq .05$ was considered significant. Statistical analysis was performed using SPSS version 23 (IBM Corp, Armonk, New York, USA). GraphPad Prism 7.02 (GraphPad Software, La Jolla, California, USA) was used to generate graphs.

Results

Clinical and demographic characteristics

Characteristics of patients are shown in Table 1. There was no age difference between AL patients with and without PNP. AL patients with PNP had higher serum levels of NT-proBNP and Troponin T compared to patients without PNP.

TTRv carriers were younger than ATTRv patients with PNP. Twelve of the ATTRv patients with PNP were treated with tafamidis. ATTRv patients had higher serum levels of NT-proBNP and Troponin T compared to *TTRv* carriers.

Genotype distribution of the ATTRv patients with PNP: TTRV30M (p.Val50Met) ($N=5$), TTRE89K (p.Glu109Lys) ($N=3$), TTRS23N (p.Ser43Asn) ($N=2$), TTRG47E (p.Gly67Glu) ($N=1$), TTRA45G (p.Ala65Gly) ($N=1$), TTRY114C (p.Tyr134Cys) ($N=1$), TTRV122del (p.Val142Del) ($N=1$) and TTRV71A (p.Val91Ala) ($N=1$). Genotype distribution of the *TTRv* carriers: TTRV30M (p.Val50Met) ($N=9$), TTRE89K (p.Glu109Lys) ($N=2$),

Table 1. Characteristics of the patients with AL and ATTRv amyloidosis, TTRv carriers and healthy controls.

	AL/PNP- (N = 10)	AL/PNP+ (N = 10)	HC/AL (N = 10)
Age, years	65 ± 3	68 ± 2	66 ± 3
Gender (male/female)	5/5	6/4	5/5
sNfL, pg/mL	22.7 (18.6–37.6)	149 (64.2–329)***	13.6 (9.8–17.3)†,§
NT-proBNP, ng/L	518 (334–652)	4462 (910–10,964)**	NA
Troponin T, ng/L	23 (11–38)	113 (44–131)*	NA
Creatinine, μmol/L	84 (77–118)	82 (69–169)	NA
FLC difference, mg/L	169 (61–356)	132 (62–570)	NA
Grade polyneuropathy, N			
1	0	9	NA
2	0	1	NA
	TTRv carriers (N = 15)	ATTRv/PNP+ (N = 15)	HC/TTRv (N = 15)
Age, years	43 ± 3	59 ± 4***	46 ± 3
Gender (male/female)	7/8	10/5	6/9
sNfL, pg/mL	6.9 (4.8–11.8)	66.4 (18.2–138)****	8.8 (6.5–11.4)§§
NT-proBNP, ng/L	56 (22–85)	586 (79–1409)****	NA
Troponin T, ng/L	4 (1–5)	30 (10–59)****	NA
Creatinine, μmol/L	76 (64–84)	73 (66–91)	NA
PND score, N			
I	0	8	NA
>I	0	7	NA

Unless stated otherwise, data are expressed as mean ± standard deviation when normally distributed and median (interquartile range) when non-normally distributed.

NA: not assessed.

AL amyloidosis without PNP (AL/PNP-) and with PNP (AL/PNP+); Healthy controls matched for age and sex with AL (HC/AL) and with TTRv carriers (HC/TTRv); ATTRv amyloidosis with PNP (ATTRv/PNP+) and asymptomatic carriers of pathogenic TTR gene mutations (TTRv carriers).

AL/PNP+ versus AL/PNP- and ATTRv/PNP+ versus TTRv carriers: * < .05, ** < .01, *** < .005, **** < .0001.

AL/PNP- versus HC/AL and ATTRv/PNP- versus HC/TTRv: † < .005.

AL/PNP+ versus HC/AL and ATTRv/PNP+ versus HC/TTRv: § < .001, §§ < .0001.

TTRY114C (p.Tyr134Cys) (N = 2), TTRV71A (p.Val91Ala) (N = 1) and TTRV94A (p.Val114Ala) (N = 1).

sNfL levels in AL amyloidosis

In AL patients with PNP the median sNfL level was 6.6-fold higher compared to AL patients without PNP and 11-fold higher compared to matched healthy controls, whereas a significant, yet smaller, increase was found in AL patients without PNP compared to matched healthy controls (Table 1 and Figure 1).

sNfL levels in ATTRv amyloidosis

In ATTRv patients with PNP the median sNfL level was 9.6-fold higher compared to TTRv carriers and 7.5-fold higher compared to matched healthy controls, whereas sNfL levels did not differ between the TTRv carriers and the matched healthy controls group (Table 1 and Figure 1).

sNfL levels and PNP disease severity

sNfL levels were increased in patients with ATTRv amyloidosis and a PND score of I compared to asymptomatic carriers. sNfL levels were increased in ATTRv patients with a PND score > I compared to those with a PND score of I (Figure 2(A)). sNfL levels were increased in patients with ATTRv amyloidosis and EMG findings indicating PNP, compared to asymptomatic carriers with normal EMG findings. sNfL levels were even higher in patients in whom no response could be elicited in the sural nerve. The

classification of patients based on EMG findings largely corresponds to the classification based on PND score (Figure 2(B)). sNfL levels correlated with the sural nerve amplitude in ATTRv patients with the amplitude set on 0 in patients in whom no response could be elicited ($r = -0.5$, $p = .05$). However, sNfL levels did not correlate with the sural nerve amplitude in TTRv carriers. sNfL levels did not correlate with digit 5 ulnar nerve amplitude. sNfL levels correlated with Troponin T levels in AL patients without PNP ($r = 0.7$, $p = .02$), in AL patients with PNP ($r = 0.8$, $p = .005$) and in ATTRv patients with PNP ($r = 0.59$, $p = .02$). sNfL levels did not correlate with NT-proBNP levels or creatinine levels.

sNfL levels and age

sNfL levels in a group comprising all healthy controls (HC/Total; median 9.9, IQR 7.9–15.0 pg/mL) correlated with age ($r = 0.57$, $p = .007$; Figure 3). A correlation was also found in TTRv carriers ($r = 0.76$, $p = .001$; Figure 3), but not in patients with AL and ATTRv amyloidosis.

Discussion

This study demonstrates that sNfL levels are increased in patients with PNP due to AL amyloidosis, and confirms previous studies showing that sNfL levels are increased and correlate with severity of PNP in patients with PNP due to ATTRv amyloidosis [18,19]. This study indicates that sNfL is a useful biomarker for PNP diagnosis and severity, not only in ATTRv, but also in AL amyloidosis.

The increased sNfL levels found in amyloidosis patients with PNP are probably the result of axonal degeneration,

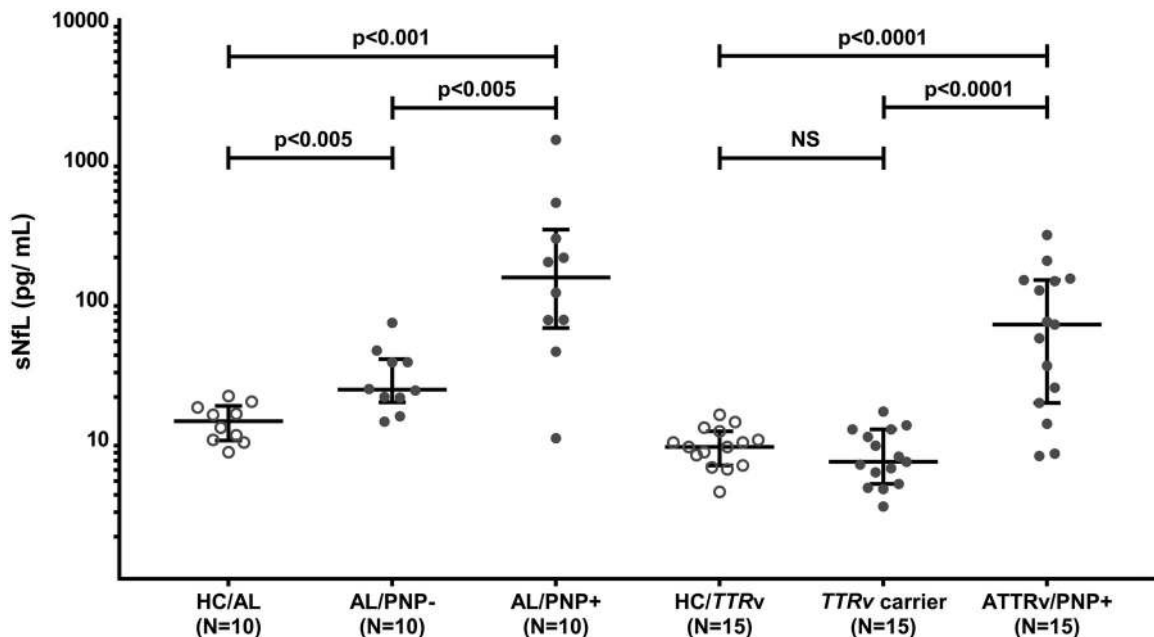


Figure 1. Serum neurofilament light chain (sNfL) concentration in patients with AL amyloidosis without (AL/PNP⁻) and with polyneuropathy (AL/PNP⁺), asymptomatic *TTRv*-gene mutation carriers (*TTRv* carriers), ATTRv amyloidosis patients with polyneuropathy (ATTRv/PNP⁺) and age- and sex-matched healthy controls (HC/AL & HC/*TTRv*). Data are presented as median with interquartile range.

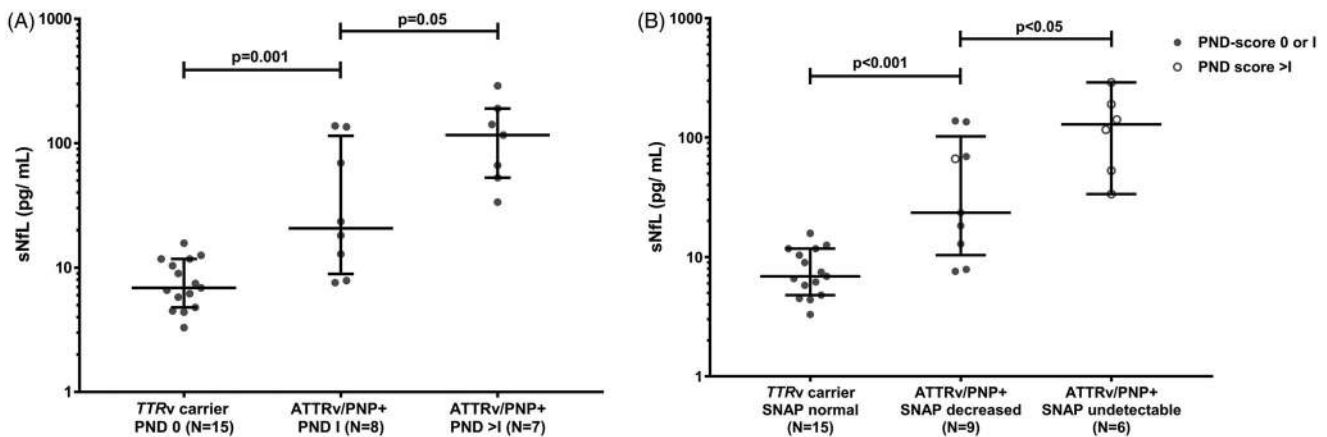


Figure 2. (A) Serum neurofilament light chain (sNfL) concentration in asymptomatic *TTRv*-gene mutation carriers (*TTRv* carrier) and ATTRv amyloidosis patients with polyneuropathy (ATTRv/PNP⁺). ATTRv/PNP⁺ patients were divided into two subgroups, those with solely sensory disturbances (polyneuropathy disability (PND) score I) and those with impaired walking capability (PND score >I). Data are presented as median with interquartile range. (B) Serum neurofilament light chain (sNfL) concentration in asymptomatic *TTRv*-gene mutation carriers (*TTRv* carrier) and ATTRv amyloidosis patients with polyneuropathy (ATTRv/PNP⁺). ATTRv/PNP⁺ patients were divided into two subgroups based on the sural sensory nerve action potential (SNAP), those with a decreased SNAP and those with an undetectable SNAP. In all *TTRv* carriers SNAP was normal. Data are presented as median with interquartile range. Unfilled circles indicate patients with a PND score >I.

which is the final common pathway leading to release of NfL in many inherited and acquired neuropathies [16,17]. Our current understanding of the underlying pathophysiological mechanism leading to axonal degeneration in amyloidosis is accumulation of amyloid fibrils within the endoneurium and around nerve blood vessels as well as direct toxicity to the nerve of prefibrillar oligomers [23,24].

Interestingly, in AL amyloidosis sNfL levels were not only increased in patients with PNP, but also in those without PNP, compared to healthy controls. These results are suggestive of subclinical axonal damage in patients with AL amyloidosis without clinically overt PNP, which could be caused by amyloid deposits or by direct neurotoxicity of free light chains (FLCs) [2]. sNfL might be a sensitive

marker for early axonal damage in a presymptomatic stage of AL amyloidosis. This might be of particular importance for diagnosis, making treatment decisions (stratification of patients at risk of developing symptomatic PNP) and monitoring of patients.

Levels of sNfL in *TTRv* carriers were comparable to sNfL levels in healthy controls, suggesting that neuropathy in this group of carriers is indeed absent. It should be noted, however, that subclinical neuropathy can already be present in the *TTRv* carriers despite the use of strict selection criteria (no signs or symptoms at all, normal EMG and a biopsy without amyloid).

Compared to the *TTRv* carriers, levels of sNfL were increased in early symptomatic patients (PND I) and more

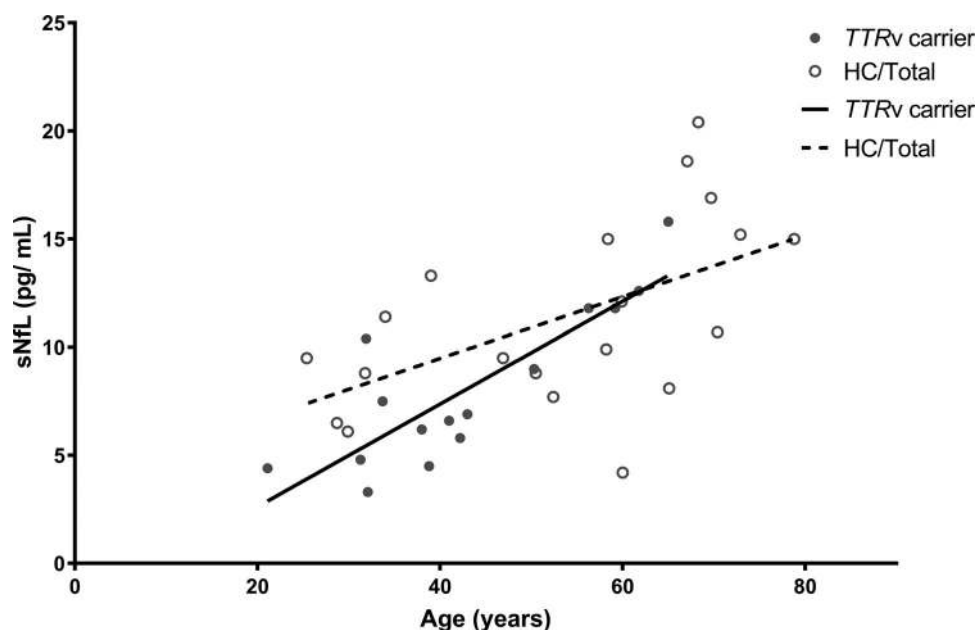


Figure 3. Correlation between the serum neurofilament light chain (sNfL) concentration and age at blood sample collection in a group comprising all healthy controls (HC/Total) and in asymptomatic *TTR* gene mutation carriers (*TTRv* carriers). The two regression lines show the linear correlations.

greatly increased in patients with progressive PNP (PND > I). Likewise, the highest sNfL levels were found in patients with the most pronounced EMG abnormalities. These findings indicate that sNfL is a sensitive biomarker for the detection of PNP in an early disease stage, and correlates with severity of PNP. The results of our cohort of patients with diverse *TTR* genotypes are in line with a recent study of two independent cohorts of ATTR-V30Met patients [18] and a recent study involving diverse *TTR* genotypes [19].

Serum levels of NT-proBNP and Troponin T were increased in patients with PNP compared to patients without PNP and *TTRv* carriers. sNfL levels correlated with Troponin T in all patient groups, but not with NT-proBNP. Troponin T is a marker for cardiac involvement and reflects disease severity in systemic amyloidosis. As neurofilament light chain is a neuron specific protein [25] we think it is unlikely that cardiac involvement itself has biased the results. However, cardiac neuronal damage might explain the correlation between sNfL and Troponin T. Further studies are warranted to confirm this finding.

The positive relationship between NfL levels and age observed in individuals without PNP (healthy controls and *TTRv* carriers) has previously been reported [17,18]. We did not find an age-dependent increase in sNfL levels in patients with PNP. In these patients with PNP the severity of disease-induced axonal degeneration has a much greater effect on sNfL levels (ranging between 10 and 1000 pg/mL) than age (ranging between 10 and 30 pg/mL) and thus masking a moderate underlying age-dependent increase.

Limitations

This study was designed to explore the applicability of serum NfL as a biomarker for PNP in systemic amyloidosis. For this purpose, a relatively small number of patients, with

and without PNP, were studied cross-sectionally. There are some limitations to this study. First, all but one of the AL/PNP + patients had grade 1 PNP. Therefore, it was not possible to study the relationship between disease severity and sNfL in patients with AL amyloidosis. Unfortunately, neuropathy impairment scores (NIS) were not available for most of the patients with AL and ATTRv amyloidosis because of the retrospective nature of our study. Using NIS scores should be considered for future prospective studies as it is a more sensitive way of quantifying neurological impairment [26]. Second, the diagnosis of PNP in patients with AL amyloidosis was based on clinical symptoms only and no objective test was used to diagnose PNP or assess disease severity. Third, the cross-sectional design of our study, leaves us unable to investigate whether NfL is a useful biomarker to detect neuronal damage in a presymptomatic stage. Fourth, which is both a strength and a weakness and inevitable given the rarity of ATTRv, the genotype distribution was quite heterogeneous and the degree of PNP varies among mutations. This limits the generalizability of the findings.

Conclusion

NfL is a promising biomarker for the detection of PNP, not only in ATTRv but also in AL amyloidosis. Serum NfL is able to detect PNP in an early symptomatic disease stage and correlates with severity of PNP. Longitudinal studies are necessary to evaluate whether NfL is a sensitive marker for the detection of both PNP and small fibre neuropathy early in an asymptomatic stage in AL and ATTRv amyloidosis.

Disclosure statement

H. L. A. Nienhuis and B. P. C. Hazenberg received consultancy fees from Pfizer and Alnylam. The other authors report no competing interests.

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