Received: 29 July 2021 | Accepted: 2 November 2021

DOI: 10.1111/ene.15176

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Changes in nerve conduction studies predate clinical symptoms onset in early onset Val30Met hereditary ATTR amyloidosis

José Castro[1,2] | Bruno Miranda[2] | Isabel de Castro[1,2] | Isabel Conceição[1,2]

[1]Department of Neurosciences and Mental Health, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal

[2]Faculdade de Medicina, Instituto de Fisiologia, Instituto de Medicina Molecular João Lobo Antunes, Universidade de Lisboa, Lisbon, Portugal

Correspondence
José Castro, Faculty of Medicine, University of Lisbon, Institute of Physiology, Av. Professor Egas Moniz, Lisbon 1649-028, Portugal.
Email: jose.zecastro25@gmail.com

Funding information
This study did not receive any funding

Abstract

Background and purpose: Hereditary amyloidosis related to transthyretin (ATTR) is a rare and progressive disease that, despite the phenotypic heterogeneity, a length-dependent sensorimotor axonal neuropathy (ATTR-PN) is the classic hallmark. Timely diagnosis is paramount for early treatment implementation.

Methods: Sixty-nine asymptomatic gene carriers (Val30Met) were assessed during a 4-year period to identify those remaining asymptomatic versus those converting to ATTRV30M-PN. Conversion to symptomatic was defined as presenting with two definite symptoms of ATTRV30M-PN. Composite neurophysiological scores of sensory (SNS), motor (MNS), and sympathetic skin response (SSRS) amplitudes were used to assess neuropathy progression. We used mixed-effects modeling and ordinal logistic regression to assess neurophysiological evolution over time.

Results: Of all asymptomatic gene carriers, 55.1% (n = 38/69) converted over the period of this analysis. The progression of the SNS relative to baseline was different between groups (asymptomatic gene carriers vs. converters), the decline being greater in the converter group (time × group interaction $p = 0.040$), starting about 2 years before symptom onset. No significant change occurred regarding MNS or SSRS. Moreover, the percentage of cases with an annual decline on the SNS of at least 25%, gradually and significantly increased in the converter group, representing a 1.92 increase in risk of developing symptoms for those with such reduction on the last evaluation.

Conclusions: A simple composite neurophysiological sum score can predict the onset of ATTRV30M-PN symptoms by as much as 2 years, highlighting the importance of a systematic follow-up of asymptomatic gene carriers, allowing a timely diagnosis, and management of symptomatic disease.

KEYWORDS
hereditary amyloidosis, nerve conduction studies, neuropathy, transthyretin

INTRODUCTION

Hereditary amyloidosis related to transthyretin (ATTR) is a rare, progressive, and life-threatening heterogeneous autosomal dominant disease that results from extracellular deposition of variant (ATTRv) [1,2] transthyretin (TTR) amyloid fibrils in multiple organs and tissues, including somatic and autonomic nerves, heart, kidney, gastrointestinal tract, eye, and central nervous system [3–6].

With a high genotype-phenotype variability, the clinical presentation includes sensory, motor, autonomic, and cardiac symptoms,

José Castro and Bruno Miranda have equally contributed to this article.

with the vast majority of patients displaying a mixed phenotype of both polyneuropathy and cardiomyopathy [5–8]. Despite its clinical heterogeneity, the polyneuropathy is a classic hallmark of this disease, particularly in the V30M genotype (ATTRV30M-PN) [1,9]. Typically, patients develop a progressive, length-dependent axonal sensorimotor and autonomic neuropathy, which classically is described as an initial involvement of sensory and autonomic small fibers and later involvement of large myelinated sensory and motor fibers [1,10]. The progressive nature of this neuropathy is well documented in untreated patients [11,12].

Significant morbidity and mortality are associated with ATTR amyloidosis, with a median survival of 10–12 years after the onset of symptoms if untreated [9]. The presence of cardiac involvement is associated with a worse prognosis, with a reduced survival (3.4 years) reported in these patients [13].

Considering the variable and insidious nature of the ATTRV30M-PN, with symptoms developing over the course of several years [5], and the irreversible tissue damage caused by the amyloid fibrils, a timely and accurate diagnosis is of paramount importance [14] for the implementation of early treatment strategies.

Several disease modifying treatment options are currently available, such as liver transplant [15], the first approved therapy, and new pharmacological treatments such as the TTR stabilizing drug tafamidis meglumine [16], the RNA interference therapeutic patisiran [7,17] and the antisense oligonucleotide inotersen [8,18] which have shown beneficial effects on disease progression and quality of life. However, early diagnosis and initiation of treatment may be important to prevent irreversible nerve and organ damage.

Determining the disease onset in previously asymptomatic gene carriers in ATTRV30M-PN is challenging due to the preferential involvement of small nerve fibers at early disease stages [1,19]. Some previous studies have looked for early markers on ATTRV30M-PN, namely neurophysiological [12,20–22], plasma neurofilament light chain [23], and advance neuroimaging techniques [24].

The main objective of this single-center, hospital-based, retrospective study was to assess if neurophysiological changes occur in asymptomatic ATTRV30M gene carriers, before the development of clinical objective symptoms, which can be used as an early disease marker.

METHODS

Participants

Data were retrospectively collected from ATTRV30M carriers followed at an ATTR amyloidosis referral center in Lisbon, Portugal during a 4-year follow-up period.

Subjects were divided in two groups. One group was comprised of asymptomatic ATTRV30M gene carriers. The other group included subjects that converted to symptomatic ATTRV30M-PN patients. The conversion to symptomatic was based on clinical criteria (Table 1), independently of neurophysiological results, considering the presence of at least two symptoms (reported by the patient by a systematic questioning) or signs related to the onset of symptomatic ATTRv amyloidosis. These are adapted from previously proposed criteria published in the literature [19].

TABLE 1 List of symptoms considered to define conversion to symptomatic ATTRV30M and its prevalence in the study population

	Prevalence, %
Paresthesia	74%
Neuropathic pain	68%
Sexual dysfunction (only in males)	33%
Constipation/diarrhea	26%
Sensory loss	24%
Unintentional weight loss	24%
Early satiety	18%
Orthostatic dizziness	13%
Impaired bladder function	3%

Note: ATTRV30M, Hereditary amyloidosis related to transthyretin Val30Met.

Subjects with concomitant diseases that could affect the peripheral nervous system were not included.

The study was approved by the local ethics committee, and written informed consent was obtained from all participants.

Neurophysiological studies

Asymptomatic gene carriers were evaluated yearly using a protocol of upper and lower limbs nerve conduction studies (NCSs).

For the converter group, NCS data were collected at symptom onset (±6 months), T_0, and four previous annual assessments, T_{-1}, T_{-2}, T_{-3}, and T_{-4}. For the asymptomatic gene carriers, data from a group of age- and gender-matched subjects, comprising five annual assessments, were collected. None of the asymptomatic subjects have developed symptoms to this date. These assessments have an interval of 1 year (±6 months).

All NCS were performed according to international accepted standards [25], using either a Keypoint Classic or a Keypoint G4 (Natus Medical Inc.).

Sensory NCS were performed antidromically, with a distance of 14–16 cm for the median nerve (recording on the third digit) and 8–10 cm for the sural nerve (recording posterior to the lateral malleolus). Motor nerve conduction studies were performed at a distance of 6–7 cm for the median nerve (recording at the abductor pollicis brevis) and 5–6 cm for the peroneal nerve (recording at the extensor digitorum brevis). Recordings were made with a bar electrode, with a 2-cm distance between active and reference electrodes. Sympathetic skin response was recorded from the palm of the right hand and the sole of the right foot with disposable electrodes. Reference electrodes were placed at the dorsum of the hand and foot, respectively. Recordings were made with the patient laying down, in a calm environment, after an electrical stimulation of 70 mA on the left median nerve at the wrist.

Because the use of composite neurophysiological scores is considered more adequate than individual NCS values to assess disease progression [26], we considered a previous methodology that seems to be consistent with the natural history of the disease [12]. Three scores were considered: sensory neurophysiological score (SNS), derived by the sum of median and sural nerves sensory amplitudes; motor neurophysiological score (MNS), derived by the sum of the compound muscle action potential amplitude from the median and peroneal nerves; and sympathetic skin response score (SSRS), derived by the sum of the palm of the hand and sole of the foot sympathetic skin response amplitude after electrical stimulation. All neurophysiological measurements were registered on one side, typically on the right side. The same examiner (J.C.) performed all measurements.

Statistical analysis

Data analysis was performed using MATLAB R2019b (MathWorks Inc.), and a value of $\alpha = 0.05$ was accepted as significant. The χ^2 statistic (for gender) and the two-sample *t* test (for age, SNS, MNS, and SSRS) were used to compare characteristics between converter and asymptomatic groups at inclusion and 48 months before. For each group, a paired-sample *t* test was used to evaluate significant changes on each composite neurophysiological score from the initial assessment (i.e., from T_{-4} to T_0). If a neurophysiological score was found to have a significant decline from the initial assessment, we further investigated its longitudinal progression (i.e., the respective score of each follow-up evaluation) with a linear mixed-effects regression (fitlmematrix function in MATLAB) to account for the repeated measures over time. The fixed-effects predictors included: a continuous variable of time in months (from T_{-4} to the respective assessment); a binary variable indicating whether the subject was part of the converter group; the interaction term between time and being part of the converter group; along with other baseline covariates such as age, gender, and the initial composite neurophysiological score (i.e., at T_{-4}). The intercept and time were subject-specific random effects. Coefficient estimates with their associated 95% confidence intervals and significance were calculated.

For each NCS measure, we also calculated the annual percentage change at inclusion (T_0) and in the previous 12 (T_{-1}), 24 (T_{-2}), and 36 (T_{-3}) months by subtracting the previous measurements from the ones obtained at each respective time, and then dividing by the respective previous values. Changes in scores (MNS, SNS, and SSRS) were then calculated by summating the percentages of change on the respective NCS measures. Three categories were arbitrarily defined as a function of the annual percentage change: a reduction ≥50%, a reduction >25% and <50%, and a reduction not >25%. An ordinal logistic regression analysis was then performed (mnrfit function) to assess differences between both symptomatic and asymptomatic groups in those three categories of annual percentage change at the different time points of evaluation while controlling for demographic characteristics.

RESULTS

A total of 69 ATTRV30M asymptomatic gene carriers (43 females) were included in the analysis. Of these, 38 converted to symptomatic patients, whereas 31 remained asymptomatic. Of the 38 subjects that converted to symptomatic, 27 had a salivary gland biopsy at the time of diagnosis (±6 months). Amyloid deposition was detected in 24 (89%) of these patients. The demographic variables of both groups at the time of inclusion (T_0), together with the

TABLE 2 Demographic characteristics and neurophysiological measures of converter and asymptomatic groups

	Patients converting from asymptomatic to symptomatic, *n* = 38	Gene carriers remaining asymptomatic, *n* = 31	*p* value
Age, years	40.6 (9.0)	43.2 (13.6)	0.341
Gender, male	12 (31.6)	14 (45.2)	0.247
Sensory neurophysiological score, μV			
T_0	59.9 (25.4)	79.8 (27.0)	0.003
T_{-4}	74.9 (28.6)*	79.0 (27.3)	0.616
Motor neurophysiological score, mV			
T_0	21.4 (4.9)	26.0 (5.0)	<0.001
T_{-4}	23.3 (5.9)	26.4 (4.9)	0.055
Sympathetic skin response score, mV			
T_0	3.0 (2.8)	3.8 (1.9)	0.173
T_{-4}	4.0 (2.5)	4.7 (3.2)	0.438

Note: Data are given as mean (SD) or *n* (%). Statistics are two-sample *t* test or χ^2 *p* values. Sensory neurophysiological score is the summation of both median and sural sensory nerve action potential amplitudes. Motor neurophysiological score is the summation of both median and peroneal compound muscle action potential amplitudes. Sympathetic skin response score is the summation of sympathetic skin response amplitude from the palm of the hand and the sole of the foot. Scores at T_0 and T_{-4} corresponds to measurements at inclusion and 48 months before, respectively.

*The *p* value <0.001 in the paired-sample *t* test between T_0 and T_{-4}.

composite neurophysiological scores at both T_0 and 4 years before (T_{-4}), are shown in Table 2. There were no significant differences between both groups regarding age and gender (all $p > 0.05$). No significant differences were observed at T_{-4} regarding neurophysiological data between both groups (all $p > 0.05$). However, the converter group had significantly worse SNS ($t_{67} = -3.15$, $p = 0.003$) and MNS ($t_{67} = -3.79$, $p < 0.001$) scores at T_0. Moreover, a significant decrease in the SNS at T_0 compared to T_{-4} was found in the converter group ($t_{24} = -4.47$, $p < 0.001$), but not in the asymptomatic group ($t_{22} = -1.04$, $p = 0.312$). We also did not observe significant differences from T_{-4} to T_0 in the MNS or the SSRS for either group (all $p > 0.05$). Given these findings, we focused our subsequent analysis on the changes across time on the SNS.

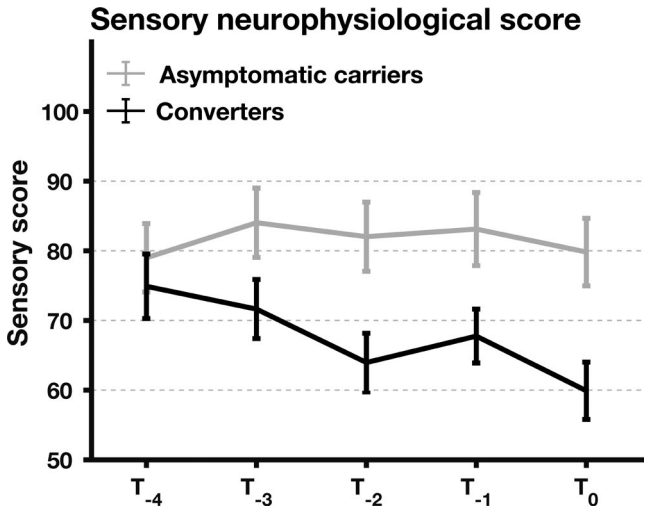

FIGURE 1 Mean (±SEM) of the sensory neurophysiological score (SNS) for both asymptomatic (in gray) and converter (in black) groups at the time of inclusion (T_0) and in the previous 12 (T_{-1}), 24 (T_{-2}), 36 (T_{-3}), and 48 (T_{-4}) months. The presented results include only data from subjects performing neurophysiological assessments at each respective time (asymptomatic group with $n = 23/28/29/29/31$ and converters with $n = 25/22/26/29/38$ for each respective time). SNS is the sum of median and sural nerves sensory amplitudes

The progression of the SNS from T_{-4} to T_0 for both groups is presented in Figure 1. The neurophysiological data in the asymptomatic group remained relatively stable with time, whereas a gradual decline was observed in the converters at T_0 (with a mean annual change in the SNS at T_{-3}, T_{-2}, T_{-1}, and T_0 of −0.67, −2.67, −0.06, and −5.97, respectively). To further quantify the longitudinal changes across groups, a linear mixed-effects regression was performed (Table 3). We found that the decline in the SNS for the converter group was significantly different from the asymptomatic group (time × converter group interaction effect with $\beta = -0.20$, $p = 0.040$) after controlling for age, gender, and the initial score values.

Next, we compared the annual percentage change on the SNS from T_{-4} to T_0 neurophysiological assessment between groups and as a function of three defined categories of reduction: ≥50%, ≥25% and <50%, and <25% (Figure 2). The converter group showed a gradual increase in percentage of cases with reduction of at least >25% on the SNS, being significantly different from the asymptomatic group at T_0 after adjusted ordinal regression ($\beta = -1.75$, $p = 0.018$). We also assessed the proportion of those who were asymptomatic (4%, 17%, and 78%) and converters (44%, 20%, and 36%) across the three respective categories of reduction when T_0 was compared to T_{-4}. Moreover, those subjects with a reduction of at least 25% within 1 year of symptom onset had 1.92 times the risk of developing symptoms and 1.48 times the risk if a similar reduction was considered in any of the two most recent observations.

DISCUSSION

In this work we retrospectively evaluated the neurophysiological data of a group of ATTRV30M asymptomatic gene carriers, separated into two groups, according to the appearance of symptoms (asymptomatic vs. converters to symptomatic). Our results showed significant changes in NCS, starting 1–2 years before the development of ATTRV30M-PN symptoms. An annual decrease of at least 25% in the SNS in the 2 years before symptom onset represented a 1.48 increase in the risk of conversion to symptomatic.

TABLE 3 Linear mixed-effects regression results for the fixed-effects variables on the longitudinal sensory neurophysiological score measurements

	Sensory neurophysiological score			
	β (SE)	**95% CI**	***t* statistic**	***p* value**
Constant	34.53 (9.85)	15.08–53.98	3.51	0.001
Age	−0.29 (0.14)	−0.55 to −0.02	−2.11	0.036
Male gender	−4.00 (3.44)	−10.79 to 2.78	−1.17	0.246
Baseline sensory neurophysiological score	0.78 (0.06)	0.66–0.91	12.40	<0.001
Converter group	−4.95 (3.94)	−12.73 to 2.84	−1.25	0.211
Time	−0.09 (0.07)	−0.22 to 0.05	−1.31	0.191
Time × converter group	−0.20 (0.10)	−0.39 to −0.01	−2.07	0.040

Note: Baseline sensory neurophysiological score corresponds to the measurements 48 months before inclusion (i.e., T_{-4}).
Abbreviations: β, coefficient estimates; CI, confidence interval.

In ATTRV30M, axonal damage to the peripheral nerves due to amyloid deposition is one of the main pathophysiological mechanisms [9]. The natural history of the disease is characterized by a rapid progressive neuropathy [10–12,27], with involvement of both large and small fibers [1]. Given the typically irreversible nature of the axonal damage to the peripheral nerves [28,29], and the greater efficacy of the current available therapies in initial disease stages [19,30], early detection of symptomatic conversion is crucial. Considering the typical presentation of ATTRV30M-PN, with impaired pain and/or temperature sensation in the feet [9], several studies have looked at early small-fiber damage [20–22]. Reduction of intraepidermal nerve fiber density in skin biopsies was reported in early symptomatic as well as asymptomatic ATTRV30M gene carriers [31]. Involvement of large myelinated fibers, detected by magnetic resonance neurography, in early symptomatic and asymptomatic ATTR gene carriers has also been reported [24]. Hence, there are cumulative data suggesting that structural changes occur in the peripheral nerves before the development of ATTRV30M-PN symptoms. Our work expands this evidence by showing functional changes in peripheral nerves, because there is a gradual decline of large myelinated sensory axons function, which can occur as early as 2 years before symptom onset (Figure 2b).

Although the SNS showed a significant decline before the conversion to symptomatic, both the MNS and the SSRS did not show the same pattern. In other neurodegenerative diseases, such as amyotrophic lateral sclerosis, loss of motor axons is, at least partly, counterweighted by compensatory reinnervation [32]. There are estimates suggesting that a loss of about 50% of the motor units in motor neuron disease patients could occur before the compound muscle action potential showed a significant change [33]. Because we are analyzing very early disease stages, compensatory reinnervation of motor units could mask early loss of motor axons in ATTR. Although most patients in this study presented with manifestations related to small-fiber impairment, and previous reports suggested a potential role of feet sympathetic skin response (SSR) amplitude as an early marker of disease in ATTR [20], the SSRS was not a predictor of conversion to symptomatic. This finding may seem somewhat contradictory; however, in our opinion, it is not unexpected. The high intra- and interindividual variability of this technique is well documented [34], limiting its role as a longitudinal marker. Recent work from our group [22] has also shown that SSR was not an independent predictor of symptom onset in ATTRV30M, whereas electrochemical skin conductance (ESC), another measure of postganglionic C-fibers, was. Moreover, ESC (and not SSR) has been found to be a promising tool to assess treatment efficacy in these patients [35]. Nonetheless, future work with ESC in ATTRV30M-PN is needed to confirm it as a good neurophysiological marker for small-fiber impairment.

In endemic areas, diagnosis of conversion to symptomatic in ATTRV30M-PN relies mainly in clinical symptoms [35,36], although some authors recommend serial evaluations, and a change from baseline in nerve conduction studies as a criterion for conversion [19]. In our experience, at the time of symptomatic conversion, most

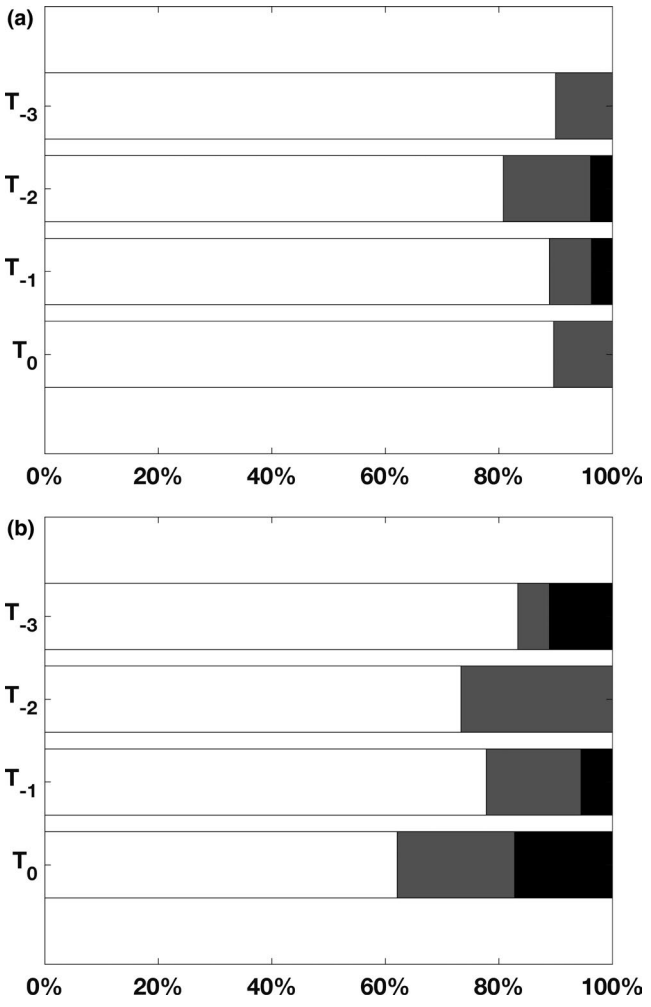

FIGURE 2 Distribution in the asymptomatic (a) and converter (b) groups of the annual percentage of change on the sensory neurophysiological score (SNS) (black for a reduction >50%, gray for a reduction >25% and <50%, and white for a reduction not >25%) at inclusion (T_0) and in the previous 12 (T_{-1}), 24 (T_{-2}), and 36 (T_{-3}) months. To note that the mean (standard deviation) overall change of SNS during the 4-year period for each individual time point was, respectively: 3.9% (24), 1.1% (33), −1.1% (31), and 1.3% (28) for the asymptomatic; and 5.6% (37), −6.4% (22), −0.8% (28), and −19.7% (29) for the converters. SNS is the sum of median and sural nerves sensory amplitudes

of ATTRV30M-PN carriers still have nerve conduction values within normal range for age and gender. In our present data, only three subjects (8%) in the converter group had abnormal sural sensory nerve action potential amplitude, considering our laboratory reference values (<8 μV). Given the determined 1.92 increase in risk of conversion after an annual decline >25% in the SNS, we propose that this magnitude of change could be used as a red flag in the evaluation of ATTRV30M asymptomatic carriers.

Our study has some limitations that should be mentioned. This is a retrospective study that collected data from asymptomatic carriers routinely followed in our clinic. Despite being our protocol, some subjects do not agree to annual observations, leading to missing data in some follow-up years. Nevertheless, 91% of our included subjects

had at least three out of five neurophysiological assessments. The results reported here are only from ATTRV30M gene carriers. Generalization of our findings to other genotypes must be done with caution. Moreover, only subjects with a neuropathic phenotype were included in the converter group. Subjects with exclusive cardiac involvement were excluded from this work, given the absence of neuropathy. Finally, we did not include other small-fiber assessments besides SSR, such as electrochemical skin conductance, due to lack of sufficient data. Given the preferential early involvement of small fibers in ATTR, longitudinal assessment with a reproducible technique, such as the electrochemical skin conductance, could be interesting.

In ATTRV30M-PN, it is critical to determine the best way of monitoring asymptomatic gene carriers for prompt diagnosis and early therapeutic intervention. Here, we show that changes in the follow-up assessments of NCS, a technique known to be reproducible, noninvasive, painless, and relatively easy to perform, could provide an invaluable contribution for the early identification of carriers at risk. Our findings, in particular an annual decline >25% in the SNS, could be a clinical marker predating symptom onset in previously asymptomatic carriers, allowing early implementation of adequate therapies.

CONFLICTS OF INTEREST

José Castro declares no conflicts of interest. Bruno Miranda declares no conflicts of interest. Isabel de Castro declares no conflicts of interest. Isabel Conceição declares no conflicts of interest.

AUTHOR CONTRIBUTIONS

José Castro: Conceptualization (lead), – curation (lead), formal analysis (equal), investigation (equal), methodology (lead), writing–original draft (equal). **Bruno Miranda:** Conceptualization (equal), – curation (equal), formal analysis (lead), software (lead), writing–original draft (equal). **Isabel de Castro:** – curation (supporting), investigation (supporting), methodology (supporting), writing–review & editing (supporting). **Isabel Maria Conceição:** Conceptualization (equal), investigation (equal), methodology (equal), supervision (lead), validation (lead), visualization (equal), writing–review & editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

José Castro https://orcid.org/0000-0001-8984-475X
Bruno Miranda https://orcid.org/0000-0003-4660-6051

REFERENCES

1. Said G, Ropert A, Faux N. Length-dependent degeneration of fibers in Portuguese amyloid polyneuropathy: a clinicopathologic study. *Neurology*. 1984;34(8):1025-1032.
2. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. *Amyloid*. 2018;25(4):215-219.
3. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
4. Sekijima Y, Ueda M, Koike H, Misawa S, Ishii T, Ando Y. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom clusters and treatment algorithm. *Orphanet J Rare Dis*. 2018;13(1):6.
5. Conceicao I, Gonzalez-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21(1):5-9.
6. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. *Nat Rev Neurol*. 2019;15(7):387-404.
7. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21.
8. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):22-31.
9. Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol*. 2011;10(12):1086-1097.
10. Luis ML. Electroneurophysiological studies in familial amyloid polyneuropathy–Portuguese type. *J Neurol Neurosurg Psychiatry*. 1978;41(9):847-850.
11. Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. *Neurology*. 2015;85(8):675-682.
12. Conceicao I, Miranda B, Castro J, de Carvalho M. Hereditary amyloidosis related to transthyretin V30M: disease progression in treated and untreated patients. *Eur J Neurol*. 2018;25(11):1320-e115.
13. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J*. 2012;33(9):1120-1127.
14. Plante-Bordeneuve V. Update in the diagnosis and management of transthyretin familial amyloid polyneuropathy. *J Neurol*. 2014;261(6):1227-1233.
15. Holmgren G, Steen L, Ekstedt J, et al. Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met30). *Clin Genet*. 1991;40(3):242-246.
16. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79(8):785-792.
17. Adams D, Polydefkis M, González-Duarte A, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol*. 2021;20(1):49-59.
18. Brannagan TH, Wang AK, Coelho T, et al. Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. *Eur J Neurol*. 2020;27(8):1374-1381.
19. Conceicao I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations. *Amyloid*. 2019;26(1):3-9.
20. Conceicao I, Costa J, Castro J, de Carvalho M. Neurophysiological techniques to detect early small-fiber dysfunction in transthyretin amyloid polyneuropathy. *Muscle Nerve*. 2014;49(2):181-186.
21. Lefaucheur JP, Ng Wing Tin S, Kerschen P, Damy T, Plante-Bordeneuve V. Neurophysiological markers of small fibre neuropathy in TTR-FAP mutation carriers. *J Neurol*. 2013;260(6):1497-1503.
22. Castro J, Miranda B, Castro I, de Carvalho M, Conceicao I. The diagnostic accuracy of Sudoscan in transthyretin familial amyloid polyneuropathy. *Clin Neurophysiol*. 2016;127(5):2222-2227.

23. Maia LF, Maceski A, Conceicao I, et al. Plasma neurofilament light chain: an early biomarker for hereditary ATTR amyloid polyneuropathy. *Amyloid*. 2020;27(2):97-102.
24. Kollmer J, Hund E, Hornung B, et al. In vivo detection of nerve injury in familial amyloid polyneuropathy by magnetic resonance neurography. *Brain*. 2015;138(Pt 3):549-562.
25. Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle*, 4th edn. Oxford University Press; 2013.
26. Herlenius G, Wilczek HE, Larsson M, Ericzon BG, Familial Amyloidotic Polyneuropathy World Transplant R. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. *Transplantation*. 2004;77(1):64-71.
27. Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain*. 1952;75(3):408-427.
28. Adams D, Samuel D, Goulon-Goeau C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. *Brain*. 2000;123(Pt 7):1495-1504.
29. de Carvalho M, Conceiçato I, Bentes C, Sales Luis ML. Long-term quantitative evaluation of liver transplantation in familial amyloid polyneuropathy (Portuguese V30M). *Amyloid*. 2009;9(2):126-133.
30. Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. *Ther Clin Risk Manag*. 2020;16:109-123.
31. Masuda T, Ueda M, Suenaga G, et al. Early skin denervation in hereditary and iatrogenic transthyretin amyloid neuropathy. *Neurology*. 2017;88(23):2192-2197.
32. Swash M, Ingram D. Preclinical and subclinical events in motor neuron disease. *J Neurol Neurosurg Psychiatry*. 1988;51(2):165-168.
33. Bromberg MB, Brownell AA. Motor unit number estimation in the assessment of performance and function in motor neuron disease. *Phys Med Rehabil Clin N Am*. 2008;19(3):509-532, ix.
34. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response: basic mechanisms and clinical applications. *Clin Auton Res*. 2003;13(4):256-270.
35. Adams D, Ando Y, Beirao JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol*. 2020;268(6):2109-2122.
36. Benson MD, Dasgupta NR, Rao R. Diagnosis and screening of patients with hereditary transthyretin amyloidosis (hATTR): current strategies and guidelines. *Ther Clin Risk Manag*. 2020;16:749-758.

How to cite this article: Castro J, Miranda B, de Castro I, Conceição I. Changes in nerve conduction studies predate clinical symptoms onset in early onset Val30Met hereditary ATTR amyloidosis. *Eur J Neurol*. 2022;29:826–832. doi:10.1111/ene.15176

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