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Electrophysiological Monitoring of Asymptomatic Transthyretin Mutation Carriers

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ABSTRACT

Introduction/Aims: It is imperative to screen asymptomatic carriers of transthyretin (TTR) mutations to initiate treatment early. The protocol for repeated electrodiagnostic (EDX) assessments over time lacks standardization. Our aim was to report the electrophysiological evolution of a cohort of asymptomatic carriers and to determine which biomarkers were most sensitive to change.

Methods: We performed a retrospective review of medical records of asymptomatic carriers identified by screening families with amyloid neuropathy. Carriers who underwent two EDX assessments with a minimum 1-year interval between studies were selected. EDX included analysis of median, ulnar, tibial, fibular and sural nerves, motor unit number index (MUNIX), electrochemical skin conductance, sympathetic skin response, and heart rate variability on deep breathing. Measurements were compared at first and second examinations.

Results: Twenty-three carriers were included with a median age of 49 years (interquartile range 37–58). Median time between examinations was 3 years (2–4). Compound muscle and sensory nerve action potential (CMAP and SNAP) amplitudes, nerve conduction velocities, autonomic small fiber testing and MUNIX remained stable except for motor distal latency of the median nerve (+0.07 ms/year) and CMAP duration of the ulnar (+0.10 ms/year) and fibular (+0.12 ms/year) nerves. The CMAP duration of the ulnar nerve was the most sensitive biomarker to change when performed within 10 years preceding the age of the youngest case in the family, with a standardized response mean of 0.91.

Discussion: Nerve conduction parameters remain relatively stable in asymptomatic TTR carriers. Changes can only be detected using multimodal and extensive electrophysiological tests.

1 | Introduction

Familial amyloid polyneuropathy (FAP) is an inherited genetic disorder characterized by an autosomal dominant mutation in the transthyretin (TTR) gene. This mutation leads to the formation of amyloid deposits in tissues, predominantly affecting the heart and peripheral nerves. These manifestations often result in severe disability and a survival of approximately 10 years from time of symptom onset [1]. Treatment options, including liver transplantation and drugs limiting amyloidosis,

Abbreviations: ADM, abductor digiti mini; APB, abductor pollicis brevis; CMAP, compound muscle action potential; EDX, electrodiagnostic testing; ESC, electrochemical skin conductance; FAP, familial amyloid polyneuropathy; HRV, heart rate variability on deep breathing; MUNIX, motor unit number index; SNAP, sensory nerve action potential; SSR, sympathetic skin response; TA, tibialis anterior; TTR, transthyretin.

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have provided stabilization for patients. However, early diagnosis and intervention are crucial to minimize functional disability.

With available treatments, there is a growing interest in screening asymptomatic individuals carrying the TTR mutation within families diagnosed with FAP [2]. It is imperative to monitor asymptomatic carriers to detect the disease onset at the earliest possible stage [3]. Currently, there are no generally-accepted guidelines for the monitoring of asymptomatic carriers, although it is acknowledged that such surveillance is crucial, especially in the decade leading up to the age of the youngest known case of FAP within the family [4]. Late diagnosis increases the risk of disease-related complications, while starting a treatment as soon as the mutation is detected, before symptoms appear, exposes carriers to potentially long-term effects of drugs with unknown outcomes. For instance, recent drugs inhibit hepatic synthesis of TTR or pre-albumin, a protein involved in transporting thyroid hormones and vitamin A [5, 6]. While the absence of pre-albumin is well tolerated over a few years, long-term effects over several decades remain unknown.

The factors that can predict the transition from the asymptomatic to the symptomatic form of the disease have not been conclusively identified [7]. The follow-up protocol for asymptomatic carriers is not standardized, and there is a lack of clarity regarding the nature and frequency of electrophysiological examinations. The objective of this study was to analyze changes in electrophysiological parameters during the follow-up of asymptomatic TTR mutation carriers and to detect the biomarker most sensitive to change over time.

2 | Methods

This research encompassed all asymptomatic individuals carrying the TTR mutation (asymptomatic carriers) who underwent two electrophysiological assessments with a minimum one-year interval between 2017 and 2023 at the Referral Centre for Neuromuscular Diseases and ALS of Marseille, France. The TTR mutations were identified by screening families of patients diagnosed with FAP in the department. The carriers gave informed consent for this study, which was approved by the local ethics committee (PADS 23-118).

Carriers had to be asymptomatic both at the first and at the second examinations, meaning absence of symptoms compatible with FAP, normal neurological clinical examination, and normal cardiological assessment (echocardiography, electrocardiography, troponin, NT-proBNP).

Age, sex, TTR mutation, age of youngest FAP case in the family and time between electrophysiological examinations were collected.

Electrodiagnostic testing (EDX) included nerve conduction studies, motor unit count and small-caliber autonomic fiber study performed on a Medtronic Keypoint G4 device. EDX of the median, ulnar, tibial and fibular motor nerves and the sural, median and ulnar sensory nerves was performed on the non-dominant side. Distal motor amplitudes, distal motor latencies, conduction velocities, F-wave latencies, distal compound muscle action potential (CMAP) duration, sum of the distal CMAP amplitudes, sum of the distal CMAP amplitudes of the lower limbs (tibial and fibular nerves), sum of the amplitudes of the sensory nerve action potentials (SNAPs) (median, ulnar and sural nerves) and sensory conduction velocities were collected. For median motor nerve assessment, anatomical landmarks were used and the distance between the stimulating and recording electrodes was measured for each study participant.

Motor units were counted using the MUNIX (motor unit index) method on the abductor digiti mini (ADM), abductor pollicis brevis (APB) and tibialis anterior (TA) muscles of the non-dominant side. The sum of the MUNIX and MUSIX (motor unit size index) of the ADM, APB and TA muscles were collected [8].

The small-caliber autonomic fibers were analyzed through electrochemical skin conductance (ESC) measured by Sudoscan (Impeto Medical, Issy-les-Moulineaux, France), sympathetic skin response (SSR) and heart rate variability on deep breathing (HRV) [9, 10].

Electrophysiological parameters, including the durations of the CMAP of the ulnar nerve were compared with findings from a previous study that involved 12 healthy subjects [11] and 11 symptomatic TTR gene mutation carriers followed in the department for a familial amyloid polyneuropathy (FAP).

Quantitative data were expressed as median (interquartile range), qualitative data as number (%). Measurements at first and second examinations were compared using the non-parametric Wilcoxon test for paired data, and the Mann–Whitney test for comparisons between asymptomatic carriers, symptomatic TTR gene mutation carriers and healthy subjects. Correlations were calculated using the Spearman's non-parametric test. Intrinsic biomarker variability was assessed by calculating the standardized response mean (SRM = mean/standard deviation). An SRM greater than 0.80 defines a variable that is highly sensitive to change over the course of repeated measurements [12]. Statistical analyses were performed using Graph Pad Prism 5 (GraphPad Software, San Diego, CA, USA) and SPSS statistics version 20 (IBM, Armonk, NY). A p-value < 0.05 was considered significant in bivariate analysis.

3 | Results

3.1 | Variation of Electrophysiological Data Between Two Examinations in Asymptomatic Carriers

We included 23 asymptomatic carriers of a TTR mutation, whose main characteristics are presented in Table 1. Ten asymptomatic carriers had a V30M mutation, two were of Portuguese origin but were born in France.

EDX, MUNIX and autonomic small fiber analysis results were within normal limits for all the tests.

There was no significant difference between the two measurements for MUNIX, electrochemical skin conductance and HRV

TABLE 1 | Characteristics of the asymptomatic carriers.

Patient	Sex	TTR mutation	Age at first EDX (AFE) years	Age of earliest familial onset (AEFO) years	Difference between AFE and AEFO years	Time between 2 EDX years
1	F	Val30Met	26	30	**−4**	1.0
2	F	Val30Met	26	65	−38	2.5
3	M	Val30Met	62	65	**−2**	2.2
4	F	Val30Met	33	65	−31	2.2
5	F	Val30Met	33	Unknown	Unknown	2.0
6	M	Val30Met	49	70	−20	1.3
7	M	Val30Met	51	70	−19	1.3
8	M	Val30Met	57	70	−12	1.3
9	F	Val30Met	53	75	−21	1.8
10	M	Phe64Leu	46	69	−22	4.0
11	M	Val30Met	38	60	−21	4.0
12	F	Ile107Val	39	65	−25	1.0
13	M	Phe64Leu	64	Unknown	Unknown	1.6
14	F	Ala36Pro	34	56	−21	3.0
15	M	Val122Ile	41	35	**+6**	1
16	M	Val30Met	56	65	**−8**	1.3
17	M	Val30Met	24	65	−40	3.0
18	F	Val30Met	58	65	**−6**	1.1
19	F	Glu89Gln	69	50	**+19**	2.0
20	F	Glu89Gln	66	50	**+16**	2.0
21	F	Val30Met	56	68	−11	5.0
22	F	Phe64Leu	66	69	**−2**	4.9
23	F	Phe64Leu	48	72	−24	2.0
Total	10 M/13F	14 V30M (61%)	49 (37–58)	65 (60–69)	−19 (22–5)	3 (2–4)

Note: Values in bold in the penultimate column correspond to the 8 carriers for whom the first examination was carried out in the 10 years prior to or at any time after the age of the youngest case in the family.

(Table S1). Among all the analyzed data, only distal motor latencies (DML) of the median nerve and CMAP durations of the ulnar and fibular nerves were significantly different between the two examinations (Figure 1).

DML of the median nerve increased by 0.18 ms (0.01–0.41) between the two examinations, that is, 0.07 (0.002–0.163) ms/year. This variation was not due to a variation in the positioning of the recording electrodes on the APB muscle; there was no significant correlation between the variation of the DML and the variation of the distance between the recording electrodes and the stimulation site at the wrist ($r = -0.6$; $p = 0.80$). The duration of the CMAP of the fibular nerve increased by 0.40 ms (0–0.93) between the two EDX, that is, 0.12 (0–0.3) ms/year. The duration of the CMAP of the ulnar nerve increased by 0.45 ms (0.1–1) between the two EDX, that is, 0.10 (0.05–0.33) ms/year.

Variations of the DML of the median nerve and of the CMAP duration of the ulnar and fibular nerves were not correlated with age, interval between the two EDX, V30M mutation, or age of the youngest case of FAP in the family (Figure 2).

SRM was 0.57 for the DML of the median nerve, 0.47 for the fibular nerve CMAP duration and 0.86 for the ulnar nerve CMAP

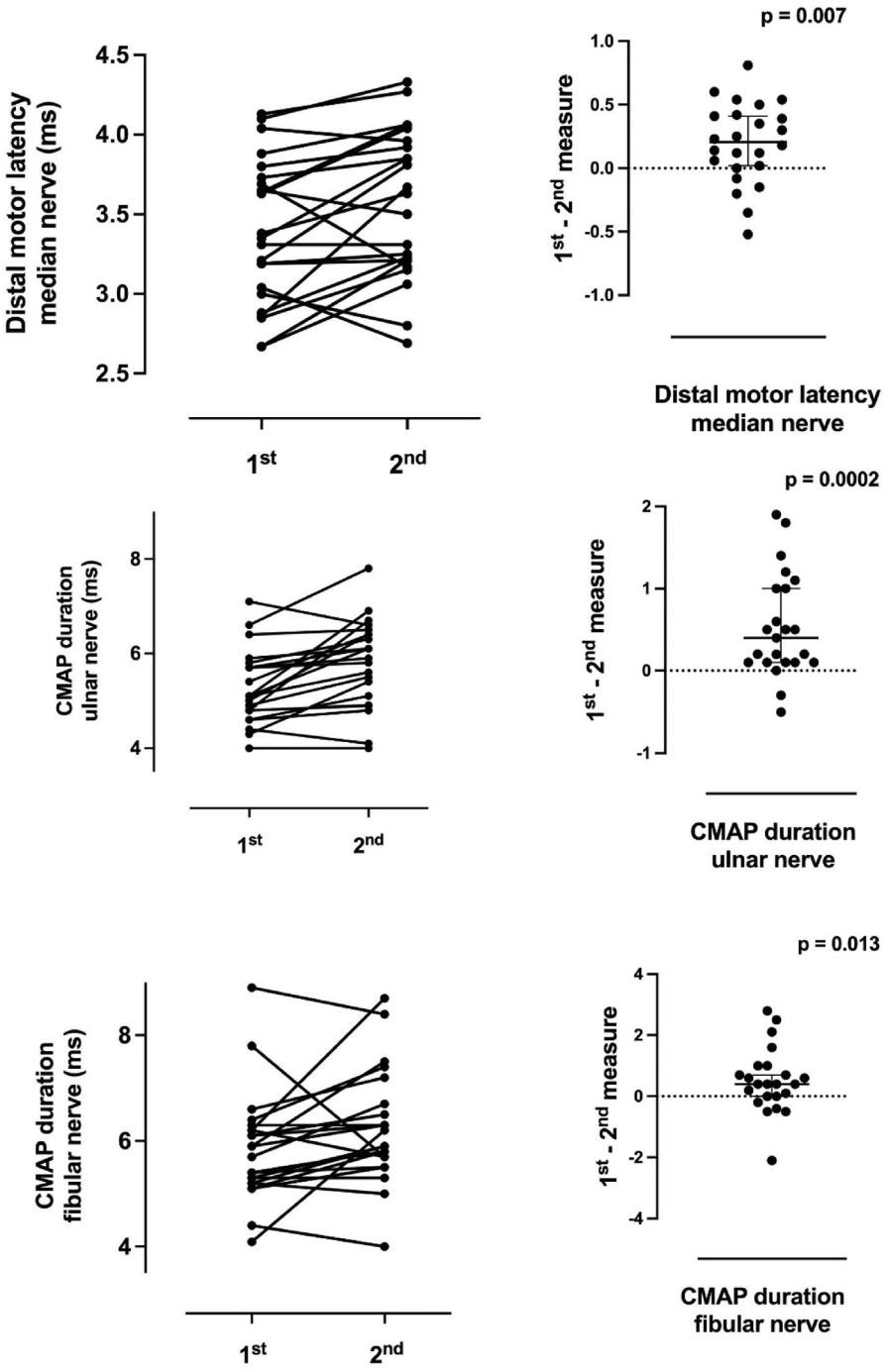

FIGURE 1 | Electrophysiological data varying significantly between two examinations in asymptomatic carriers. CMAP, compound muscle action potential.

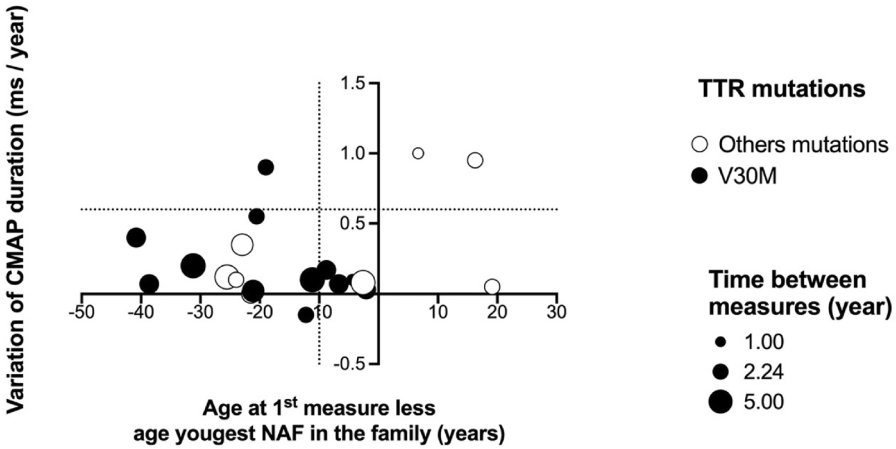

FIGURE 2 | Variation of the CMAP duration of the ulnar nerve. Variation of the duration of the CMAP of the ulnar nerve CMAP duration in ms/year is not correlated with TTR V30M mutation (full circles), delay between measurements (size of circles) and age at first measurement. Circles to the right of the vertical dotted line are asymptomatic carriers for whom the first examination was carried out in the 10 years prior to or at any time following the age of the youngest case in the family ($n = 8$). Circles above the horizontal dotted line correspond to a variation greater than the 99th percentile of the variation observed in healthy control subjects. CMAP, compound muscle action potential.

duration variations. The duration of the CMAP of the ulnar nerve, therefore, appears to be the parameter most sensitive to change between two EDX.

3.2 | Variation of Electrophysiological Data According to the Age of Onset of FAP in the Family

The first examination was carried out more than 10 years prior the age of the youngest case in the family for 13 asymptomatic carriers. For these carriers, the variation of the distal latency of the median nerve was no longer significant: 3.19 ms (2.88–3.73) versus 3.25 (3.15–3.85), $p = 0.22$. The variation of the fibular nerve CMAP duration remained significant: 6 ms (5.2–6.2) versus 6.25 (5.78–6.35), $p = 0.045$. The variation of the ulnar nerve CMAP duration remained significant: 5.1 (4.78–5.75) versus 6 (5.48–6.43), $p = 0.01$.

The first examination was carried out in the 10 years preceding or at any time following the age of the youngest case in the family for 8 asymptomatic carriers (Figure 3). For these carriers, the variation of the distal latency of the median nerve was no longer significant: 3.51 (3.34–3.79) versus 3.74 (3.3–4.10), $p = 0.14$. The variation of the fibular nerve CMAP duration was no longer significant: 5.80 (5.40–6.25) versus 6.30 (5.78–7.43), $p = 0.20$. The variation of the ulnar nerve CMAP duration remained significant: 4.95 (4.8–5.7) versus 5.95 (4.9–6.2), $p = 0.01$. SRM was calculated at 0.91.

3.3 | Comparison of Asymptomatic Carriers With Healthy Subjects and Symptomatic Carriers With Familial Amyloid Polyneuropathy (FAP)

We included 11 healthy subjects from a previous study in which ulnar nerve CMAP duration was measured at two separate examinations. There was no significant difference in age at first examination, 46 (39–51) versus 49 (37–58) years ($p = 0.61$), and time between the two electrophysiological examinations, 4 (1–4) versus 3 (2–4) years ($p = 0.60$).

In contrast, the variation of the ulnar nerve CMAP duration was significantly greater in asymptomatic carriers than in healthy subjects: + 0.45 ms (0.1–1) versus − 0.2 ms (−0.3–0.5); $p = 0.016$. The variation of the duration per year was also greater in asymptomatic carriers ($p = 0.035$): −0.04 ms/year (−0.2–0.11) for healthy subjects and + 0.1 ms/year (0.05–0.33) for asymptomatic carriers (Figure 4).

Next, we compared the asymptomatic carriers with 11 symptomatic TTR gene mutation followed in the department for FAP. The delay between the two EDX and the variation of the ulnar nerve CMAP durations were comparable between symptomatic and asymptomatic carriers ($p > 0.05$), respectively 3 (2–4) versus 4 (3.5–4) years and + 0.1 (0.05–0.33) versus +0.05 (−0.05–0.25) ms/year.

4 | Discussion

In this study, we assessed electrophysiological biomarkers recorded at a median interval of 3 years in asymptomatic carriers of a TTR mutation. All the collected data remained stable except for motor distal latency of the median nerve and CMAP duration of the ulnar and fibular nerves. Patients with different genetic mutations were included to reflect our routine care, as almost half of the patients treated at our center have a mutation different from V30M. The EDX protocol was performed on the non-dominant side to minimize abnormalities of mechanical origin, similar to the approach adopted in the follow-up of Charcot–Marie–Tooth disease [13].

When they become symptomatic, carriers of a TTR mutation usually describe dysautonomia, symptoms of compression of the median nerve in the carpal tunnel and paraesthesia of the toes [3, 14]. Electrophysiological studies show a decrease in the sensory amplitudes of the sural nerves, a prolonged distal motor latency of the median nerve and abnormalities of the SSR and ESC [15, 16]. We might have expected to observe modifications of the sensory potentials in our study, but we did not see an asymptomatic decrease in the sensory amplitudes of the sural nerves. This parameter is therefore robust and

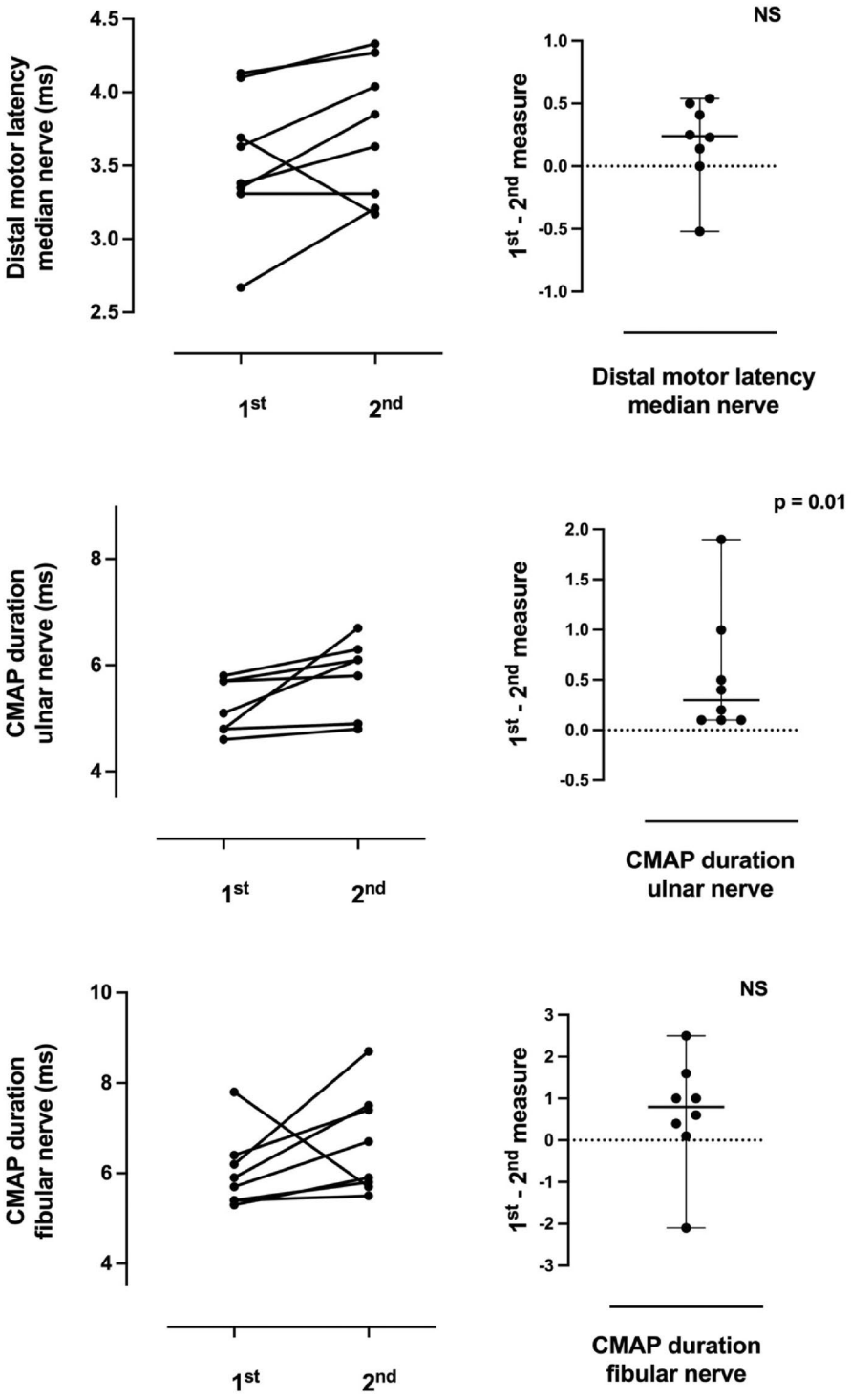

FIGURE 3 | Variation of electrophysiological data in asymptomatic carriers evaluated in the 10 years preceding or at any time following the age of the youngest case in the family. Variations in ulnar CMAP duration remain significant.

changes little over a three-year period in carriers who remain asymptomatic.

Autonomic testing results did not change over time in asymptomatic carriers in this study. Early pathological involvement of small autonomic fibers [17, 18] have been well documented in FAP, essentially in Portuguese patients, where the neuropathy onset is characterized by dysautonomia and painful paraesthesia. SSR and ESC are perhaps not sufficiently sensitive to change, and we could have carried out other explorations such as laser-evoked potentials or quantitative sensory testing [18]. Finally, as autonomic involvement is less obvious in late-onset FAP seen in France [19], these small fiber explorations may not be appropriate for our cohort where only two people were of Portuguese origin but born in France.

In this study, CMAP durations of the fibular and ulnar nerves remained within normal ranges, but were significantly prolonged

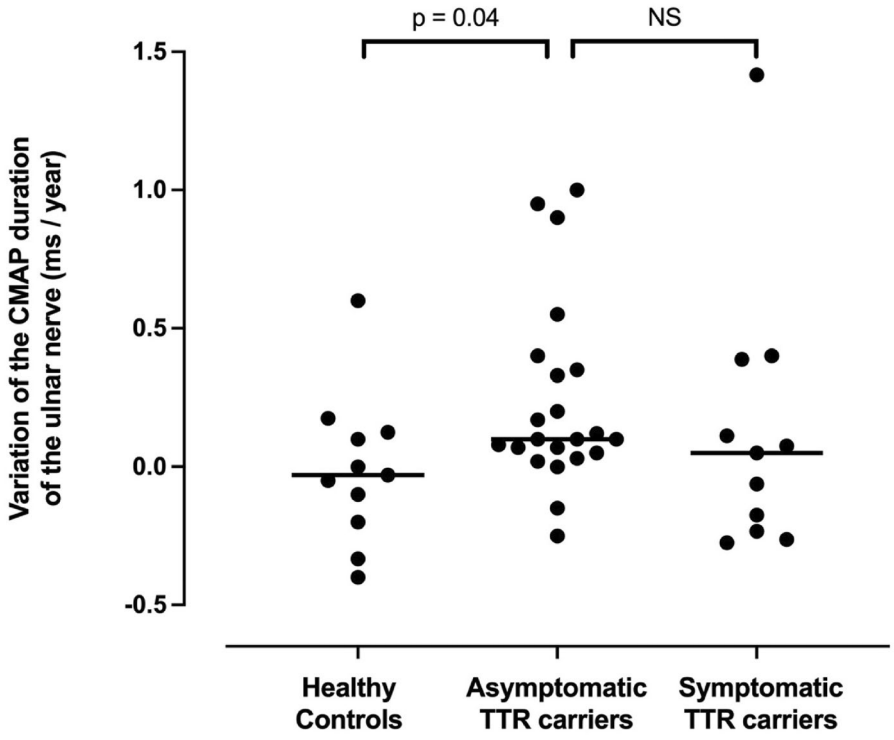

FIGURE 4 | Variation of the CMAP duration of the ulnar nerve between two different examinations in asymptomatic TTR mutation carriers, symptomatic TTR mutation carriers, and healthy controls. Median time between two EDX was 3 years. The bars represent the medians.

over time. Prolonged CMAP duration reflects the desynchronization of conduction of large nerve fibers [20] in a short portion of the nerve between stimulation and recording site. Therefore, damage to a few nerve fibers can significantly increase the duration of the potential. Amyloid deposition usually affects small diameter nerves, but in FAP diagnosed in France, both small and large fibers are often affected [1, 19, 21].

In addition to a rigorous clinical and EDX evaluation, other tests may be considered for the monitoring of asymptomatic carriers. Nerve ultrasound shows larger cross-sectional area in symptomatic patients [22]. Quantified MRI of muscles and nerves correlates with disease severity and may show abnormalities in asymptomatic carriers [23, 24]. Promising results have been observed with biological tests such as neurofilaments and cardiac biomarkers, particularly in symptomatic patients [1, 25]. Histopathological examinations, including nerve, accessory salivary gland, and skin biopsies, are highly specific as they confirm the presence of amyloid deposits. However, these examinations pose challenges for repetition in asymptomatic carriers [7].

Monitoring of asymptomatic carriers requires multimodal electrophysiological assessment to detect the first changes suggestive of a transition to a symptomatic form of the disease. This study shows that nerve conduction parameters remain relatively stable in the asymptomatic phase of the FAP. Based on our study, it appears that serial EDX testing may not be of value in detecting changes in carriers who remain asymptomatic or may need to be performed at intervals greater than 3 years.

Author Contributions

Nicolas Berard: conceptualization, investigation, writing – original draft. **Annie Verschueren:** validation, investigation. **Etienne Fortanier:** investigation. **Aude-Marie Grapperon:** validation. **Ludivine Kouton:** validation. **Hadia Rebouh:** investigation. **Julien Gallard:** validation. **Emmanuelle Salort-Campana:** validation. **Shahram Attarian:** conceptualization, methodology, validation. **Emilien Delmont:** conceptualization, investigation, writing – review and editing, validation, methodology.

Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study has been validated by the local ethics committee (PADS 23-118) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent

All persons involved in this study gave inform consent for participation and publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.