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Clinical and electrophysiological characteristics of women with X-linked Charcot–Marie–Tooth disease

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Abstract

Background: X-Linked Charcot–Marie–Tooth disease type 1 (CMTX1) is characterized by gender differences in clinical severity. Women are usually clinically affected later and less severely than men. However, their clinical presentation appears to be heterogenous. Our aim was to extend the phenotypic description in a large series of women with CMTX1.

Methods: We retrospectively evaluated 263 patients with CMTX1 from 11 French reference centers. Demographic, clinical, and nerve conduction data were collected. The severity was assessed by CMT Examination Score (CMTES) and Overall Neuropathy Limitations Scale (ONLS) scores. We looked for asymmetrical strength, heterogeneous motor nerve conduction velocity (MNCV), and motor conduction blocks (CB).

Results: The study included 137 women and 126 men from 151 families. Women had significantly more asymmetric motor deficits and MNCV than men. Women with an age of onset after 19 years were milder. Two groups of women were identified after 48 years of age. The first group represented 55%, with women progressing as severely as men, however, with a later onset age. The second group had mild or no symptoms. Some 39% of women had motor CB. Four women received intravenous immunoglobulin before being diagnosed with CMTX1.

Conclusions: We identified two subgroups of women with CMTX1 who were over 48 years of age. Additionally, we have demonstrated that women with CMTX can exhibit an atypical clinical presentation, which may result in misdiagnosis. Therefore, in women presenting with chronic neuropathy, the presence of clinical asymmetry, heterogeneous MNCV, and/or motor CB should raise suspicion for X-linked CMT, particularly CMTX1, and be included in the differential diagnosis.

KEYWORDS

Charcot-Marie-Tooth, clinical trial, CMTX, connexin 32, hereditary peripheral neuropathy

INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of hereditary sensory-motor polyneuropathies characterized by slowly progressive symmetrical distal involvement associated with muscular atrophy. It affects about 1 in 2500 individuals at birth [1], and more than 100 genes are involved [2]. Inheritance can be either autosomal dominant, autosomal recessive, or X-linked. CMT is classified according to the mode of inheritance, the causative gene, and the median motor nerve conduction velocity (MNCV) dividing the type of neuropathy into axonal, intermediate, or demyelinating form. X-Linked inherited neuropathy (CMTX) with a mutation in *GJB1* is the second most common subtype of CMT, after CMT1A, accounting for 10%–11% of CMT [3, 4].

CMTX1 is caused by a mutation in the *GJB1* gene [5], which leads, in most cases, to a loss of normal function of the connexin 32 protein [6]. Cx32, present in the peripheral nervous system, is an intrinsic membrane protein in gap junctions [7, 8]. Six connexins assemble to form a hemichannel, or a connexon, arranged around a central pore. Two connexons form gap junction channels and facilitate the diffusion of metabolites across the layers of the myelin sheath [9] and play a role in the homeostasis of myelinated axons. Cx32 is also expressed by oligodendrocytes, coupling them to astrocytes [10].

The disease classically begins in childhood, with difficulty running or repeated ankle sprains. Clinically there is usually a distal motor deficit of the lower and upper limbs, associated with muscle atrophy and bone deformities. In addition to peripheral neuropathy, CMTX1 is also characterized by acute episodic dysfunctions in the central nervous system [11–18]. Nerve conduction studies show in male patients intermediate slowing of conduction and distal axonal loss [19].

Previous studies have shown that men and women with CMTX1 exhibit phenotypic differences, with women usually being clinically affected later and less severely than men, with less slowed MNCV and axonal loss [11, 20–23]. However, the phenotype of women with

CMTX1 appears to be very heterogeneous. Siskind et al. [24] suggested that there were various phenotypic subgroups in women, but this hypothesis has not been verified.

We aimed to extend the phenotypic description of women with CMTX1, delineate different subgroups of patients, and report the atypical clinical presentation and motor conduction results compared to men and other types of CMT patients.

PATIENTS AND METHODS

Subjects and clinical assessment

We retrospectively reviewed clinical, neurophysiological, and genetic data of adult patients with CMT associated with *GJB1* mutations in France. Patients were assessed between 2000 and 2022 (mean 2020) in 11 neuromuscular reference centers (Marseille, Lyon, Paris Pitié-Salpêtrière, Paris Kremlin Bicêtre, Strasbourg, Angers, Saint-Etienne, Nantes, La Réunion, Limoges, and Toulouse).

Patients were included if they had a mutation in the *GJB1* gene or neuropathy with a first-degree family history of a *GJB1* mutation. Variants not observed in public databases, including ClinVar and the Hereditary Peripheral Neuropathy Mutation Database, were considered new variants. Data concerning sex, age, age at disease onset, mode of onset, clinical examination, presence of walking aids (orthosis, canes, crutches, wheelchair), history of stroke-like syndrome or orthopedic surgery of the lower limbs, and treatment for neuropathic pain (gabapentin, pregabalin, duloxetine, or transcutaneous electrical neurostimulation) were collected. We considered that patients were clinically asymmetrical if at least two points of difference were in the Medical Research Council (MRC) scale testing between each side for the same muscle. We also looked for associated signs, such as scoliosis, tremor, deafness, optic nerve atrophy, or cognitive disorders. We noted deafness if an audiogram was performed and

optic atrophy if the patient had undergone visual evoked potential testing. Similarly, cognitive disorders were only recorded if they had been objectively assessed through neuropsychological testing.

The CMT Examination Score version 2 (CMTEsv2), a standardized and validated composite score for CMT patients assessing clinical and functional severity, was established for each patient [25]. This score was calculated during the consultation or was retrospectively calculated for patients for whom the relevant data were available. This scale comprises seven items, each scored from 0 to 4, with a maximum score of 28. The Overall Neuropathy Limitations Scale (ONLS) score [26] was also calculated for each patient. On this scale, impairment in upper limbs is scored from 0 to 5, and lower limbs from 0 to 7. The total maximum ONLS score is 12. For both CMTEsv2 and ONLS, a higher score indicates a more severe phenotype. Phenotypes were classified according to their CMTEsv2 score as mild (CMTEsv2 0–7), moderate (CMTEsv2 8–16), and severe (CMTEsv2 >16) [27].

Motor nerve conduction study data were collected, including MNCV, compound muscle action potential (CMAP), distal motor latency, and F wave latency on the ulnar and median nerves. We also looked for the presence of conduction blocks (CB) and temporal dispersion in the forearm. Motor CB was considered if there was a reduction in amplitude of >30% between the proximal and the distal negative CMAP peak (excluding the tibial nerve, the fibular nerve at the fibula, and the ulnar nerve at the elbow) if the distal CMAP was >1 mV [28]. Motor CB was classified as severe if this reduction in amplitude was >50%. Temporal dispersion was defined as an increase in the duration of >30% between the proximal and distal negative CMAP peak [28]. Patients with median MNCV below 25 m/s were categorized as having 'demyelinating' neuropathy, those with more than 38 m/s had 'axonal' neuropathy, and those between 25 and 38 m/s were classified as having 'intermediate' neuropathy [29].

We compared the right and left MNCV in both ulnar and median nerves and considered MNCV to be asymmetric if there was more than a 10 m/s difference between the right and left nerves. This threshold was chosen because 10 m/s is more than two standard deviations of the mean MNCV [30].

Statistical analysis

For our analyses, we artificially subdivided patients according to their median current age (Figure 3) or median age of onset (Figure 5). We used the medians because the distributions were not normal. Continuous variables were described by their mean, standard deviation, minimum and maximum value, or by their median and first and third quartiles. Categorical variables were described by their number and percentage. Continuous variables were compared by the non-parametric Wilcoxon rank sum test, depending on the conditions of the application. Categorical variables were compared by the chi-square test or Fisher's test, depending on the application conditions. For multivariate analyses, linear regressions were performed for continuous variables. Pearson correlation analysis was used to assess the correlation between age and clinical score and between the

age at disease onset and clinical scores. The tests were performed in a two-sided situation and were considered statistically significant for $p \leq 0.05$. Statistical analysis was performed with RStudio software (version 4.1.1).

RESULTS

General population

Two hundred and sixty-three patients (137 women and 126 men), from 151 families, followed for CMTX1 were included in the study. We identified 84 different *GJB1* mutations; among these, 27 were new mutations (Figure 1). Clinical characteristics are shown in Table 1. The median age at clinical assessment was 45 years (IQR 32–58; range: 18–84 years), 48 years for women (IQR 33–60; range: 18–83 years), and 40 years for men (IQR 30–56; range: 18–84 years) and did not differ significantly between the genders ($p = 0.060$). Age at disease onset was 19 (IQR 10–32) years for women versus 12 (IQR 7–15) years for men ($p < 0.001$).

CMTEsv2 score was significantly lower in women (mean score 7.5 [± 5.3]) than in men (mean score 11.0 [± 4.5], $p < 0.001$). This significance was reinforced after adjustment for patient age ($p < 0.001$).

The gender difference was statistically significant for each item of the CMTEsv2 score, as shown in Figure 2, except for the first item relating to subjective sensory symptoms. Some 19.2% (23/120) women followed a treatment for neuropathic pain, compared with 12.6% (14/111) of men; and the difference was not significant. The phenotype (mild, moderate, or severe) differed significantly between the genders. Seventy-one of 137 (51.8%) women had a mild phenotype, whereas 87/126 (69%) men had a moderate phenotype. The ONLS score, correlated to the CMTEsv2 score, showed a similar trend in which men were more severely affected than women (mean ONLS score was 2.3 for women and 3.5 for men, $p < 0.001$). The difference was also significant when the upper and lower limbs ONLS scores were compared separately between genders. Ten percent (13/127) of women and 16% (19/118) of men used canes or walkers. A wheelchair was used by 3% (3/118) of men but not by women. Twenty-five percent (32/127) of women and 36% (42/118) of men had moderate or severe difficulty in buttoning. Four percent (5/127) of women and 16% (19/118) of men were unable to cut most foods.

Fifteen percent (18/120) of women had asymmetrical strength, compared with only 3.6% (4/111) of men ($p = 0.003$).

Associated signs (scoliosis, tremors, deafness, optic nerve atrophy, stroke-like syndrome, cognitive disorders) did not differ between genders.

Five women and three men received an inaccurate diagnosis before a *GJB1* mutation was detected. Of these patients, four women and two men were initially diagnosed with CIDP, leading to the prescription of immunoglobulin or steroids. One woman was diagnosed with traumatic lower plexus injury associated with bilateral entrapment syndrome, and one man was initially diagnosed with spinal muscular atrophy type IV.

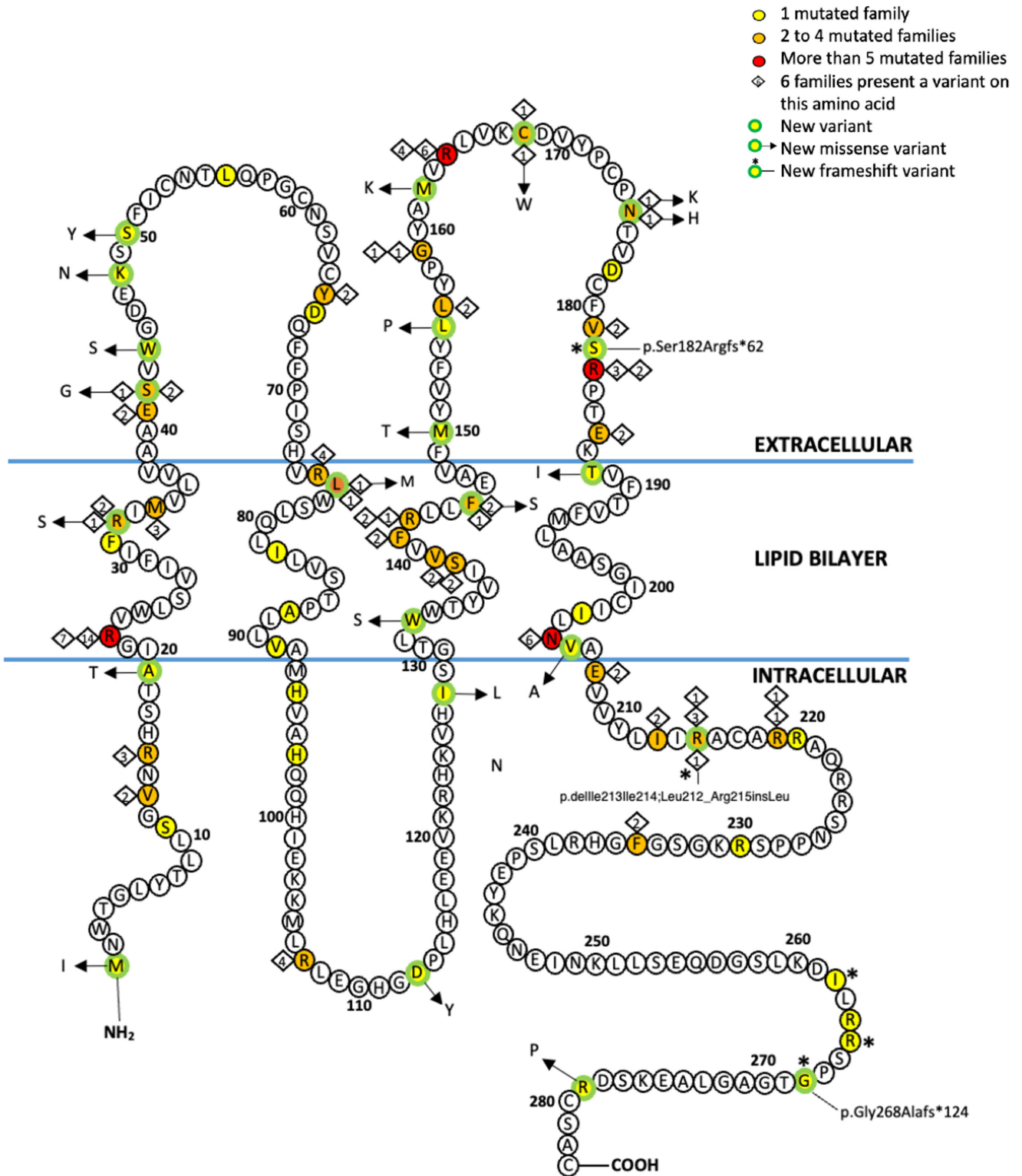


FIGURE 1 Schematic diagram of gap junction protein beta 1 and GJB variants in our cohort, from Bone et al. [47]. All reported missense, nonsense, and frameshift GJB1 mutation are indicated with a colored circle. Novel variants are indicated with a green circle. New variants not related in the figures: three mutations located in the 5'-untranslated region (c.-16-459G>A, c.-16-529T>C, c.-16-581G>A). One whole gene deletion (c.1_852del) is not indicated. [Colour figure can be viewed at wileyonlinelibrary.com]

Women's phenotype

Women were more often asymptomatic at diagnosis than men; 17.2% (21/130) and 0.8% (1/124), respectively ($p < 0.001$). When women were symptomatic, symptoms at disease onset were not

different from those of men (Table 2). The disease mostly started in women with foot deformities (30.8% or 36/117), recurrent ankle sprains (20.5% or 24/117), or progressive motor deficits of the lower limbs (23.1% or 27/117). However, cramps (14.5% or 17/117), paresthesias (9.4% or 11/117), and progressive upper limbs deficit (7.8%

TABLE 1 Clinical characterization by gender.

Characteristic	Women (N = 137)	Men (N = 126)	P-value
Age at the evaluation, median (IQR)	48 (33–60)	40 (30–56)	0.060 ^a
Age of onset, median (IQR) (NA)	19 (10–32) (9)	12 (7–18) (8)	<0.001 ^a
CMTES, mean [±SD]	7.5 [±5.3]	11.0 [±4.5]	<0.001 ^a
Sensory symptoms, mean [±SD] (NA)	0.6 [±0.9] (10)	0.6 [±1.0] (8)	0.671 ^a
Motor symptoms, legs mean [±SD] (NA)	1.3 [±1.0] (10)	1.8 [±0.8] (8)	<0.001 ^a
Motor symptoms arms, mean [±SD] (NA)	0.7 [±0.9] (10)	1.2 [±1.1] (8)	<0.001 ^a
Pinprick sensibility, mean [±SD] (NA)	0.9 [±1.1] (10)	1.5 [±1.1] (8)	<0.001 ^a
Vibration, mean [±SD] (NA)	1.5 [±1.2] (10)	2.1 [±1.1] (8)	<0.001 ^a
Strength (legs), mean [±SD] (NA)	1.5 [±1.2] (10)	2.4 [±1.0] (8)	<0.001 ^a
Strength (arms), mean [±SD] (NA)	1.0 [±0.9] (10)	1.6 [±1.0] (8)	<0.001 ^a
Phenotype			<0.001 ^b
Mild (CMTES 0–7), % (n)	51.8 (71)	21.4 (27)	
Moderate (CMTES 8–16), % (n)	41.6 (57)	69.0 (87)	
Severe (CMTES >16), % (n)	6.6 (9)	9.5 (12)	
ONLS, mean [±SD]	2.3 [±1.8]	3.5 [±1.7]	<0.001 ^a
ONLS–upper limb, mean [±SD]	0.9 [±1.0]	1.6 [±1.1]	<0.001 ^a
ONLS–lower limb, mean [±SD]	1.3 [±1.0]	1.9 [±0.8]	<0.001 ^a
Walking aids (cane or walker), % (n)	10 (13/127)	16 (18/118)	
Wheelchairs, % (n)	0 (0/127)	3 (3/118)	
Orthosis, % (n)	37.0 (47/127)	64.4 (76/118)	<0.001 ^b
Orthopedic surgery of the lower limbs, % (n)	15.0 (19/127)	26.3 (31/118)	0.028 ^b
Treatment for neuropathic pain, % (n)	19.2 (23/120)	12.6 (14/111)	0.175 ^b
Asymmetric, % (n)	15.0 (18/120)	3.6 (4/111)	0.003 ^b
Scoliosis, % (n)	10.6 (13/123)	11.0 (13/118)	0.911 ^b
Tremor, % (n)	16.3 (20/123)	23.7 (28/118)	0.147 ^b
Deafness, % (n)	2.4 (3/123)	5.9 (7/118)	0.209 ^c
Optic nerve atrophy, % (n)	0.8 (1/124)	0.8 (1/118)	>0.999 ^c
Stroke-like syndrome, % (n)	2.4 (3/123)	0.8 (1/118)	0.622 ^c
Cognitive impairment, % (n)	0 (0/123)	1.7 (2/118)	0.239 ^c

Abbreviations: CMTES, Charcot–Marie–Tooth Examination Score version 2; IQR, interquartile range; NA, not available; ONLS, Overall Neuropathy Limitation Score; SD, standard deviation.

^aWilcoxon rank sum test.

^bPearson's chi-squared test.

^cFisher's exact test.

or 9/117) were also observed, as well as tremors (6% or 7/117) or scoliosis (3.4% or 4/117) as a mode of onset of the disease. Of note, 2.6% (4/117) started with another symptom such as subacute motor deficit or balance disorder.

We identified two groups among patients over the age of 48 years (Figure 3). Of the women aged over 48 years, 45% had a mild phenotype (CMTES 0–7), while 55% had a moderate (CMTES 8–16) or severe (CMTES >16) phenotype. We chose 48 years as the cutoff since it represents the median age of the women included in this study. The group of 30 minimally symptomatic women represents 45% of women aged over 48 years (30/67). For this subgroup, the CMTES score was 3.2, and the age of onset was 40 years. For the remaining 37 women aged over 48 years (37/67 patients, 55%), with moderate or severe phenotype the CMTES score was 12.7, and the age of onset was 19 years. For men over 48 years, CMTES was 12.9, and the age of onset was 13 years. For the more severely affected women, the CMTES score did not differ significantly from that of

men over 48 years. However, their age of onset was later and differed significantly ($p < 0.001$).

Women who developed the disease before the age of 19 years had a CMTES score of 9.5, while those who developed the disease after the age of 19 years had a score of 5.6 (Figure 4a, $p < 0.0001$). We chose 19 years as the cutoff since it represents the median age of the women in this study's disease onset. The ONLS score was 2.8 for women who developed the disease before the age of 19 years and 1.6 for women who developed the disease after the age of 19 years (Figure 4b, $p < 0.001$). CMTES score correlated significantly with age for women ($p < 0.001$), as shown in Figure 3. The CMTES score correlated significantly with the age of symptom onset (Figure 5, $p < 0.001$).

Among women with CMTX1, the most commonly associated symptoms were tremors (20/123 patients, 16.3%) and scoliosis (13/123 patients, 10.6%). Additionally, 3/123 patients experienced sensorineural deafness, and 1/123 had optic nerve atrophy, while none of the patients exhibited cognitive disorders.

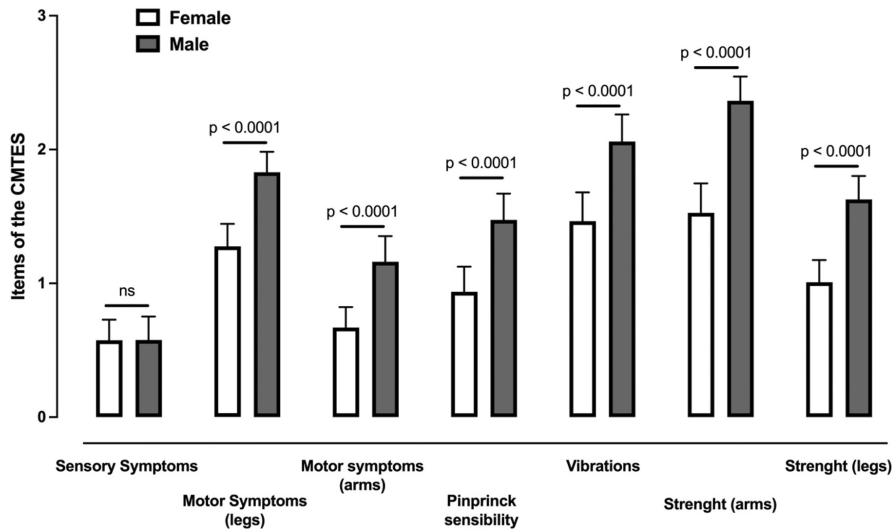


FIGURE 2 Details of Charcot-Marie-Tooth Examination Score (CMTES) version 2 by gender.

Characteristic	Women % (n)	Men % (n)	P-value
Foot deformities, % (n)	30.8 (36/117)	49.0 (51/104)	0.006 ^a
Recurrent ankle sprain, % (n)	20.5 (24/117)	28.8 (30/104)	0.152 ^a
Lower limb motor deficit, % (n)	23.1 (27/117)	38.5 (40/104)	0.013 ^a
Upper limb motor deficit, % (n)	7.8 (9/116)	5.8 (6/104)	0.559 ^a
Paresthesia, % (n)	9.4 (11/117)	7.7 (8/104)	0.651 ^a
Cramp, % (n)	14.5 (17/117)	9.6 (10/104)	0.265 ^a
Tremor, % (n)	6.0 (7/117)	3.8 (4/104)	0.466 ^a
Scoliosis, % (n)	3.4 (4/117)	1.0 (1/104)	0.374 ^b
Asymptomatic, % (n)	17.2 (21/130)	0.8 (1/124)	<0.001 ^a
Other, % (n)	2.6 (3/116)	4.8 (5/104)	0.481 ^b

^aPearson's chi-squared test.

^bFisher's exact test.

TABLE 2 Symptoms present at the onset of the disease by gender.

We identified three women with the stroke-like syndrome. The symptoms included a right hemiparesis associated with dysarthria for 20min, left upper limb hemiparesis for 1h, and flaccid tetraparesis for 10min, recurrent. Two patients had brain MRIs showing T2-weighted images with white matter hyperintensities without gadolinium enhancement. Unfortunately, we do not have access to the MRI images. The third patient had a normal MRI. There was no mention of triggering factors for any of the three patients.

We found that women who presented with a missense variant in the lipid bilayer domain had a more severe clinical presentation and earlier onset of disease compared to those with variants located in the intra- and extracellular domains (respectively, CMTES 9.1 and 6.6, $p=0.009$; ONLS 2.9 and 1.8, $p=0.001$; the age of onset 17.3 and 26.3 years, $p=0.001$). However, there was no significant association between gene domain localization and asymmetry.

Nerve conduction study

We collected 128 motor nerve conduction study data: 66 for women and 62 for men (Table 3). MNCV was more frequently asymmetric in women (13/43 patients, 30%) than in men (3/43

patients, 7%). The difference between gender was statically significant ($p=0.024$). Motor CB in upper limbs was more frequent in women than in men (26/66 patients, 39.4% vs. 18/64 patients, 28.1%), but this difference was not significant ($p=0.175$). Eight of 66 (12%) women and 6/64 (9%) men had severe motor CB ($p=0.614$). MNCV of the median nerve and ulnar nerve were significantly less slowed in women than in men (median nerve MNCV was 42.2m/s [± 10.2] for women, 35.6m/s [± 6.4] for men, $p<0.001$). Women had axonal neuropathy in 64.6% of cases (42/65), while men had intermediate neuropathy in 72.6% of cases (45/65, $p<0.001$). Median and ulnar nerve CMAP were significantly less reduced in women (median nerve CMAP was 5.1 mV [± 3.8] for women, 3.5 mV [± 3.7] for men, $p=0.024$). Distal latency and F wave latency were significantly less prolonged in women ($p<0.001$ and $p=0.008$, respectively).

DISCUSSION

This study describes the phenotype of 137 women with CMTX1. Among them, we identified two subgroups of women over the age of 48 years. The first subgroup, representing 55% of the cohort,

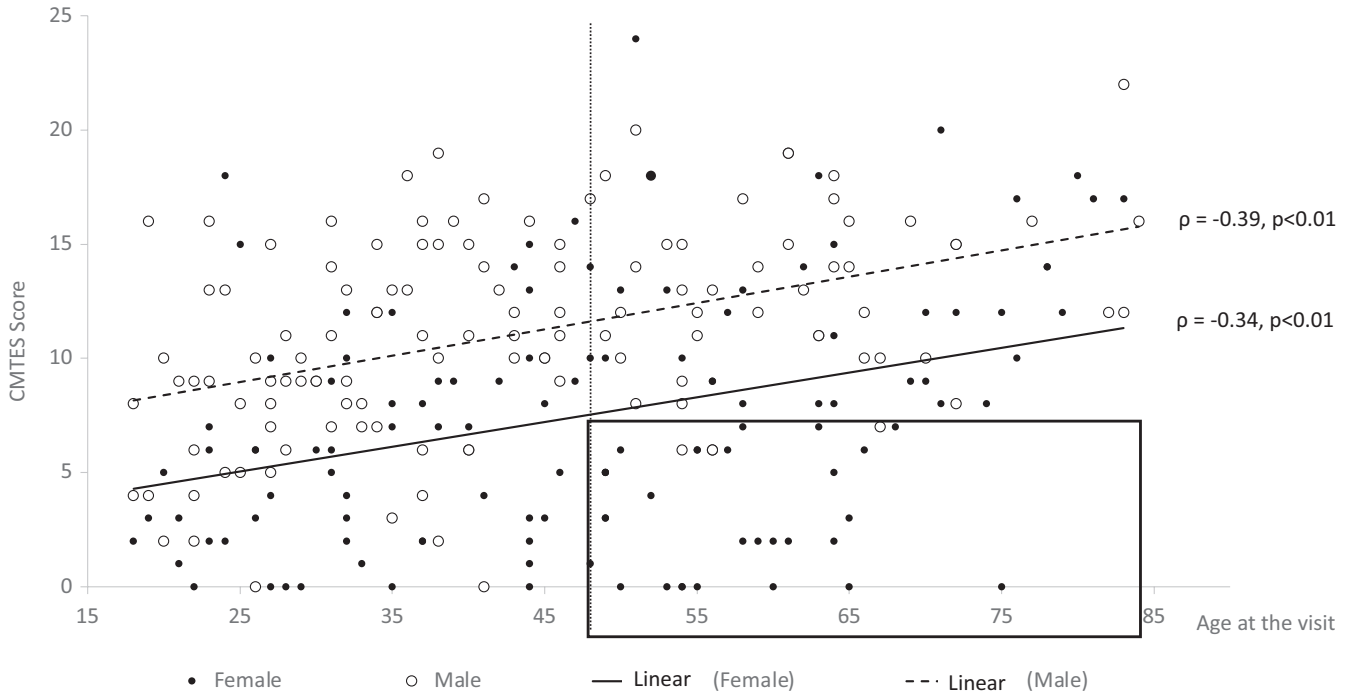
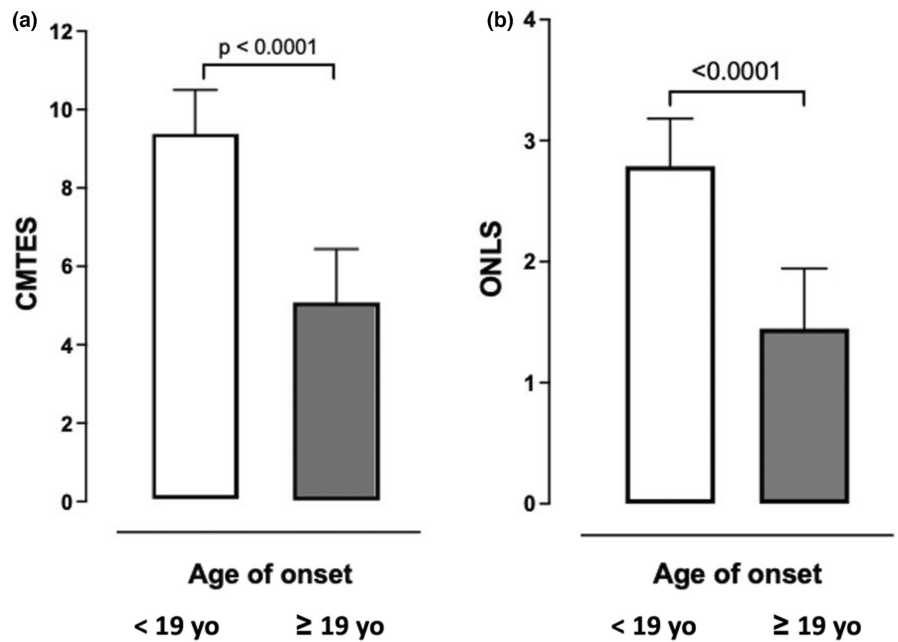


FIGURE 3 Charcot-Marie-Tooth Examination Score (CMTES) version 2 score in relation to age at the clinical visit. The square shows patients aged over 48 years with CMTES score ≤ 5 .

FIGURE 4 Phenotype of women with Charcot-Marie-Tooth disease type 1 (CMTX) in relation to the age of onset. Nineteen years old is the median of age of onset for women. (a) Mean Charcot-Marie-Tooth Examination Score (CMTES) score in relation to the age of onset, with standard deviation. (b) Mean Overall Neuropathy Limitations Scale (ONLS) score in relation to age of onset, with standard deviation.



had a disease progression as severe as that observed in men but with a later onset age. The second subgroup, comprising the remaining 45% of women, had either mild or no symptoms. Notably, women who developed the disease after the age of 19 years had a significantly milder phenotype than those with an earlier onset age. Moreover, we observed that women had significantly more asymmetric motor deficits and heterogeneous MNCV than men. Additionally, 39% of women in our cohort had motor conduction blocks.

General population: women's phenotype compared to men

Our results regarding the general phenotypic description of women compared to men are in agreement with previous CMTX1 cohorts [11, 20, 23, 31–33]. It is noteworthy that due to the large sample size of this study, we were able to identify significant differences in each item of the CMTES score, except for the first item, which assesses neuropathic pain. The results for this item were consistent with the

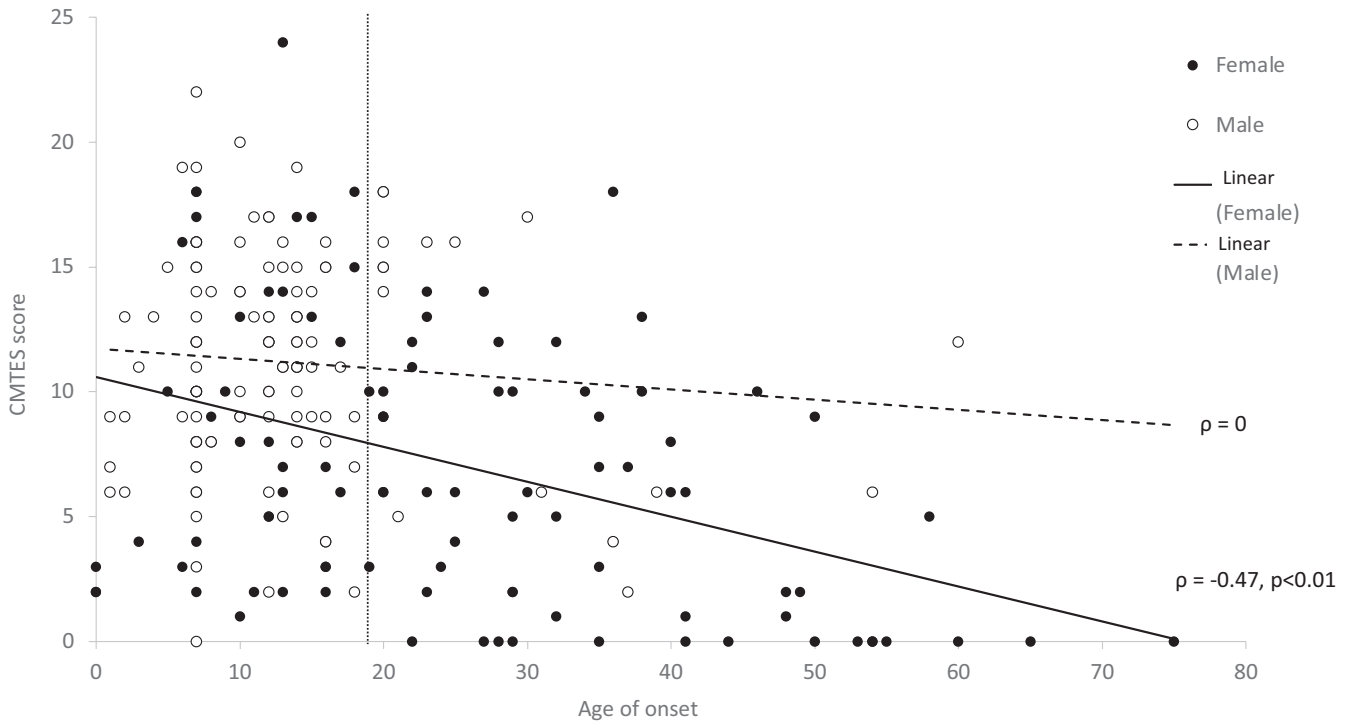


FIGURE 5 Charcot-Marie-Tooth Examination score (CMTES) version 2 score in relation to the age of onset. For women, the Pearson correlation coefficient was $\rho = -0.47$, $p < 0.01$. For men, $\rho = 0$, and there is no linear relationship between the CMTES score and the age of onset.

comparable percentage of patients, both men and women, who used analgesic treatment. Consistent with our findings, Panosyan et al. [20] previously reported similar frequencies of paresthesia and burning feet between men and women. Although this study has a limitation of retrospective calculation of CMTES scores, the results were consistent with a previous study [11, 20].

We did not observe significant differences in the signs associated with the disease between men and women. However, women tended to exhibit tremors less frequently (16.3% vs. 23.7%). This difference could be attributed to the less severe neuropathy and lower degree of disability observed in women.

We identified three women with a stroke-like syndrome. However, in the previous cohort, stroke-like attacks were more frequently reported in men [11–16] than in women. These central symptoms should prompt a discussion of differential diagnoses [34, 35].

Clinical heterogeneity in women

Women with CMTX1 exhibit a more heterogeneous clinical presentation than men. Specifically, 10% of women in our cohort used canes or crutches, whereas 17.2% were asymptomatic.

In our study, 45% of women over the age of 48 years exhibited a mild phenotype (CMTES 0–7). The remaining female CMTX1 patients over 48 years of age (55%) experienced disease progression as severe as that observed in men, albeit with a later onset of symptoms.

These findings corroborate those reported by Siskind et al. [24], who studied 31 women with CMTX1. The largest subgroup in their cohort consisted of approximately 60% of female CMTX1 patients with mild symptoms and stable neuropathy. The second subgroup included women with moderate impairment, which worsened with age, similar to male CMTX1 patients. The third group included three asymptomatic women.

In our cohort, the age of symptom onset was more variable in women than in men. We found a significant linear correlation between the age of symptom onset and the CMTES score in women but not in men. Notably, we demonstrated that patients with a late onset of the disease (after 19 years) exhibited a significantly milder phenotype. We can hypothesize that these women are more likely to belong to the subgroup of women with mild symptoms after the age of 48 years. The heterogeneous phenotype observed among women with CMTX1 could be explained by the X inactivation mechanism. The inactivation of pathogenic X could potentially account for the subgroup of asymptomatic women, a hypothesis that has yet to be tested [24].

Asymmetry in women

In our cohort, we observed that 15% of women exhibited an asymmetric motor deficit compared with only 3.6% of men ($p = 0.003$). We excluded patients with other causes of motor deficit from these results. Asymmetry in motor or sensory deficits is atypical in CMT

TABLE 3 Electroneurographic characteristics by gender.

Characteristic	Women	Men	P-value
Demyelinating (MNCV <25 m/s), % (n)	1.5 (1/65)	0 (0/62)	<0.001 ^c
Intermediate (MNCV 25-38 m/s), % (n)	33.8 (22/65)	72.6 (45/62)	
Axonal (MNCV >38 m/s), % (n)	64.6 (42/65)	27.4 (17/62)	
MNVC median nerve, mean [±SD] (n)	42.2 [±10.2] (65)	35.6 [±6.4] (62)	<0.001 ^a
MNCV median difference right/left, mean [±SD] (n)	5.9 [±4.7] (37)	3.2 [±2.4] (36)	0.007 ^a
MNCV ulnar, mean [±SD] (n)	48.3 [±8.4] (60)	38.6 [±7.7] (63)	<0.001 ^a
MNCV ulnar difference right/left, mean [±SD] (n)	5.6 [±6.1] (35)	3.7 [±4.5] (39)	0.047 ^a
CMAP median, mean [±SD] (n)	5.1 [±3.8] (66)	3.5 [±3.7] (59)	0.013 ^a
CMAP ulnar, mean [±SD] (n)	7.1 [±2.9] (61)	5.3 [±3.2] (59)	<0.001 ^a
Asymmetrical MNCV (>10%), % (n)	30 (13/43)	7 (3/43)	0.024 ^b
Distal latency >4 ms, % (n)	54.0 (34/63)	83.3 (45/54)	<0.001 ^b
Distal latency >6 ms, % (n)	14.3 (9/63)	16.7 (9/54)	0.722 ^b
Percentage of distal latency increase, mean [±SD]	135.8 [±37.8]	135.8 [±25.9]	0.998 ^a
F wave latency >30 ms, % (n)	52.8 (19/36)	82.4 (28/34)	0.008 ^b
F wave latency >45 ms, % (n)	0 (0/36)	17.6 (6/34)	0.01 ^c
Percentage of F wave latency increase, mean [±SD]	119.9 [±11.2]	135.2 [±25.0]	<0.029 ^a
Motor conduction block ≥30% and/or temporal dispersion, % (n)	43.9 (29/66)	42.2 (27/64)	0.84 ^b
Motor conduction block ≥30%, % (n)	39.4 (26/66)	28.1 (18/64)	0.175 ^b
Motor conduction block between 30% and 50%, % (n)	27.3 (18/66)	18.8 (12/64)	0.249 ^b
Motor conduction block ≥50%, % (n)	12.1 (8/66)	9.4 (6/64)	0.614 ^a

Abbreviations: CMAP, compound muscle action potential (in mV); MNCV, motor nerve conduction velocity (in m/s); SD, standard deviation.

^aWilcoxon rank sum test.

^bPearson's chi-squared test.

^cFisher's exact test.

patients, as reported in previous clinical descriptions of CMT1X cohorts [20–22, 24]. However, one study of pediatric CMT patients reported asymmetry in foot alignment and ankle flexibility in 3%–5% of patients, with the asymmetry associated with greater severity of neuropathy according to the CMTNS scale, but without analysis according to the type of CMT [36]. Another study of patients with CMT1A found pinprick or vibration sensory asymmetry in 23/180 patients (12.8%), but no asymmetry was observed for other items in the CMTES score [37].

The heterogeneous phenotype observed among women with CMTX1 may be due to the X inactivation mechanism. When most Schwann cells in a nerve have a pathological X chromosome inactivated, demyelination is expected to be less severe. Therefore, the inactivation of the pathogenic X could explain the subgroup of asymptomatic women, although this hypothesis requires further testing. Siskind et al. in 2011 [24] investigated whether the presence of a GJB1 mutation affected the pattern of X inactivation in white blood cells. They did not observe any difference in the X-inactivation pattern between 14 affected women (CMTNS score ranged from 0 to 19) and the control group. However, the pattern of X inactivation is not homogeneous between different tissues [38, 39]. Thus, to test this hypothesis, the pattern of X inactivation should be directly evaluated in nerve cells in future investigations. Dubourg et al. in 2001 [23] suggested that the asymmetry in women could also be

explained by this mechanism if X inactivation is not homogeneous and is too variable from one nerve to another.

Motor conduction in women

In our study, MNCV and CMAP were less impaired in women than in men, consistent with previous findings [20–23]. We also found that women exhibited less prolonged distal latency and F wave latency. MNCV was significantly more asymmetric in women than men, consistent with clinical presentation. Gutierrez et al. in 2016 [40] described five patients from a family with the R15W mutation (two women and three men) who exhibited significant heterogeneity in MNCV in women. Dubourg et al. in 2001 [23] reported greater ulnar and median CMAP amplitude heterogeneity in 37 CMTX1 women compared to male CMTX1 patients and CMT1A patients.

Interestingly, 39% of women in our cohort exhibited motor conduction blocks in the upper limbs. Although these were frequently mild, 31% of patients had blocks greater than 50%. Unfortunately, data on CMAP duration was often missing, preventing an investigation of the rate of temporal dispersion. Some previous studies [19, 40, 41] reported a few cases of CMTX1 patients with temporal dispersion, suggesting it as a characteristic of CMTX1 neuropathy. These results are consistent with previous studies. Some authors

have suggested that the high rates of conduction blocks and temporal dispersion are indicative of a primary demyelination process, although this remains a matter of debate [21, 42–45] and requires further exploration.

Misdiagnosis

The atypical clinical and electrophysiologic patterns observed in female CMTX patients, such as asymmetric clinical and electrophysiologic patterns associated with the presence of motor conduction blocks, can lead to misdiagnosis. In our cohort, four women received immunosuppressive therapy before being diagnosed with CMTX1.

Conduction blocks, as observed in some of our patients, can lead to an inaccurate diagnosis favoring chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), as previously reported by Hauw et al. [46]. Clinicians should be cautious of certain red flags when diagnosing CIDP, such as young patient age, a family history of neuropathy, motor difficulties or foot deformities in childhood, scoliosis, and a lack of response to treatments like intravenous immunoglobulin (IVIG), steroids, and immunosuppressants.

CONCLUSIONS

In conclusion, our cohort of 137 women with CMTX1 showed that female patients have a heterogeneous phenotype. Fifty-five percent of women after the age of 48 years were as severely impaired as male patients, while the remaining 45% remained asymptomatic for a prolonged period. We also demonstrated that women with CMTX1 may exhibit atypical clinical presentations or motor conduction results that can lead to diagnostic wandering and misdiagnosis. Therefore, in women presenting with chronic neuropathy, the presence of clinical asymmetry, heterogeneous MNCV, and/or motor conduction blocks should raise suspicion for X-linked CMT, particularly CMTX1, and be considered in the differential diagnosis.

AUTHOR CONTRIBUTIONS

Luce Barbat du Clozel: Conceptualization (equal), methodology (equal), data curation (equal), formal analysis (equal), investigation (equal), formal analysis (equal), project administration (equal), writing—original draft (equal), review and editing (equal). Nathalie Bonello-Palot: Conceptualization (equal), methodology (equal), investigation (equal), validation (equal), writing—original draft (equal), review and editing (equal). Yann Péréon: Investigation (supporting), validation (supporting). Andoni Echaniz-Laguna: Investigation (supporting), validation (supporting). Jean Philippe Camdessanche: Investigation (supporting), validation (supporting). Aleksandra Nadaj Pakleza: Investigation (supporting), validation (supporting). Jean-Baptiste Chanson: Investigation (supporting), validation (supporting). Simon Frchet: Investigation (supporting), validation (supporting). Laurent Magy: Investigation (supporting), validation (supporting). Julien Cassereau: Investigation (supporting),

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CONFLICT OF INTEREST STATEMENT

The authors report no disclosures relevant to the article.

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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