Different nerve excitability measurements in a rare case of Charcot-Marie-Tooth 1H (CMT1H)

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INTRODUCTION: CMT1H is a rare forms of autosomal dominant CMT, caused by mutations in Fibulin-5 gene (*FBLN5*). The onset of the disease is usually observed in adulthood and sensory disturbances are the initial and predominant clinical features. Here, we document electrophysiological abnormalities in a 42-years old paucisymptomatic patient carrying a pathogenic heterozygous *FBLN5* c.1117C>T (p.Arg373Cys) variant.

MATERIALS AND METHODS: Conventional nerve conduction studies, and motor axonal excitability assessments of the median nerve at the wrist including threshold tracking (TT) and manual measurements (MM) of rheobase, strength-duration time constant (SDTC), iMAX parameters (for ulnar and fibular nerves also), refractory periods and early-supernormal and late-subnormal periods were done. In addition, an ultrasound evaluation of the median nerve was performed.

RESULTS : Conventional nerve conduction studies revealed a homogenous sensory-motor demyelinating polyneuropathy (median nerve motor conduction velocity < 38 m/s), without significant sensory-motor axonal loss (Figure 1). The three iMAX procedure parameters (minimal threshold, iUP, iMAX) were increased at all three stimulus sites (Figure 2). Ultrasound of the median nerve showed increased cross-sectional area at the wrist and elbow (Figure 3).

Motor nerves	Amplitude (mV)	LN	DL (ms)	LN	CV (m/s)	LN	F-M latency (ms)	LN
Right median								
Wrist– APB	8.5	> 4.4	8.3	< 4.5			32.3	< 26.0
Above Elbow					32.4	> 50.0		
Left median								
Wrist – APB	9.0	> 4.4	8.1	< 4.5			32.6	< 26.0
Above Elbow					36.1	> 50.0		
Right ulnar								
Wrist– ADM	8.3	> 6.8	5.8	< 3.5			35.7	< 27.0
Above Elbow					29.0	> 49.0		
Left ulnar								
Wrist– ADM	10.0	> 6.8	6.2	< 3.5			34.2	< 27.0
Above Elbow					29.0	> 49.0		
Right fibular								
Ankle – EDB	3.3	> 2.3	6.7	< 5.5			66.2	< 54.0
Popliteal fossea					27.9	> 40.0		
Left fibular								
Ankle – EDB	3.6	> 2.3	7.8	< 5.5			66.4	< 54.0
Popliteal fossea					26.2	> 40.0		
Right tibial								
Ankle – AHB	5.4	> 5.3	6.7	< 5.8			65.9	< 56.0
Popliteal fossea					27.6	> 40.0		
Left tibial								
Ankle – AHB	5.9	> 5.3	7.5	< 5.8			69.6	< 56.0
Popliteal fossea					30.1	> 40.0		

Sensory nerves	Amplitude (µV)	LN	CV (m/s)	LN
Right radial	20.1	> 25.0	37.0	> 50.0
Left radial	16.1	> 25.0	38.6	> 50.0
Right sural	9.0	> 15.0	43.0	> 40.0
Left sural	13.1	> 15.0	44.9	> 40.0

Figure 1. *Nerve conduction studies. DL = distal latency; CV = conduction velocity; APB = abductor pollicis brevis muscle; ADM = abductor digiti minimi muscle; EDB = extensor digitorum brevis muscle; AHB = abductor hallucis brevis muscle; LN = limits of normality established in our laboratory*

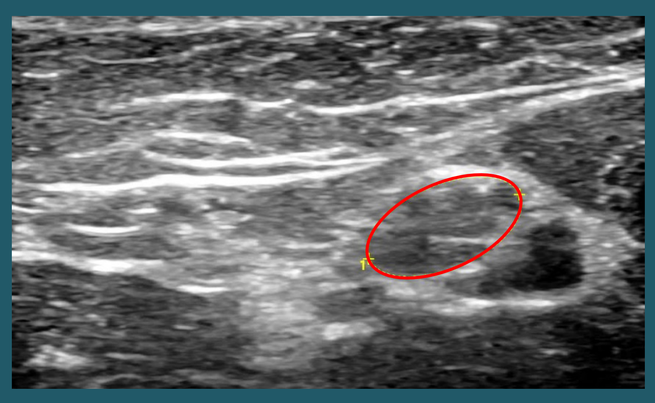

Figure 3. *Cross-sectional area of the median nerve at the left elbow ;**17 mm² (upper limit of normal: 12mm²)***

CMT1H	Minimal threshold	ULN N = 31	iUP	ULN N = 31	iMAX	ULN N = 31	Slope	LLN N = 31
Median (wrist)	2.9 mA	2.8	12 mA	7.0	11.7 mA	6.9	1.1	2.3
Ulnar (elbow)	5.8 mA	2.2	13 mA	8.0	11.2 mA	7.4	1.9	1.8
Fibular (knee)	6 mA	2.9	18 mA	9.0	17.3 mA	8.5	0.9	1.8

Figure 2*. iMAX procedure. ULN/LLN : upper and lower limits of normal; in red : values outside limits of normal*

Rheobase was increased (9.11 mA by TT) and SDTC decreased (0.217 ms by TT) (Figure 4). The recovery cycle study showed reduction in the absolute (MM) and the relative refractory periods (TT and MM) without other striking abnormalities (Figure 5 and 6). Threshold electrotonus revealed a decrease in TEd(40-60) and the current-threshold relationship was steeper than in controls (Figure 7).

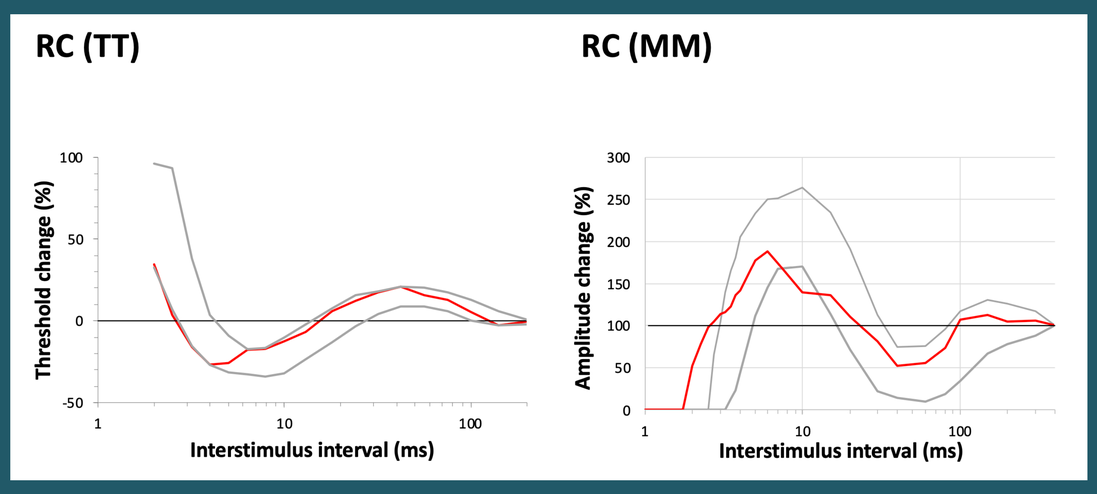

Figure 5 and 6. *Recovery cycle (RC) evaluated by the TT and MM techniques, respectively. TT studied threshold variations of test stimuli (intensity required to produce 40% of maximal CMAP) after supramaximal conditioning stimulus with interstimulus interval from 2 to 200 ms. MM measured motor response amplitude variations of test stimuli after supramaximal conditioning stimulus with interstimulus interval from 1 to 400 ms. Grey curves: P5/P95 from 31 healthy controls; red curve: CMT1H data.*

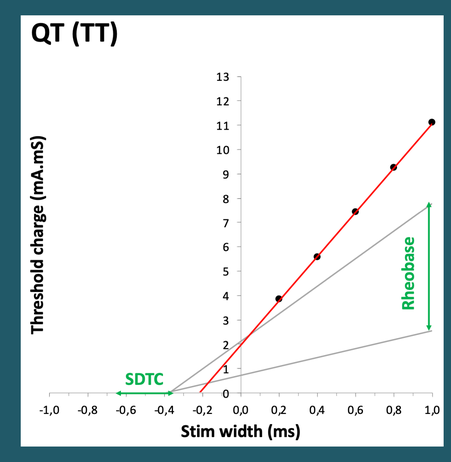

Figure 4. *Relationship between the delivered charge (current X stimulus duration) and the stimulus duration (QT) evaluated by the TT technique. The rheobase was defined by the slope of the linear relationship and the SDTC by the intercept on the x-axis. Grey curves : P5/P95 from 31 healthy controls; red curve : CMT1H data; in green : range of normal limits for rheobase and SDTC.*

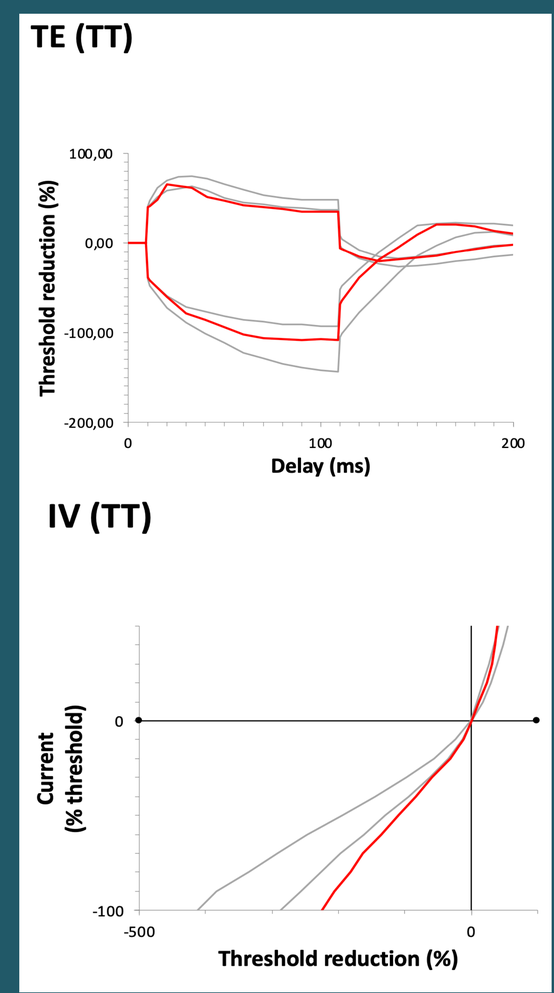

Figure 7. *Threshold electrotonus (TE) and current-threshold relationship (IV) evaluated by the TT technique.*
Grey curves : P5/P95 from 31 healthy controls; red curve : CMT1H data.

CONCLUSION: This case of CMT1H could be considered a good model of hypertrophic demyelinating neuropathy, without secondary axonal loss. Motor axonal excitability evaluations show:

- **Increased resting threshold currents (iMAX parameters and rheobase), reflecting the need for higher currents to compensate for internodal leakage currents, similar to CMT1A patients**
- **A reduction in the relative refractory period, also observed in patients with CMT1A and chronic inflammatory demyelinating polyneuropathy**
- **A steeper current-threshold relationship than in controls, indicating a greater activation of IH (= inward rectifying K^+ and Na^+ currents) during hyperpolarizing currents, as observed in CMT1A patients**
- **A decrease in SDTC, which could be due to a lower density of persistent sodium channels, linked to demyelination**

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