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Tremor in Charcot-Marie-Tooth disease: No evidence of cerebellar dysfunction

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HIGHLIGHTS

- This is the first pathophysiological study of tremor in hereditary neuropathies.
- This study reveals features that distinguish it from other forms of tremor, in particular the finding of a normally functioning cerebellum.
- 'Neuropathic tremor' is for the first time distinguished from other types of neuropathic tremor on the basis of mechanism, reframing this movement disorder as aetiologically heterogenous.

ABSTRACT

Objectives: Tremor in Charcot-Marie-Tooth disease (CMT) can be disabling. Cerebellar abnormalities are thought to underpin neuropathic tremor. Here, we aim to clarify the potential role of the cerebellum in CMT tremor.
Methods: We assessed prevalence of tremor by questionnaire in 84 patients with CMT. Of those, 23 patients with CMT with and without arm tremor and healthy controls underwent a clinical assessment, classical eye-blink conditioning, electro-oculography, visuomotor adaptation test, tremor recording with surface EMG and accelerometry, and retrospective correlation with nerve conduction studies to investigate the possible mechanisms of tremor generation.
Results: The prevalence study revealed tremor in 21% of patients and in 42% of those it caused impairment of function. Tremor recordings revealed a mild-to-moderate amplitude tremor with a weight load-invariant 7.7 Hz frequency component. Performance on classical eyeblink conditioning, visuomotor adaptation and electro-oculography were no different between tremulous and non-tremulous patients and healthy controls.
Conclusions: These results argue against a prominent role for an abnormal cerebellum in tremor generation in the patients studied with CMT. Rather, our results suggest an enhancement of the central neurogenic component of physiological tremor as a possible mechanism for tremor in the patients studied.
Significance: This study is the first to propose differing pathogenic mechanisms for subtypes of neuropathic tremor.

1. Introduction

Tremor can occur as part of Charcot-Marie-Tooth disease (CMT) due to a variety of mutations. In paediatric CMT, tremor is one of the most disabling symptoms (Burns et al., 2010) and also predicts

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other disabling symptoms (Blyton et al., 2011). The mechanisms that give rise to this tremor is not known although various hypotheses have been postulated (Barbieri et al., 1984; Cardoso and Jankovic, 1993). Cerebellar dysfunction is one hypothesis, as has been shown for tremor in inflammatory neuropathies (Bain et al., 1996; Brooks et al., 1992; Saifee et al., 2013; Schwingenschuh et al., 2013). Co-existence of essential tremor has also been considered, where cerebellar dysfunction would also be expected. Another possibility is fatigue causing entrainment of motor units resulting in an enhanced physiological tremor (Elble and Randall, 1978; Stiles, 1976, 1980; Young and Hagbarth, 1980). Fatigue is commonly recognised in CMT and represents an important outcome measure in clinical trials (Pareyson et al., 2011). Understanding tremor mechanisms is important as little is known about treating tremor in CMT, why only some patients seem predisposed and why it predicts other disabling symptoms.

Here we investigate clinical and pathophysiological aspects of the tremor associated with CMT, with an emphasis on techniques sensitive to cerebellar dysfunction such as eyeblink classical conditioning (EBCC) (Christian and Thompson, 2003; De Zeeuw and Yeo, 2005; Linden, 2003; Yeo and Hesslow, 1998), visuomotor adaptation (Galea et al., 2011) and eye movement recording (Helmchen et al., 2003). We hypothesise that these should be abnormal if the cerebellum is functioning abnormally or entrained in a pathological network in tremor in CMT.

2. Methods

2.1. Screening for tremor in a large cohort of CMT

Questionnaires (see Supplementary material) were sent to all patients with CMT attending a peripheral nerve outpatient clinic at the National Hospital for Neurology and Neurosurgery, London, UK (see eTable 1 and eTable 2 in the Supplementary material) to assess clinical features of tremor. Patients completed a spiral drawing with their dominant hand to assess tremor using the Bain and Findley spiral score (0 representing no tremor; 10 representing severe tremor) (Bain and Findley, 1993).

2.2. Clinical assessment

Twenty-three patients with CMT with and without tremor were recruited. Each group was matched for age, gender, diagnosis and severity of neuropathy (see Table 1). Detailed clinical assessment was performed. Patients taking tremorgenic medications were excluded. Summed scores for limb strength (MRC score) (Brain, 2000), sensation (subset of CMT neuropathy score) (Shy et al., 2005) and deep tendon reflexes (NINDS myotactic reflex scale for biceps, supinator, triceps, knee and ankle) (Litvan et al., 1996) were calculated. Tremor was assessed using the Fahn-Tolosa-Marin score (Stacy et al., 2007). Saccadic and pursuit eye movements were examined as well as a Dix-Hallpike positional manoeuvre for signs of cerebellar dysfunction (Bertholon et al., 2002 and Leigh and Zee, 2006). Neuropathy severity was assessed with the CMT neuropathy score (Shy et al., 2005) and disability measured by the overall neuropathy limitation scale (Graham and Hughes, 2006). Patients were divided into two groups for subsequent analysis depending on the clinical presence of tremor (tremulous and non-tremulous groups). Any rhythmic EMG or accelerometric signal was considered physiological tremor if within the appropriate frequency range (8–12 Hz) and not detectable clinically. Such patients were considered non-tremulous as physiological tremor is a phenomenon recordable in most healthy controls. Patients' nerve conduction studies were reviewed.

2.3. Motor control studies

Differing numbers of patients were recruited for each of the following studies. The combined study duration for all experiments was not feasible for all subjects.

2.3.1. Accelerometry and EMG

16 patients (10 tremulous and 6 non-tremulous) participated. As detailed previously (Schwingenschuh et al., 2011), a triaxial accelerometer (Biometrics Ltd; sensitivity ±50 mV/G) was attached to the dorsal surface index finger bilaterally. Surface EMG was recorded simultaneously, from biceps brachii (BB), forearm flexors (FF), forearm extensors (FE) and abductor pollicis brevis (APB) bilaterally. Recordings were performed: (a) with arms outstretched (postural condition) and (b) postural condition with 500 g mass attached to the hand (weight loading).

2.3.2. Eye movement recordings

Five tremulous patients underwent electro-oculography (EOG) to record horizontal saccadic and pursuit eye movements. Subjects were seated 84 cm from a target light source (Fig. 1A). For saccades, LEDs were randomly presented at 10, 20, or 30 degrees in rightward and leftward directions, with inter-stimulus interval of 4 s. Smooth pursuit eye movements were assessed using 8 cycles of a target moving horizontally about a centre point with a sinusoidal velocity curve. This was repeated for 0.1 Hz, 0.2 Hz, 0.3 Hz and 0.4 Hz (target displacement ±20 degrees, peak velocities from 12.5, 25, 37.5, and 50 degrees/s respectively). Subjects were instructed to maintain

Table 1
Clinical features.

Variable	Tremulous patients	Non-tremulous patients	*p*-value
Number of patients	13	10	n/a
Age (years)	54.7 (12.6)	48.5 (13.4)	0.41
Sex	31% female	33% female	1.00
Diagnosis	CMT1A (92%) CMT1B (8%)	CMT1A (80%) CMT1B (10%) CMT2 mitofusin (10%)	
MRC score (arm)	35.9 (5.1)	34.1 (9.7)	0.34
NINDS reflex score (arm)	1.3 (3.6)	3.8 (5.3)	0.11
Sensory score (arm)	22.8 (7.5)	23.3 (4.5)	0.83
CMT neuropathy score	17.5 (7.2)	16.5 (8.6)	0.82
ONLS score (arm)	1.9 (1.1)	2.0 (1.4)	0.60
Median nerve conduction velocity (wrist to elbow) (m/s)	21.2 (9.0)	21.7 (12.5)	0.92
Median nerve CMAP (wrist) (mV)	4.2 (3.4)	2.8 (2.1)	0.29
Median nerve F-wave latency (wrist) (ms)	56.9 (18.4)	42.9 (16.0)	0.32

Mean (standard deviation); n/a – not applicable.