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SLOW ORTHOSTATIC TREMOR IN MULTIPLE SCLEROSIS

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Keywords

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While several forms of tremor are common in multiple sclerosis (MS), orthostatic tremor (OT) has not been reported[20].

A 38 year old female, diagnosed with clinically definite relapsing remitting MS at the age of 27, presented following initial improvement from a relapse affecting ambulation, complaining of tremor affecting her legs associated with an intense feeling of unsteadiness. The tremor was not present when sitting but appeared upon standing (see video). It was reduced but not relieved by walking. Neurological examination demonstrated increased tone in the legs, ankle clonus, pyramidal weakness in the left leg (MRC grade 4), symmetrical

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Documentation of authorship

Dr Mark Baker designed the experiments, organized and executed the experiments, analysed the data, performed statistical analysis, produced the figures and wrote the manuscript.

Ms Karen Fisher organized and executed the experiments, analysed the data, performed statistical analysis, and reviewed and critiqued the manuscript.

Dr Ming Lai executed the experiments and reviewed and critiqued the manuscript.

Dr Martin Duddy referred the patient, wrote the case report section and reviewed and critiqued the manuscript.

Professor Stuart Baker designed the experiments, executed the experiments, wrote the statistical and data analysis software, analysed the data, and reviewed and critiqued the manuscript.

Disclosure statement

MRB is employed by the NHS and NIHR. MED and HML are NHS employees. SNB and KMF are employees of Newcastle University.

SNB and KMF are engaged as consultants to Cambridge Pharmaceuticals on an unrelated project.

MED has received honoraria from BiogenIdec, Bayer Schering, Merck Serono and Teva.

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Video Legend

A. Standing. Initially the patient is seated and there is no lower limb or axial tremor. As she stands up marked axial and lower limb tremor appears. **B. Walking.** As the patient walks, with the aid of two sticks, the tremor appears to improve. However, there was no subjective change in the sensation of unsteadiness. **C. Lower limb examination**. The patient demonstrates evidence of mild heel-shin ataxia, which is worse on the left. **D. Co-contraction.** While supine the patient was asked to raise her legs with her feet in plantar flexion and to co-contract her leg muscles. During this manoeuvre there is no visible tremor (tremor can only be detected with accelerometry). **E. Upper limb examination.** Assessment of tremor in the upper limbs only demonstrated mild terminal tremor on the left. **F. Eye movements.** Only smooth pursuit was tested, which was normal.

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hyperreflexia, extensor plantar responses, mild left upper limb dysmetria, mild bilateral heel-shin ataxia, impaired proprioception at the hallux bilaterally and absent vibration sense to the knee. These examination findings had remained stable for several years (outside of acute relapses) and until she developed OT had not prevented independent ambulation.

MRI showed active disease with several periventricular lesions in frontal and parietal cortex, and one lesion within the left *brachium pontis* (Figure A), which enhanced with gadolinium (Figure B).

Electrophysiology showed no evidence of axial or appendicular tremor while seated, but as the patient stood tremor appeared in the legs and trunk. The tremor power spectrum obtained from an accelerometer affixed to the left patella (Figure C) showed a dominant peak at ~4Hz and a smaller sub-harmonic at ~8Hz. Raw rectified EMG recorded using adhesive electrodes from left *tibialis anterior* (gain 500-5000; band pass filtered 30Hz-2kHz; 5kHz digitization) whilst standing contained four 100ms bursts of EMG per second (Figure D). Frequency domain analysis (see normalised power spectra in Figure E) confirmed that the dominant frequency was ~4Hz. In the left *gastrocnemius-soleus* and *tibialis anterior* power spectra there were small additional 8-15Hz sub-peaks. Coherence analysis (see [14 15]) confirmed that there was significant unilateral and bilateral EMG-EMG coherence not only at tremor frequency but also in the 8-12Hz and 13-18Hz ranges, suggesting that other common frequencies might also be driving lower limb tremor (Figure F).

The effects of patella tendon stimulation on OT were also investigated (Figure G). The linear relationship between tremor phase before and after a tendon tap confirmed that this form of muscle afferent stimulation could not reset the phase of the tremor, as previously described in slow[4] and fast OT[16, 17].

Pharmacological treatment (i.e. clonazepam, levetiracetam, L-DOPA, gabapentin) was either ineffective or produced intolerable side effects.

Orthostatic tremor (OT) is a rare form of action tremor affecting the legs and trunk. It appears on standing, is associated with a profound and disabling sense of unsteadiness and is relieved by sitting, walking or the use of a support. Two types of OT are recognized: fast OT, characterised by bursts of muscle activity at 13-18 Hz [1-3]; and slow OT [4, 5], with a frequency of 3-8 Hz.

Slow OT was first described in 1986 in a family with essential tremor[5]. Subsequently it has been described in patients with Parkinson's disease and parkinsonism[6-8], and in one patient two months after resection of a cavernoma involving the right *brachium pontis* [9] (cf. Figure A-B). Idiopathic slow OT, in the absence of primary or associated neurological disease has also been described [4].

In slow OT EMG recordings from leg, trunk and arm muscles demonstrate regular 70-120 ms bursts of activity in the 4-6 Hz range[8]. Coherence analysis reveals powerful coupling between EMG recorded from lower limb, upper limb and axial muscles both unilaterally and bilaterally, at tremor frequency, which is absent in controls under normal conditions [10] and patients with orthostatic myoclonus [8]. Treatment with clonazepam is reportedly helpful; if there is associated parkinsonism anecdotal evidence to supports the use of L-dopa, dopamine receptor agonists or trihexyphenidyl, with or without clonazepam [11, 12].

Although OT has not previously been described in MS, the spastic-ataxic gait sometimes encountered in MS can be mistaken for OT[22]. This is partly because of the subjective sense of unsteadiness, but also because the frequency of clonus (~4 Hz) [23] can resemble tremor. Clonus, which is easily re-set by stimulating muscle afferents [24], did not contribute to the

OT observed in our patient because her tremor could not be entrained by tendon vibration (see Fig. G).

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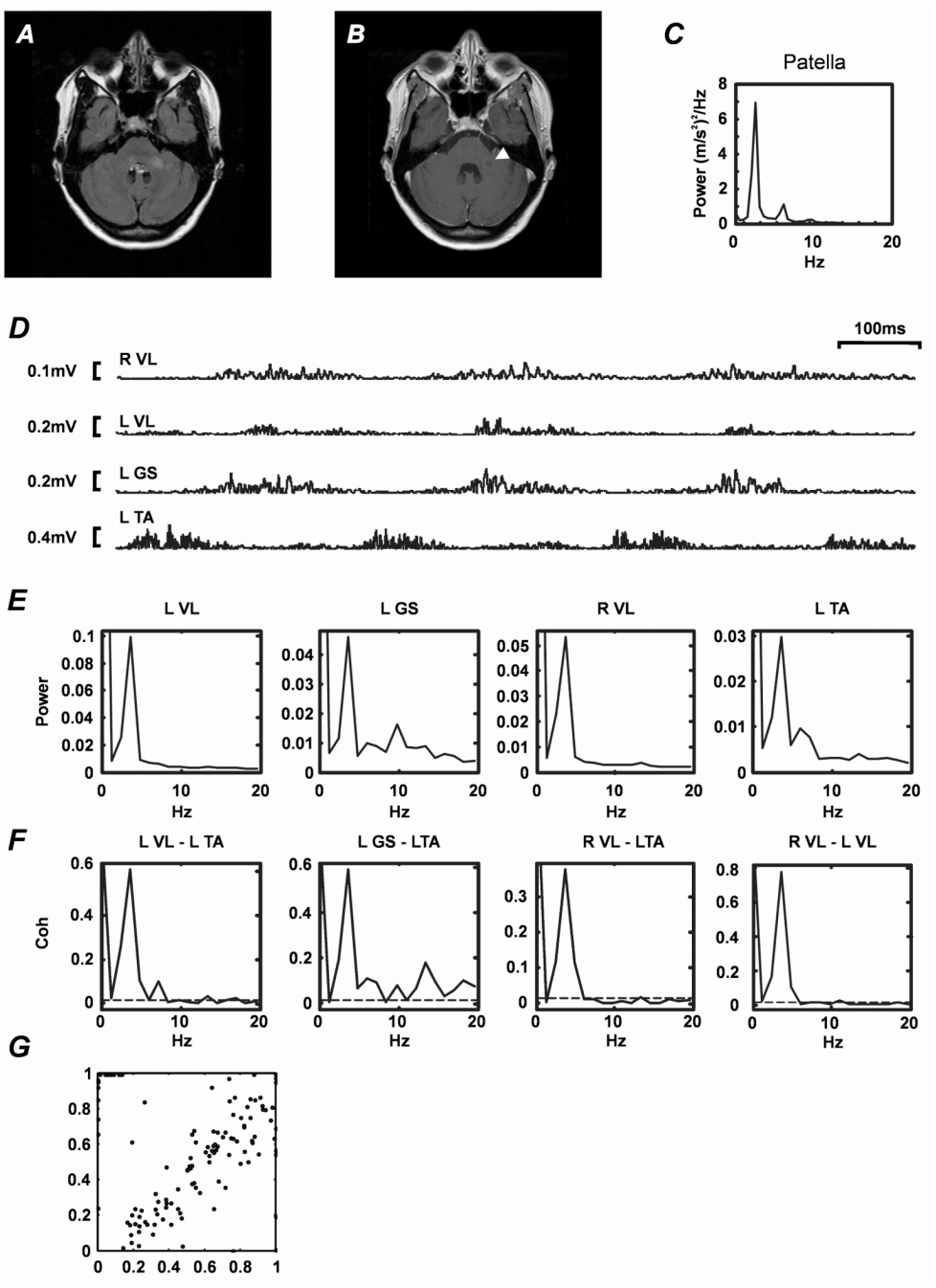

Figure. Radiology and clinical neurophysiology

A. MRI brain. Axial FLAIR sequence showing left middle cerebellar peduncle *(brachium pontis)* lesion consistent with demyelination. ***B.*** Equivalent axial gadolinium enhanced T1-weighted MRI sequence. Note that the area of active inflammation (indicated by arrow head) co-localises with the lesion shown in A. ***C.*** Tremor power spectrum (data obtained from accelerometer attached to the left patella during stance). ***D.*** Rectified EMG recorded from left *tibialis anterior* (L TA), left *gastrocnemius-soleus* (L GS), left *vastus lateralis* (L VL) and right *vastus lateralis* (R VL) muscles while the patient was standing. Each trace represents one second of data. EMG bursts have a duration of approximately 100 ms (see timebase, top right). Voltage calibration bars are shown to the left of each trace. ***E.*** EMG

power spectra (expressed as a fraction of total power) derived from EMG recordings illustrated in A (data length 340s). ***F.*** Intermuscular coherence spectra. Muscle pairs used to calculate coherence spectra are indicated above each plot. Data points above the dashed lines indicate significant coherence ($P<0.05$)[15] ***G.*** Phase resetting plot. Each point represents the effects of one tendon tap stimulus delivered to the patella tendon. Abscissa represents phase of 4Hz oscillation in patella acceleration prior to a tap and ordinate represents phase one cycle following stimulation; phase in both cases is expressed as a fraction of an oscillation cycle. Linear dependence indicates that the tap stimulus did not affect the phase of ongoing tremor.

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