

## Supplementary Online Content

Crompton DE, Sadleir LG, Bromhead CJ, et al. Familial adult myoclonic epilepsy: recognition of mild phenotypes and refinement of the 2q locus. *Arch Neurol*. 2012;69(4):474-481.

**eAppendix.** Methods and Results.

**eFigure.** Neurophysiology Demonstrates Features of Cortical Myoclonus.

This supplementary material has been provided by the authors to give readers additional information about their work.

## **eAppendix. Methods and Results**

### **Methods**

#### Neurophysiological Testing

Nicolet Viking equipment (Nicolet Biomedicals, Madison, WI, USA) was used with bandpasses of 0.5 to 100Hz for EEG, 30Hz to 3kHz for SEP, 30Hz to 20KHz for multi-channel surface EMG, and 2Hz to 5kHz for median motor nerve conduction and long loop reflex studies. EEG electrode placement was according to the standard international 10-20 system. All EEG recordings included hyperventilation and intermittent photic stimulation. Surface EMG was recorded simultaneously from four channels using pairs of 2-cm diameter Ag-AgCl disposable disk electrodes placed 3 cm apart over the wrist flexors and extensors, biceps brachii and triceps brachii.

For back averaging, EEG gold-cup scalp electrodes with impedances of less than 5 kohm were used. Myoclonic bursts from wrist flexors were used as the trigger for acquisition, recording from C3, Cz and C4' referenced in different trials to A1, A2 or Fz.

Median somatosensory evoked potentials (SEPs) were elicited by electrically stimulating the median nerve at the wrist with 9 mm diameter surface bipolar electrodes (cathode proximal), delivering electrical square wave stimuli of 0.2ms duration just above the motor threshold and at a stimulus rate of 3.1 Hz. Scalp recording electrodes were C3' and C4' referenced to Fz. Cortical response amplitudes calculated were baseline to peak (N15-N20) and peak to peak (N20 to P25, P25 to N33). Long-loop (LLRs) reflexes were recorded at rest with stimulation the median nerve at the wrist using electrical square wave stimuli of 0.1ms duration, set above the motor threshold and recording from abductor pollicis brevis with surface disc electrodes.

### **Results**

#### **Illustrative Case Histories**

### ***Clinical Case Study 1: IV<sub>47</sub>***

A 53 year old man reported onset of tremor at 10 years of age, and myoclonic jerks at age 27. Flashing lights would exacerbate myoclonus markedly and cause him to fall without impaired consciousness. His hands were most severely affected, and he described consistently spilling hot drinks and being unable to keep peas on his fork. Climbing ladders became unsafe as his toes and feet would shake when standing on the rungs. He described a voice tremor, together with tremor of his eyelids on eye closure. Seizure onset was at the age of 48, with a nocturnal generalized tonic-clonic seizure, occurring during a time of work stress and sleep deprivation. This attack was preceded by 2 minutes of “uncontrollable body shivers and rhythmic shaking of the legs” during full consciousness. Clonazepam was commenced as a single nocturnal dose, with modest improvement in myoclonus and tremor. 5 years later a further generalised tonic-clonic seizure occurred, this time from wakefulness, leading to increase in clonazepam dose. Examination, aged 52, revealed marked tremor of hands, and eyelid tremor on eye closure (video). Multifocal myoclonus was seen, prominently affecting the proximal upper limbs, though facial muscle involvement was also evident. MRI and EEG were normal.

### ***Clinical Case Study 2: III<sub>24</sub>***

A 76 year old man reported onset of tremor and myoclonus at 44 years of age, though symptoms had worsened over the last decade. Tremor and myoclonus of the upper limbs led to spilling cups of tea, and losing food from the fork when eating. Fine tasks such as writing, and fastening buttons or cufflinks became difficult. Symptoms worsened later in the day, and he avoided signing cheques after lunchtime as his handwriting would become unrecognisable. He described prominent myoclonic jerks from flash photography or sunlight flickering through a row of trees. He suffered infrequent migraines and was prescribed propranolol, with associated improvement of his tremor. At the age of 76 he had an unprovoked nocturnal generalised tonic-clonic seizure. MRI and EEG were normal. 4 days later he suffered a further nocturnal generalised tonic-clonic seizure, this time with a 4 or 5 hour prodrome during which his wife described marked increase in myoclonic jerks and vague affect, with slight

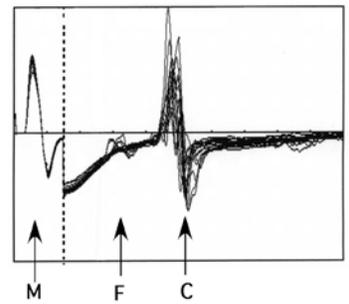
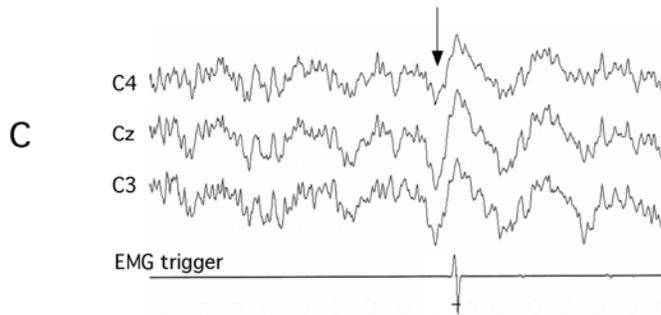
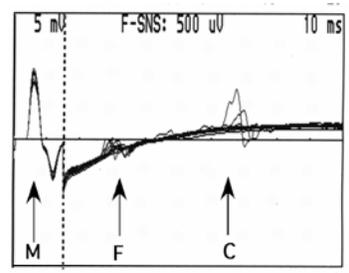
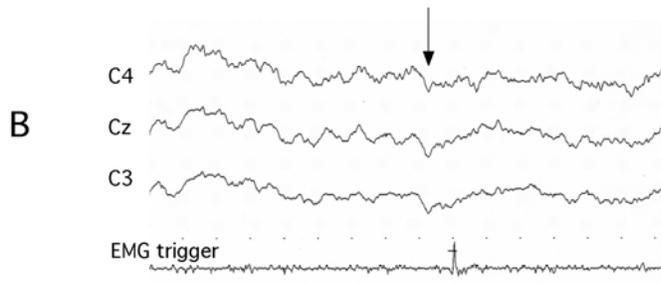
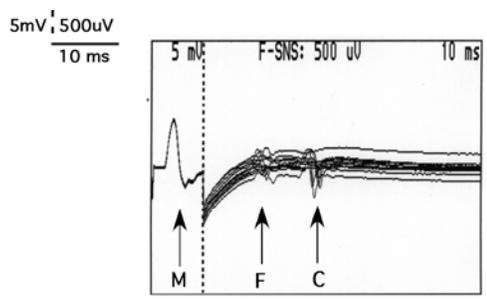
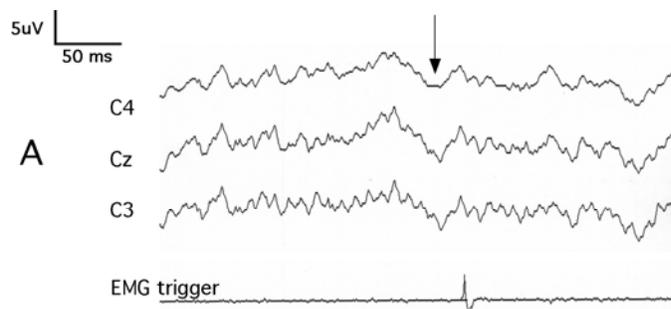
slurring of his speech. During the subsequent hospital stay, hypotension led to propranolol being weaned. Phenytoin was commenced for seizure prophylaxis. This combination of medication changes led to exacerbation of tremor and myoclonus, with lower limb myoclonus so severe as to make walking unsafe even with a frame. Following contact with the research team, phenytoin was discontinued in favour of sodium valproate and a striking improvement was noted within days, with further benefit after reintroduction of propranolol at a reduced dose. Examination at age 75 revealed hand and eyelid tremor, with a milder, semi-rhythmic leg tremor. Myoclonus affecting arms, trunk and legs was prominent (shown in video).

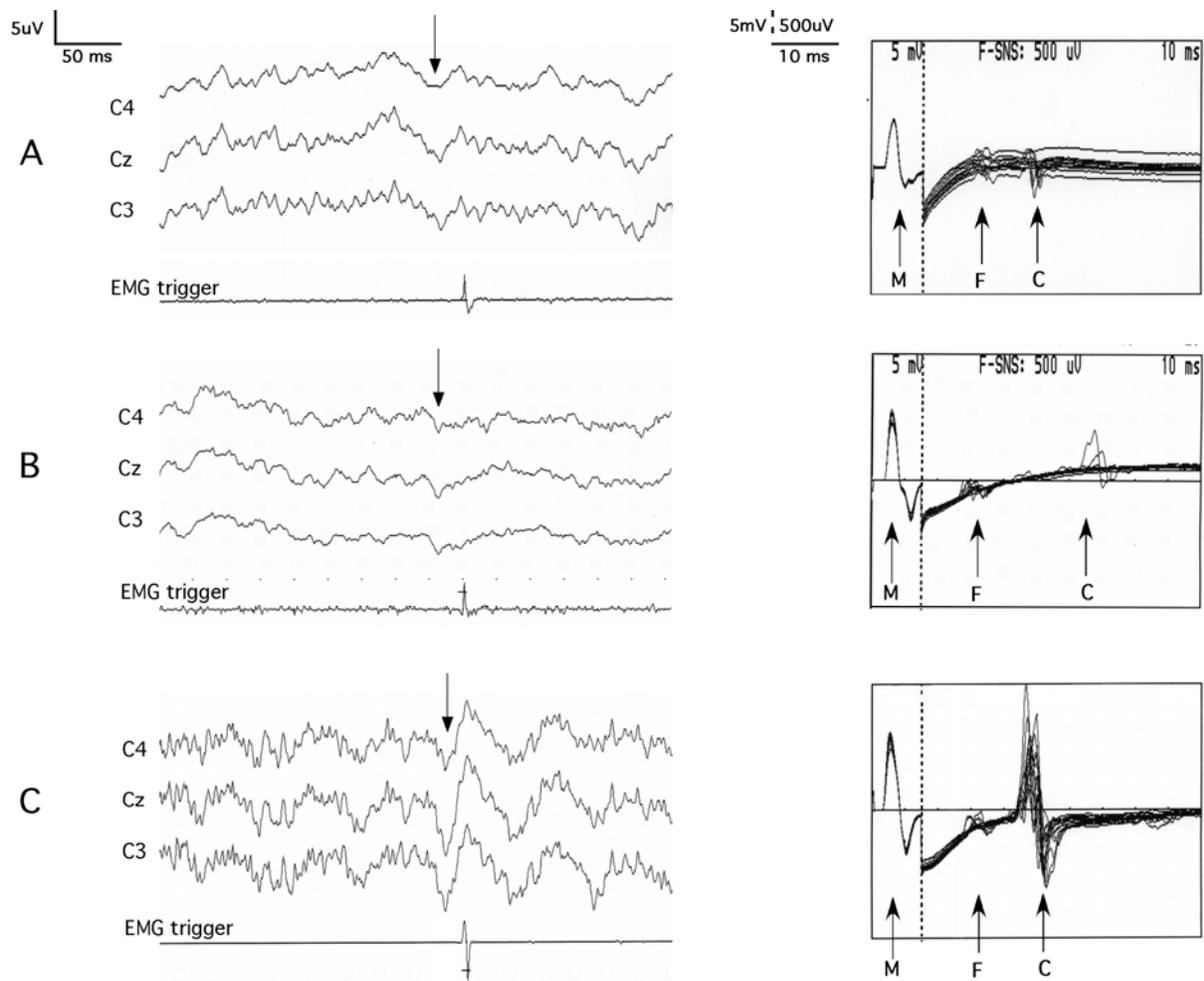
### ***Clinical Case Study 3: IV<sub>1</sub>***

A 61 year old woman developed tremor and myoclonic jerks at the age of 30. Tremor affected the hands principally, but also the eyelids, on eye closure. Fine actions such as drawing would particularly exacerbate the tremor. Myoclonic jerks affected the hands and arms, in addition to face and head/neck. Although the tremor and myoclonus would cause her to spill things, there was no other disability. Her first seizure occurred at 48 years of age, from wakefulness, and was preceded by prominent myoclonic jerks mainly affecting the head and neck. She was aware of erratic involuntary movements of the eyes giving oscillopsia, with all of her symptoms worsening on attempted eye closure. She then lost consciousness and suffered a generalised tonic-clonic seizure. Her only other attack happened at the age of 60, after sleep deprivation at a family gathering. This attack was preceded by 4-5 hours of intense unease and marked exacerbation of myoclonus affecting head, eyes and shoulders. Eye closure on trying to sleep exacerbated the myoclonus and made her feel “as if she might die”. She then lost consciousness during high amplitude rhythmic generalised myoclonus, which was followed by tonic then clonic seizure phases. After hospital admission she was commenced on lamotrigine treatment but elected not to renew her prescription and has since been seizure free for 18 months off treatment.

*Clinical Case Study 4: V<sub>27</sub>.*

A 21 year old woman described onset of tremor at the age of 10. She had not initially been aware of it herself but classmates continually would ask her if she was frightened or cold. Fatigue and stress would worsen the symptoms and she tended to avoid writing at school as she struggled to do so neatly. She would spill drinks but otherwise coped well with her involuntary movements. She has not had seizures. Examination revealed an irregular fine tremor of the hands, with superimposed low amplitude jerks (Video), in addition to myoclonus of trunk, proximal upper limbs and legs, and eyelid myoclonia on eye closure.





**eFigure.** Neurophysiology demonstrates features of cortical myoclonus. Left: EMG-EEG back averaging in three subjects (A: 43 year old male, B: 21 year old female, C: 52 year old female). A positive potential on the averaged EEG (arrow) precedes EMG spikes by 20-26 ms (horizontal scale bar = 50 ms). Right: surface EMG of abductor pollicis brevis showing M wave, F wave and positive long loop reflexes (C waves) recorded at rest following median nerve stimulation in the same individuals.