Clinical commentary with video sequences

Alcohol-responsive epilepsy partialis continua

Trevor A Steve, Donald W Gross

Division of Neurology, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

ABSTRACT – Epilepsia partialis continua is typically associated with lesions of the cerebral cortex. However, subcortical lesions can also cause this condition. We present a patient with epilepsy partialis continua who failed to respond to conventional anticonvulsant medications but experienced a dramatic transient response to alcohol and a subsequent response to primidone. This pattern of sensitivity, which is similar to that seen in essential tremor, has led to the hypothesis that the two disorders are associated with pathology within the same anatomical network. A new pathophysiological model is thus proposed for the occurrence of epilepsy partialis continua in both cortical and subcortical disease processes. [Published with video sequences]

Key words: epilepsy partialis continua, myoclonus, essential tremor, tremor

Epilepsia partialis continua (EPC) is defined as “continuous muscle jerks of cortical origin” (Cockerell et al., 1996). Patients with EPC suffer from infrequent generalised seizures and medically intractable myoclonic jerks. The most common causes of EPC are Rasmussen’s encephalitis, tumours, stroke, and focal cortical dysplasia. The pathophysiology of EPC is incompletely understood (Guerrini, 2009). It is typically associated with lesions in the contralateral cerebral cortex (Cockerell et al., 1996). However, subcortical pathology can also cause EPC (Juul-Jensen and Denny-Brown, 1966). The role of subcortical structures in maintaining cortical epileptic activity remains unclear. Presently, “no single mechanism” has been proposed to account for the occurrence of EPC with both cortical and subcortical lesions (Guerrini, 2009).

Essential tremor (ET) consists of postural-kinetic hand tremor and variable involvement of other body regions. A striking feature in ET is a dramatic temporary response of the tremor to alcohol. Many patients also experience a moderate to marked improvement with primidone (Elble, 2009). The pathophysiology of ET is believed to involve “tremorogenic oscillation and synchrony in motor networks”, involving the inferior olive, cerebellum, and cerebral cortex (Elble, 2009). We report a case of EPC which was alcohol and primidone responsive. Given the similarities of pharmacological sensitivity, we hypothesize overlap in the anatomical network involved in ET and EPC.
Case Study

In 1998, a 31-year-old, right-handed male developed new onset of continuous twitching of his right middle finger. The movements remained restricted to this finger and were not accompanied by alteration of consciousness. The patient did not seek medical attention and the twitching resolved spontaneously after three weeks.

The twitching returned again without provocation in 2004. Over the course of five days, the movements spread sequentially to contiguous fingers and the hand, and the patient then had a generalised seizure lasting two minutes. Following the generalised tonic-clonic convulsion, the patient continued to have constant rhythmic twitching of the right arm (video sequence). His right upper extremity was rendered non-functional by the movements. Initial treatment with valproic acid, carbamazepine, and phenytoin was unsuccessful. Clonazepam and levetiracetam were partially effective, but despite these medications, the movements persisted.

The EEG showed continuous rhythmic delta activity in the left frontal-central-parietal region. An MRI performed the day following his generalised convulsion showed a focal region of increased T2 signal in the left hemisphere, adjacent to the precentral sulcus (figure 1A). This region demonstrated restricted diffusion but not gadolinium enhancement. The CSF examination showed no cells and normal protein.

As the continuous focal motor seizures failed to respond to anticonvulsants, aggressive management was attempted. A sedating dose of intravenous propofol eliminated the movements, but they returned when the infusion was discontinued. Propofol and pentobarbital in combination were then titrated to burst suppression, and the patient was maintained in coma for 48 hours. During this time, EPC was again abolished, but the movements recurred immediately after discontinuation of the anesthetic.

The patient continued to have EPC over the next several years. Some benefit was noted with topiramate, but this medication was stopped due to development of kidney stones. Oxcarbazepine was partially effective and was continued. No significant improvement was achieved despite treatment with lacosamide, intravenous solumedrol, and the modified Atkin’s diet. He suffered his only additional generalised seizure in 2006. EPC remained essentially continuous and was associated with major functional impairment of the use of his right hand. Repeat MRI in 2010 demonstrated atrophy of the cerebral cortex adjacent to the precentral sulcus, without evidence of T2 hyperintensity (figure 1B).

In July of 2011, the patient presented to the clinic having made an unusual observation. He recounted that after having consumed several alcoholic beverages, his EPC resolved acutely and his hand function essentially improved to normal. At this time, he was able to pick up a grain of rice with chopsticks, something that would have been impossible in his prior state. The next morning, his EPC had not only returned, but transiently worsened.

Based on the patient’s report of alcohol responsiveness, primidone was started at a dose of 125 mg daily. Within days of starting on this medication, after nearly seven years of continuous EPC, his movements completely disappeared. In association with this, his right hand function again improved dramatically (he was able to shave with his right hand). After approximately one week, the movements returned.

With increasing doses of primidone, both the EPC and motor function improved, but complete control was not obtained. A trial of propranolol had no effect on the movements, suggesting peripheral mechanisms did not play a major role in our patient (Elble, 2009). Ethosuximide, which acts via inhibition of low-threshold (T-type) calcium channels, also had no effect on the movements. Based on reports of alcohol-responsive myoclonus responding well to gamma-hydroxybutyrate, this medication was tried for one week (Frucht et al., 2005). The patient reported worsening of EPC during this trial as well as excess sedation, and the medication was therefore discontinued. His current medications are levetiracetam at 500 mg once daily, oxcarbazepine at 600 mg twice daily, clonazepam at 0.5 mg twice daily, and primidone at 375 mg twice daily. He presently remains disabled by continuous twitching of the right hand and is unable to write or shave.

Discussion

This report describes a patient with severe medically intractable EPC. Investigation revealed a transient T2 hyperintensity adjacent to the left precentral sulcus, likely related to ongoing seizure activity in a location typical for EPC (Cockerell et al., 1996). Follow-up imaging ruled out stroke and tumour as diagnostic possibilities. The negative cerebrospinal fluid examination made encephalitis unlikely. The age of presentation is atypical for focal cortical dysplasia. The patient did not develop progressive hemispheric atrophy characteristic of adult-onset Rasmussen’s, and did not respond to a course of corticosteroids. Therefore, the underlying aetiology of EPC in this case remains uncertain.

The response to alcohol and primidone in this patient was dramatic, resulting in temporary, complete resolution of EPC, and requires mechanistic explanation. Primidone does have anticonvulsant effects, but the
A

B

Figure 1. (A) Initial fluid-attenuated inversion recovery (FLAIR) brain MRI showing increased T2 signal in the cerebral cortex adjacent to the left precentral sulcus. (B) Follow-up FLAIR brain MRI performed six years later showing resolution of T2 signal abnormality and cortical atrophy adjacent to the precentral sulcus.

patient was refractory to AEDs which act by various mechanisms. Given the limited response of the EPC to conventional anticonvulsants, we hypothesize that alcohol and primidone most likely acted in this patient via a similar mechanism to that in Essential Tremor (ET). Animal studies have suggested that alcohol eliminates ET by three mechanisms (Mostile and Jankovic, 2010), and primidone is believed to act in a similar fashion (Elble, 2009). Firstly, alcohol is capable of blocking T-type calcium channels in the inferior olive (Sinton et al., 1989). These channels are thought to be integral to the pathophysiology of ET by setting up excessive excitation of cerebellar Purkinje cells via the climbing fibres (Mostile and Jankovic, 2010). Given the lack of
Figure 2. Model depicting the proposed involvement of cerebellar micro-circuits in the pathophysiology of epilepsia partialis continua. Alcohol and primidone inhibit type 1 metabotropic glutamate receptors (A) at the climbing fibre-Purkinje cell synapse (1). Ethanol and myosoline also normalise glutamate concentrations in the deep cerebellar nuclei (2), antagonising the activity of the N-methyl-D-aspartate (NMDA) glutamate receptor (B).

response of this patient to ethosuximide, it is unlikely that this mechanism plays an important role in this patient. The climbing fibre-Purkinje cell synapse is the site of a second action, whereby alcohol is an effective inhibitor of the metabotropic glutamate receptor (Carta et al., 2006). Finally, alcohol has been shown to normalise N-methyl-D-aspartate (NMDA)-mediated increases in glutamate concentration in deep cerebellar nuclei (Manto and Laute, 2008). The response to alcohol and primidone in this patient is consistent with involvement of the cerebellar micro-circuits in EPC (figure 2) (Lisberger and Thach, 2013). This model provides a possible explanation for EPC due to both cortical and subcortical pathology.

A cortical origin is demonstrated in most cases of EPC (Cockerell et al., 1996). As our patient experienced generalised seizures and was demonstrated to have a transient discrete cortical T2 hyperintensity on presentation, we assume that the primary pathology responsible for this patient’s EPC was also cortical. However, we hypothesize that the responsiveness to alcohol and primidone is most likely explained by involvement of the cerebellar micro-circuits (figure 2). Diffuse regions of cortex contribute axons to the cortico-pontine tract, which is the main source of cortical input to the cerebellum. These fibres form glutamatergic synapses with the pontine nuclei in the brainstem. Cortical activity could thus be transmitted to the cerebellar cortex via the mossy fibres and result in excessive stimulation of cerebellar granule and Purkinje cells (Lisberger and Thach, 2013). Excessive glutamatergic stimulation of neurons in the deep cerebellar nuclei, analogous to that which occurs in ET, could then be transmitted from the cerebellum via the superior cerebellar peduncle (SCP). The authors hypothesize that excitation is conveyed via the SCP to the thalamus, resulting in excessive stimulation at ventral anterior and ventral lateral thalamic nuclei.
This hypothesis is consistent with studies indicating thalamic involvement in EPC (Guerrini, 2009). In the present model, excessive activity is subsequently conveyed from thalamic nuclei to cerebral cortex. Interruption of such thalamo-cortical fibres, in addition to cortico-pontine fibres described above, could thus result in EPC. This model therefore provides an explanation for EPC due to subcortical lesions (Juul-Jensen and Denny-Brown, 1966; Guerrini, 2009). These observations suggest that further study of glutamatergic modulation may be beneficial for the treatment of EPC, which in general, is extremely difficult to manage and often associated with considerable functional disability.

Acknowledgements and disclosures.
Jessica Rieckmann RN is acknowledged for her assistance in the clinical care of the patient. Ted Roberts MD FRCPC is acknowledged for recording the video material. The case described was presented during the Meet the Experts - Adults session at the 30th International Epilepsy Congress in June 2013. None of the authors have any conflict of interests to disclose.

Legends for video sequences
Rhythmic jerking of the right arm, recorded following the patient’s first generalised tonic-clonic convulsion. The movements remained essentially continuous since presentation and were associated with major functional impairment of the use of the right hand.

Key words for video research on www.epilepticdisorders.com
Syndrome: epilepsy partialis continua
Etiology: lesion (unknown nature)
Phenomenology: motor seizure (simple)
Localization: central (left)

References


