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Short communication

Refractory focal motor seizures controlled with intramuscular botulinum toxin

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ABSTRACT

Patients with recurrent focal motor seizures present a management dilemma, as anti-convulsants are often ineffective, and resective surgery poses a high risk of motor deficit. We describe three patients with recurrent focal motor seizures that remained refractory despite numerous anti-convulsant trials. All patients showed either hyperperfusion on Single-Photon Emission Computerised Tomography (SPECT) or hypermetabolism on Positron Emission Tomography (PET) in primary motor cortex during periods of sustained jerking, although EEG abnormalities were uncommon. After botulinum toxin (BoT) injection there was a rapid and dramatic reduction in seizure frequency in all patients despite minimal limb weakness. Seizure freedom persisted for 3–6 months following treatment in the injected area. Repeat BoT injections following seizure recurrence were again efficacious in one case. Combining data from our cases with those previously reported, it appears that BoT may be a useful therapeutic tool for recurrent focal motor seizures. We hypothesise that the toxin disrupts or down-regulates an epileptic circuit between motor cortex and muscle, in which volleys of information from muscle spindles have been perpetuating seizure discharges in the cortex.

1. Introduction

Focal motor seizures are characterised by focal twitching or posturing of a limb or muscle group, with the pattern of involvement consistent with the anatomic arrangement of the homunculus of the motor strip (Berg et al., 2010). Cognitive preservation during seizures and regionally specific muscle involvement suggest a restricted area of motor cortex is involved. EEG is often unhelpful, showing epileptiform abnormalities in only 13–22% (Cockerell et al., 1996), likely reflecting epileptiform discharges involving only a small area of cortex. Focal motor seizures may be exacerbated by active or passive movement of the involved limb, or at times by merely thinking about moving the limb (Mameniskiene et al., 2011). Epilepsia partialis continua (EPC) is a variant of focal motor seizure that is particularly medication resistant, characterised by persistent focal jerking that waxes and wanes in intensity for hours, days, or even months (Trinka et al., 2015).

Focal motor seizures can have a range of causes, including congenital or acquired focal lesions in or near motor cortex. In the absence of a readily treatable cause such as hyperglycaemia (Phabphal et al., 2012), focal motor seizures present a management dilemma. Anti-convulsants are often of limited effectiveness (Mameniskiene et al., 2011). For patients with a lesion, lesionectomy may abolish seizures, but as lesions will be in close proximity to motor cortex, surgery is likely to cause significant motor deficits.

Botulinum toxin type A (BoT) is a neurotoxin produced by *Clostridium botulinum*. It prevents acetylcholine exocytosis at the neuromuscular junction, causing chemical denervation and local weakness (Dressler et al., 2005). It has been used for a variety of conditions characterised by excessive muscle activity including hemi-facial spasm, dystonia, and limb spasticity. Following toxin injection, the compound muscle action potential amplitude declines within a few days, reaching nadir by day 21 (Hamjian and Walker, 1994; Frascarelli et al., 2011). However symptomatic improvement (eg: of dystonia) often lasts 2–3 months, more prolonged than can be explained by weakness alone, suggesting additional modes of action, possibly via afferent or central mechanisms (Kim et al., 2006; Mazzocchio and Caleo, 2015).

Here, we build on previous reports of beneficial response to BoT in EPC (Mader et al., 2012; Wilkenfeld et al., 2013; Browner et al., 2006; Lozsadi et al., 2004; Kang et al., 2009; Bedarf et al., 2015), describing three patients with recurrent focal motor seizures who had a clinically useful response to BoT therapy.

Given focal motor seizures commonly do not have a detectable EEG

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correlate, it has been suggested EPC should be classified as follows (Cockerell et al., 1996).

1. Definite EPC: presence of an EEG event time-locked to the muscle jerk at an appropriate interval for conduction in corticospinal pathways, identified via back averaging EEG activity prior to spontaneous jerks, or as an enlarged SEP prior to reflex jerks.
2. Probable EPC: no obvious EEG correlate, jerks are of short duration and synchronous in antagonist muscles, and/or other evidence of a cortical origin either from previous electrophysiology, clinical details or the results of transcranial magnetic stimulation.

Case 1 (*(probable EPC)*). This 78-year-old woman, with no history of epilepsy, presented with two weeks of persistent semi-rhythmic right shoulder jerking. Cognition was intact. Multiple anti-epileptic medications (AEDs) were used in various combinations without benefit, including phenytoin, levetiracetam, lacosamide, and clonazepam.

Blood tests and lumbar puncture were unremarkable. Magnetic resonance imaging (MRI) demonstrated a focal area of increased signal in the left precentral gyrus on fluid attenuation inversion recovery (FLAIR), consistent with seizure related oedema, corresponding to a focus of increased uptake on ictal fluro-D-glucose positron emission tomography (FDG-PET) (Fig. 1). Imaging changes resolved on repeating testing following treatment with BoT. There were no epileptifom discharges seen on the scalp EEG. Given the likely consequences of operating in the area, intracranial EEG and neurosurgical exploration of the motor cortex were not felt to be appropriate. Transcranial stimulation to the left motor cortex at 1 Hz did not improve seizure activity.

BoT was injected under electromyography control (Supplementary Table 1). Improvement in seizure frequency and intensity was noted within 24 h of BoT injection and complete resolution in one week. BoT was continued at 4–8 monthly intervals according to recurrence of clinical focal seizure activity, allowing reduction of AEDs. Repeat PET scan and MRI showed resolution of the previous changes.

Case 2 (*(definite EPC)*). This 54-year-old woman presented for management of right upper limb EPC associated with left frontal gliosis secondary to a cerebral abscess at age 19 years. After some initial convulsions, she had subsequently been seizure free for 20 years on stable doses of carbamazepine. Two months prior to presentation, she developed persistent and increasingly severe right upper limb jerking, maximal in brachioradialis. EEG demonstrated prominent slowing over the left frontal lobe associated with occasional low amplitude epileptiform discharges. Ictal FDG-PET showed high metabolic activity in the arm area of left pre-central gyrus, adjacent to the porencephalic cavity (Fig. 2). EPC was refractory to a trial of multiple AEDs (including clonazepam, phenytoin, valproate, levetiracetam, lacosamide, primidone, ketamine and thiopentone coma). She proceeded to intracranial electrode implantation followed by resection of electrographically involved areas of left precentral and postcentral gyrus. Histology of the resected specimen demonstrated mild transcortical astrocytosis.

Post-operative seizure improvement was short lived. She developed almost continuous low-amplitude right finger and wrist jerking variably spreading to shoulder and neck, exacerbated by active, passive or planned movements of the right hand. She underwent BoT injection under EMG guidance 15 months following the operation. There was a dramatic reduction in seizure frequency and severity from day 4, with resolution of her finger and wrist EPC and reduction in seizure spread to the shoulder. At 3 months post BoT injection, her right hand EPC remained quiescent and she reported improved hand function. By 6 months occasional runs of right finger and intermittent right shoulder EPC had returned, but overall function was improved, and injections were repeated.

Case 3 (*(definite EPC)*). This 40-year-old woman began developing recurrent right lower limb jerking in her teens. Focal motor seizures remained refractory despite multiple AEDs, culminating in resection of a small region of focal cortical dysplasia immediately anterior to her left precentral gyrus at age 27 years. Surgery caused temporary weakness of her right foot and knee, with only transient improvement in seizure activity. Seizures were readily triggered by active or passive movements of the foot, including walking or foot tapping, and were characterised by jerky right toe flexion variably evolving to plantar flexion with inversion of the ankle. Jerking would occasionally spread up the leg causing falls, at times associated with an unpleasant perineal sensation. There were no EEG changes during periods of foot jerking, but on reduced medications a typical focal motor seizure evolved to an asymmetric tonic seizure with sustained leg and foot dystonia, and upper limb “fencing posture”, consistent with spread to the supplementary motor area, and which had associated scalp EEG changes.

MRI demonstrated residual dysplasia adjacent to the previous resection margin. Ictal SPECT demonstrated increased perfusion of this region. Given the risk to lower limb function associated with further resective surgery, BoT was offered. The patient experienced an initial transient increase in seizure frequency followed by eventual cessation at 2–3 weeks after the injection. During the quiescent period, foot tapping or walking did not trigger seizure activity, and resulted in improved mobility. However ankle weakness (clinically graded as 4.5/5) may have contributed to a sprained ankle. Right foot EPC recurred 4

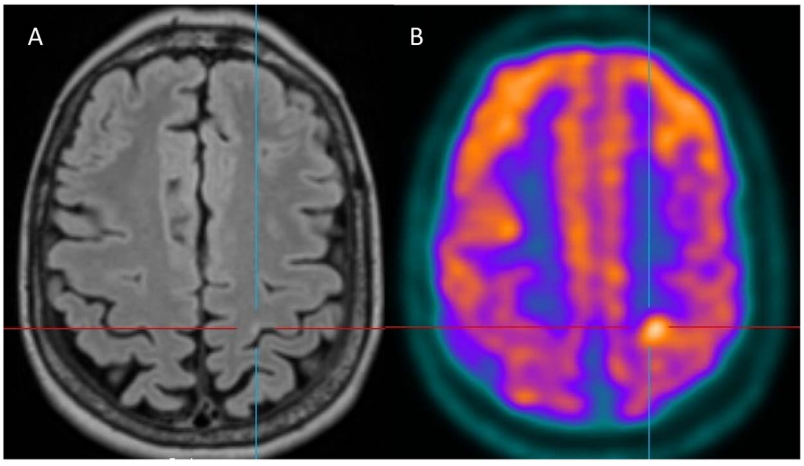

Fig. 1. Structural and functional imaging on case 1: A) Axial FLAIR (Fluid Attenuated Inversion Recovery sequence) MRI – ‘cross hairs’ indicate very focal area of high signal on anterior bank of central sulcus, just mesial to hand area of primary motor cortex. B) FDG-PET scan during persisting right shoulder jerking, showing focal hyper-metabolism in the same location.