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Case report

Successful treatment of paroxysmal ataxia and dysarthria in multiple sclerosis with levetiracetam

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ABSTRACT

Background: Paroxysmal ataxia and dysarthria (PAD) is a relatively rare symptom in Multiple Sclerosis patients. PAD involves transient dysfunction in control, coordination and initiation of speech and/or limb movements.
Objective: To describe the successful use of levetiracetam for the treatment of PAD.
Methods: Case report.
Results: A 37-year-old woman with MS developed PAD approximately 3 months after a multifocal MS relapse. Brain MRI showed a lesion in the posterior aspect of the midbrain as well as in the right posterior internal capsule, both of which were adjacent to the red nucleus. Attack frequency was reduced after starting levetiracetam at a dose of 500 mg twice daily, and attacks stopped completely once the dose was increased to 750 mg twice daily.
Conclusions: Given its advantages (in terms of side effects, safety profile and ease of use compared to other anticonvulsants), we suggest that levetiracetam be considered for management of PAD, and perhaps for other paroxysmal MS symptoms as well.

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Paroxysmal ataxia and dysarthria (PAD) was first described by Parker in 1946 (Klaas et al., 2013), and the term PAD was coined by Andermann in 1959 (Andermann et al., 1959). PAD is characterized by brief, stereotyped attacks of slurred speech that may be accompanied by clumsiness of the limbs, dizziness, and unsteady gait. PAD is a part of the spectrum of paroxysmal symptoms seen in patients with MS (along with tonic spasms, trigeminal neuralgia, Lhermitte's sign, paroxysmal itching and other sensory symptoms). These events are of sudden onset with brief duration (usually 5–15 s), and can occur multiple times per hour. In addition to MS, PAD has also been reported in Bechet's disease (Akman-Demir et al., 1995) and stroke (Matsui et al., 2004). Most of the reported cases suggest that the responsible lesion is located in the midbrain, near or involving the red nucleus, although one case involved a left cerebellar hemisphere lesion abutting the dorsal pons (Gorard, 1989). Thus, it appears that PAD results from disruption of the cerebello-thalamo-cortical pathways.

The prevalence of PAD in MS is unknown. Klaas et al. reported a total of 57 published cases in their 2013 review (Klaas et al., 2013) and two more have since been published (Iorio et al., 2014; Rossi et al., 2015). McDonald and Compston (Compston et al., 2005) reported that, in a colleague's personal case series,14/377 MS patients (4%) had paroxysmal ataxia with or without dysarthria.

Paroxysmal symptoms in MS have long been treated with membrane-stabilizing medications, particularly anticonvulsants. Several case reports have documented successful treatment of PDA with sodium channel blocking anticonvulsants such as carbamazepine (Blanco et al., 2008), lamotrigine (Valentino et al., 2011), phenytoin (Matsui et al., 2004) and oxcarbazepine (Marcel et al., 2010). There are no comparative studies to provide guidance about the best symptomatic treatment for PDA.

1. Case report

A 33 year old woman with a past medical history of atopic dermatitis, childhood asthma, and dyslexia was diagnosed with relapsing-remitting multiple sclerosis in 2011, after developing left optic neuritis followed 9 months later by new cerebral lesions on MRI. She was newly married, and opted to defer immunotherapy to pursue pregnancy. For two years after that, she was neurologically stable, but MRIs showed accumulating lesions. Glatiramer acetate (GA) was started in October 2013. She became pregnant in February 2014 and gave birth in November 2014. In January 2015, she developed new/recurrent blurry vision OS. MRI showed

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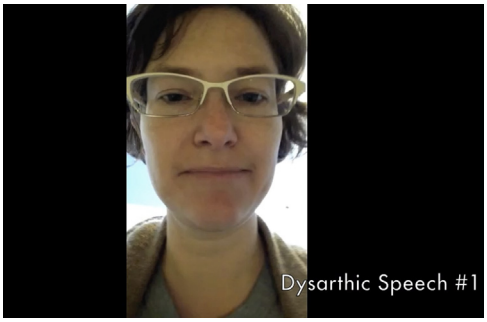

Video S1. Paroxysmal ataxia and dysarthria. The video contains three short clips of the patient described in the case report. She obtained these videos at home, in an effort to document the brief attacks of cerebellar dysfunction. The first two clips show transient cerebellar dysarthria, resolving within seconds in each case. The third clip shows dysmetria and action tremor on finger-nose testing, which again resolves within a few seconds. A video clip is available online.Supplementary material related to this article can be found online at doi:10.1016/j.msard.2016.09.003.

multiple new enhancing lesions (>10), including a lesion in the left lateral pons. She was treated with corticosteroids and restarted GA. Over subsequent weeks, she worsened clinically and radiologically, despite multiple courses of steroids and a course of plasma exchange. She developed upbeat nystagmus with oscillopsia, internuclear ophthalmoplegia, dense left hemiparesis, dysarthria and left homonymous hemianopia. In February 2015, Natalizumab was started, followed by rapid improvement in clinical status and on MRI (no more accumulating lesions, reduction in widespread enhancing lesions).

In May 2015, she developed paroxysmal dysarthria and balance impairment lasting 5–10 s, and occurring multiple times per day (see video in Supplementary materials for examples). On examination, one such episode was observed, and was associated with transient worsening of left hemiataxia. MRI showed trace residual enhancement in the right subthalamic region abutting the red nucleus, and in the posterior midbrain just below the red nucleus (Fig. 1). Treatment with carbamazepine ws discussed, but she was reluctant to start a medication requiring blood test monitoring given that she had only recently concluded prolonged hospitalization and frequent outpatient therapy and medical visits. Levetiracetam was started at a dose of 500 mg bid. Dysarthria and ataxia attacks reduced in frequency, but did not abate completely. Dosage was increased after 2 weeks to 750 mg bid, at which point the PAD stopped completely. In November of 2015, Levetiracetam was tapered and then discontinued, with no recurrence of paroxysmal dysarthria.

Levetiracetam is usually well-tolerated, simple to use, and is available in both immediate- and extended-release formulations. It has straightforward pharmacokinetics and few side effects. The precise mechanism of action of levetiracetam remains uncertain. It does not affect voltage-gated sodium channels or bind to GABA or glutamate receptors. Proposed mechanisms include modulation of neurotransmitter release via interaction with synaptic vesicle protein 2 A, and reducing intracellular calcium levels via calcium

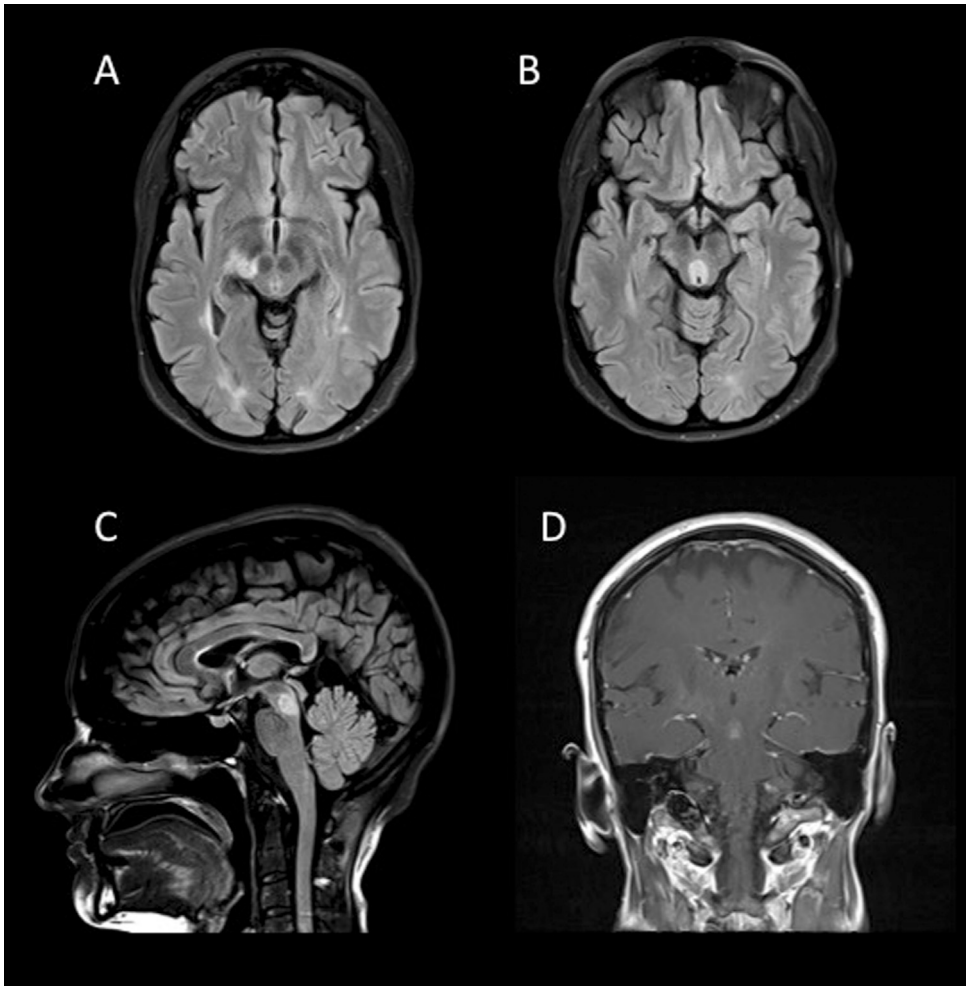

Fig. 1. MRI of the brain at the time of paroxysmal ataxia and dysarthria. Lesions included a T2 hyperintense lesion in the right subthalamus, adjacent to the red nucleus (A), and a lesion in the posterior midbrain just below the red nucleus (B, C). Both of these lesions enhanced after gadolinium administration (D).

channel blockade (Deshpande and DeLorenzo, 2014). Unlike the sodium channel antagonist anticonvulsants, levetiracetam does not require blood monitoring (e.g. for hyponatremia, leukocytopenia, drug levels, or hepatotoxicity), and has lower risk of serious dermatological adverse events (e.g. Stevens-Johnson syndrome) (Ordoñez et al., 2015). Common side effects of levetiracetam include sedation, headache, dizziness and neuropsychiatric symptoms.

This is the first reported case of levetiracetam successfully ameliorating the symptoms of PAD. Given its advantages (in terms of simplicity of use), we suggest levetiracetam be considered for first-line treatment of PAD and other paroxysmal symptoms in MS patients.

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Conflict of Interest

The authors report no conflicts of interest related to this manuscript.

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