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Tremor and Other Hyperkinetic Movements

Case Reports

Complete Resolution of Symptoms of Primary Orthostatic Tremor with Perampanel

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Abstract

Background: Primary orthostatic tremor (POT) is an infrequent disorder whose physiopathology is unknown. Current medication is largely ineffective or only offers mild benefits.

Case Report: A 75-year-old female with refractory POT treated with 4 mg/day of perampanel achieved complete symptom resolution. Owing to adverse effects, the patient reduced intake to 2 mg/day, but even at this lower dose the benefit was maintained.

Discussion: We report the complete resolution of POT symptoms using low doses of perampanel, an antiepileptic drug that blocks glutamate-mediated post-synaptic excitation. Further controlled studies are necessary to confirm this finding.

Keywords: Primary orthostatic tremor, perampanel

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Introduction

Primary orthostatic tremor (POT) is an infrequent disorder characterized by tremor and unsteadiness. It only occurs when the patient is upright and immobile, and stops once the patient walks, sits down, or lies down.[1] Patients report a feeling of instability that impacts their quality of life and may affect their activities of daily living; consequently, many such patients experience anxiety, depression, and social phobia.[2]

The physiopathology is still unclear, although neuroimaging and functional studies suggest that the brainstem, cerebellum, thalamus, and primary motor cortex are involved.[3] Medication is largely ineffective, although it may provide some mild relief. Deep brain stimulation has been shown to have some benefit in severe cases.[1]

We report the case of a patient with refractory POT that had developed 15 years previously, whose symptoms were completely resolved with low doses of perampanel, an orally active, selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist.

Case report

A 75-year-old female with a medical history of hypertension, asthma, and hypothyroidism had been diagnosed with POT 15 years earlier. This condition led to a progressive functional decline over the years that significantly affected the patient's autonomy and quality of life. She had no psychiatric or family history of tremor or other neurological diseases. The neurological examination was normal, revealing no tremor in the upper limbs or signs of parkinsonism.

A surface electromyography (EMG) study of the lumbar axial muscles with the patient in the standing position showed a 14 Hz EMG rhythmic burst pattern (Figure 1).

The patient had previously been unsuccessfully treated with several drugs (daily dose): clonazepam (1.5 mg), gabapentine (1200 mg), pregabaline (300 mg), primidone (750 mg), levodopa (300 mg), levetiracetam (1000 mg), topiramate (200 mg), and zonisamide (200 mg).

Treatment with perampanel was begun with 4 mg/day (after a 4-week introductory dose of 2 mg/day). At the 2-month follow-up

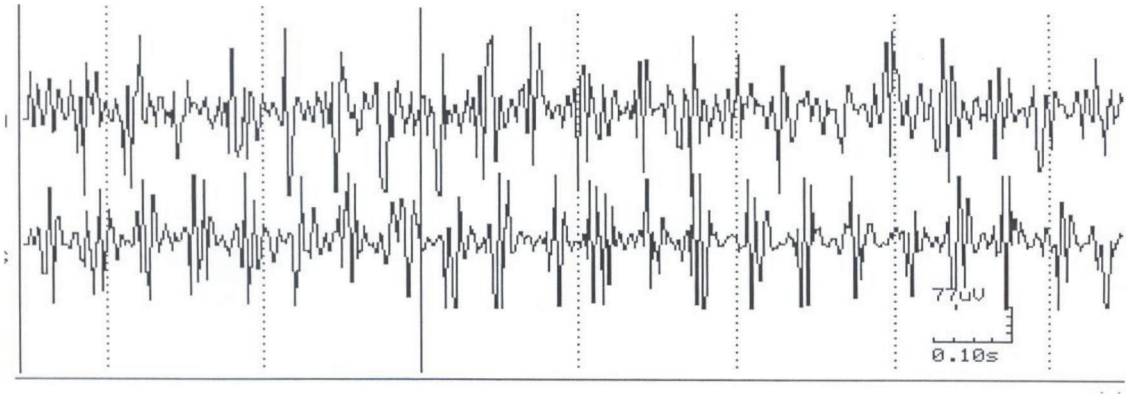

Figure 1. **Electromyography Study**. Surface electromyography recordings of right (above) and left (below) lumbar paravertebral muscles showing discharges at a frequency of 14 Hz with the patient in a standing position.

outpatient visit, the patient described full symptomatic relief, indicating, for instance, that in the kitchen and at the bus stop she could now stand rather than be forced to sit. The patient subjectively rated her improvement as 100%. As an adverse effect she experienced dizziness and reduced her dose to 2 mg/day; despite the low dose, she remains completely asymptomatic. A new EMG study revealed the persistence of 14 Hz rhythmic bursts.

Discussion

We report a case of POT, which, when treated with perampanel (2–4 mg/day), achieved complete resolution of symptoms. To the best of our knowledge, there have been no reports about the use of this drug to effectively treat POT.

The current medication for POT is only partially effective and complete resolution using those drugs is exceptional.[1] Currently, the only treatment is symptomatic rather than etiological. The effectiveness of clonazepam and gabapentine—considered to be first-line agents—has been demonstrated in small clinical trials.[4,5] Primidone has been shown to have some short-term effect,[1,4,6] and valproic acid, propranolol, and bromazepam have been shown to induce a mild response.[4] Studies have described patients in which POT preceded Parkinson disease, for whom levodopa or pramipexole may work.[4,7–9] In non-responders, bilateral thalamic deep brain stimulation of the ventral intermediate nucleus can offer some benefit.[10,11]

Perampanel is a first-in-class selective, non-competitive AMPA receptor antagonist that functions by blocking glutamate activity in the post-synaptic AMPA receptors, which are the predominant mediator of excitatory neurotransmission in the brain.[12] It has been licensed and marketed as an antiepileptic drug and is indicated for patients with partial-onset seizures and primary generalized tonic–clonic seizures. Positive effects have been reported for some patients with epileptic myoclonic jerks, idiopathic generalized epilepsy, and progressive myoclonic epilepsy.[13,14]

Interestingly, although our patient achieved a complete resolution of symptoms, neurophysiology revealed the persistence of subclinical EMG findings for POT. This would confirm a symptomatic rather than an etiological effect.

Bearing in mind its mechanism of action, the fact that perampanel has proven to be an effective treatment for our patient suggests that glutamate neurotransmitters—also involved in the pathophysiology of essential tremor[15]—are involved in the physiopathology of POT.[16,17] Another possibility is that the neurochemical circuits and structures involved in the pathophysiology of POT are segmented, with some circuits modulating tremor frequency (pacemaker function) and other circuits modulating tremor amplitude through increased glutamate-mediated excitatory activity within the pacemaker circuit. Perampanel—which prevents excitation of post-synaptic membranes by inhibiting the glutamate receptors—may therefore modulate flows in reciprocal circuits with abnormal oscillatory neuronal activity and, in this way, significantly regulate tremor amplitude, even though the primary pacemaker may not modify high tremor frequency.[18–20]

To sum up, we report a case of complete resolution of POT symptoms using low doses of perampanel. Further controlled studies are necessary to confirm this finding. We would recommend a clinical trial of perampanel in patients with refractory POT to current treatments.

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