Effect of acetazolamide for long-lasting paroxysmal dystonia in a patient with multiple sclerosis: a case report and review of literature

Pei-Chun Hsieh1
Shu-Min Chen1–3
Yao-Hong Guo1
Ta-Shen Kuan1,2
Wei-Jang Yen1
Wen-Chen Chang1
Yu-Ching Lin1–3

1Department of Physical Medicine and Rehabilitation, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China; 2Department of Physical Medicine and Rehabilitation, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China; 3Medical Device Innovation Center, National Cheng Kung University, Tainan, Taiwan, Republic of China

Correspondence: Yu-Ching Lin
Department of Physical Medicine and Rehabilitation, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng-Li Road, Tainan 704, Taiwan, Republic of China
Tel +886 62 353 535 ext 2666
Fax +886 62 766 106
Email richelin@mail.ncku.edu.tw

Abstract: Dystonia is a rare manifestation of multiple sclerosis (MS), but it always interferes with the functional performance and quality of life. We report a rare case of long-lasting paroxysmal dystonia associated with MS. The patient was a 40-year-old woman with relapsing-remitting MS for 6 years. During the latest attack of MS, she suffered from long-lasting paroxysmal dystonia in her left hand. Despite treatment with pulse high-dose intravenous methylprednisolone, interferon, and baclofen, along with occupational therapy, the dystonia persisted and significantly bothered her daily activities. Finally, she was treated with oral acetazolamide (250 mg, three times a day for 4 days), which was very effective for the control of her dystonia. The dystonic movement subsided without recurrence in a follow-up of 17 months. We advocate this effective and safe treatment for patients with paroxysmal dystonia associated with MS.

Keywords: multiple sclerosis, dystonia, acetazolamide, movement disorders, rehabilitation

Introduction
Multiple sclerosis (MS) is known as an immune-mediated multifocal demyelinating disorder, which consists of components of neuroinflammation and neurodegeneration. It mostly occurs between the ages of 18 and 45 and has a substantial economic and social burden. The most common symptoms include spasticity, fatigue, balance problems, weakness, sensory disturbance, neurogenic bladder and bowel, cognition impairment, depression, pain, sexual disorder, emotional lability, blurred vision, and speech difficulties, in the order of their frequency of occurrence. Compared with the 60%–80% prevalence rate of spasticity due to the involvement of the pyramidal system, the involuntary movement disorders due to the lesion of the extrapyramidal system, such as myoclonus, spasmodic torticollis, paroxysmal dystonia, chorea, and ballism are very rare in patients with MS. In this case report, we describe a woman with relapsing-remitting MS, complicated with disabling paroxysmal dystonia, which responded very well to the 4-day administration of acetazolamide.

Case description
This 40-year-old woman had unremarkable past medical, family, and movement disorder history. In July 2005, at age 34, the patient initially presented with blurred vision, slurred speech, dysphagia, gradual onset of left hemiparesis, and ataxia. There were no significant biochemical findings in laboratory examinations of serum and cerebrospinal fluid. Surveys of infectious diseaes were all negative, including rapid plasma regain, venereal disease research laboratory, human immunodeficiency
Discussion

Paroxysmal dystonia is characterized by intermittent onset of sustained muscle contractions causing patterned twisting and repetitive movements or abnormal postures that might last seconds to hours.\textsuperscript{1,3} The idiopathic paroxysmal dystonia can be subdivided into kinesigenic, nonkinesigenic, hypnogenic, and exercise-induced forms.\textsuperscript{3} There were also some acquired paroxysmal dystonia, induced by the lesions involving the basal ganglia, extrapyramidal tract system, or thalamus.\textsuperscript{1,4} A widely accepted mechanism of dystonia is the increased motor cortical excitability by altered thalamic signaling.\textsuperscript{5} Paroxysmal dystonia is rare in patients with MS. The pathogenesis of paroxysmal dystonia in patients with MS remains unknown.\textsuperscript{4} Several mechanisms have been proposed, including axonal irritability secondary to the release of inflammatory mediators,\textsuperscript{3} a transversely spreading ephaptic activation of axons within the partially demyelinated lesion at any level in the motor fiber tracts, which was supported by a transcranial magnetic stimulation study.\textsuperscript{3} Beyond the typical localizations, there were some sporadic case reports disclosing the demyelinated plaques in the cervical spinal cord, midbrain, medulla, internal capsule, cerebral peduncle, and even some cases without anatomic evidence in patients with MS.\textsuperscript{1,2,4,5} Some investigators explained that the nature of lacking anatomic evidence for MS may be caused by secondary immune components, such as antibasal ganglia antibodies.\textsuperscript{6}

The reported features of paroxysmal dystonia in MS were frequent attacks (several times daily), short duration (seconds to minutes mostly), and stereotyped posture of unilateral dystonia of the arm, leg, and sometimes the face and neck, which could not be attributed to an epileptic origin.\textsuperscript{2,5,7–12} There were some typical trigger factors, such as startle reaction, hyperventilation, stress, and fatigue.\textsuperscript{7} Paroxysmal dystonia in some patients may subside within a few weeks spontaneously or after treatment.\textsuperscript{3} The most common prescribed medication was carbamazepine, but some patients did not have a satisfying response.\textsuperscript{2,4,12} A few cases reported trying to suppress symptoms with acetazolamide,\textsuperscript{9,11} phenytoin,\textsuperscript{12} adrenocorticotropic hormone,\textsuperscript{13} cannabis,\textsuperscript{14} and botulinum toxin.\textsuperscript{15} The therapeutic effects varied, and acetazolamide was considered to be the one with fewer side effects. In 1992, Sethi et al\textsuperscript{a} first adopted acetazolamide alone or in combination with carbamazepine in treating three patients with central demyelinating disease and paroxysmal dystonia. Nardocci et al\textsuperscript{10} noted that paroxysmal dystonia completely receded with a 4-day treatment of acetazolamide.
(250 mg, three times a day), and paroxysmal tremor was also attenuated by a 1-month treatment in a patient. Waubant et al\textsuperscript{11} reported that the symptoms stopped in a few hours post-acetazolamide treatment (250 mg, twice a day) in their patients. Waubant et al prolonged the treatment for 1 month, and the symptoms did not recur. In addition, acetazolamide was also proven to be effective in hereditary episodic ataxia type 2, another kind of movement disorder.\textsuperscript{3,16}

The exact mechanism of acetazolamide for paroxysmal dystonia in MS remains unclear. Acetazolamide is a carbonic anhydrase inhibitor, which fosters metabolic acidosis across the blood–brain barrier, thereby lowering the intracellular pH that reduces the potassium channels' conductance and might alter the transmembranous potential and neuron excitability.\textsuperscript{16–18} In addition, it could alternate the efflux of intracellular bicarbonate through \(\gamma\)-aminobutyric acid (GABA)-activated channels.\textsuperscript{19} An animal study gave evidence that showed acetazolamide exerts antidystonic effects in the \(\text{dr}^S\) mutant hamster via inhibiting bicarbonate regeneration and reducing GABA-mediated excitation without affecting GABA-mediated inhibition.\textsuperscript{19} Therefore, the neuronal hyper-excitability might be reduced, and the paroxysmal dystonia improved consequently.

To the best of our knowledge, this type of MS with long-lasting paroxysmal dystonic posture of the hand is extremely rare in the previous literature. The common trigger factors of dystonia, such as startle reaction, hyperventilation, stress, and fatigue, did not induce the patient's dystonia. The occurrence of dystonia endangered independence in the daily basic activities of this patient. Her dystonia did not respond to treatment with steroid, interferon, and baclofen. Because of the good responses and few side effects of acetazolamide in previous case reports for typical short-lasting paroxysmal dystonia in MS,\textsuperscript{9–11} we treated our patient with this drug with a dosage of 250 mg, three times a day. The bothersome dystonia subsided after 4 days of treatment with acetazolamide. There was no recurrence of dystonia in the next 17 months of follow-up. This dramatic effect of acetazolamide in our patient with MS and dystonia was an inspiring finding that would be of great interest for further study.

**Conclusion**

Paroxysmal dystonia is rare in patients with multiple sclerosis, but it significantly endangers the independence of patients in basic daily living activities. It is worthwhile for the physician to identify this disabling but treatable movement disorder. Paroxysmal dystonia in MS may subside without treatment. In addition to the policy of “wait and see,” medications with few side effects, such as acetazolamide, might be one of the treatment alternatives. We shared our clinical experience and advocate this effective and safe treatment option with acetazolamide for individuals with multiple sclerosis and dystonia.

**Acknowledgments**

We thank Professor Chang-Zern John Hong for his assistance in reviewing this manuscript. This article was supported by a research grant from the National Science Council (NSC 100-2321-B-006-006) in Taiwan, Republic of China.

**Disclosure**

The authors report no conflicts of interest in this work.