Child Neurology Open
Volume 9: 1-3
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DOI: 10.1177/2329048X221075447
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Use of Dalfampridine in a Young Child with Episodic Ataxia Type 2

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Abstract

Episodic ataxia type 2 (EA2) is a rare autosomal dominant disorder associated with mutations of the *CACNA1A* gene.[1] Because there is no curative therapy available, EA2 is typically managed symptomatically. First line treatment has typically been with acetazolamide.[2] Dalfampridine has also been noted to decrease the frequency and duration of ataxic attacks in patients ranging in age from adolescence through adulthood.[3,4] The efficacy and dosing of dalfampridine has not yet been studied in younger pediatric populations. The lack of published experience in younger children can and has led to these patients going without potentially safe and effective treatment. Thus, we describe an 8-year-old girl with EA2 and a confirmed *CACNA1A* gene mutation whose symptoms had been previously unrelieved by acetazolamide. She was subsequently trialed on dalfampridine and experienced symptomatic relief at a dose of 0.3 mg/kg.

Keywords

ataxia, pediatric, treatment, children, quality of life

Received October 11, 2021. Received revised December 3, 2021. Accepted for publication January 6, 2022.

Introduction

Episodic ataxias (EAs) are autosomal dominant neurological conditions characterized by episodes of imbalance and incoordination.[5] Symptoms are mainly cerebellar in origin due to gene mutations resulting in potassium and calcium channelopathies, which are heavily distributed in this region of the brain.[5] At least six distinct EA syndromes have been identified, with EA2 anecdotally appearing to be the most common syndrome.[6]

EA2 is associated with mutations of the *CACNA1A* gene.[1] When compared to the other episodic ataxias, EA2 is characterized by earlier age of onset and prolonged ataxic attacks lasting hours to days accompanied by vertigo, nausea, and vomiting.[5] Attacks are often provoked by exercise or stress. Other findings include interictal nystagmus and other central ocular motor abnormalities, most frequently downbeat nystagmus.[6] EA2 has also been associated with anxiety and poor performance in school.[7]

Because there is no curative therapy available, EA2 is typically managed symptomatically with the first-line acetazolamide, a carbonic anhydrase inhibitor[2] at dosages of 250 to 1000 mg/day.[4] Acetazolamide was serendipitously found to be effective in episodic ataxia in 1978,[8] but the exact mechanism of its efficacy remains unclear.[6,9] While approximately 50 to 75% of EA2 patients report symptomatic relief with acetazolamide,[6] there have been no randomized controlled trials demonstrating its effectiveness,[2,5,10] and the adverse effects can be dose-limiting, including paresthesias, stomach upset, and nephrolithiasis.[11]

More recently, the potassium channel-blocker dalfampridine has also been found to decrease the frequency and duration of ataxic attacks in patients ranging in age from adolescence through adulthood[3,4] at a dose of 5 to 10 mg TID.[10] This drug is the extended-release form of fampridine or 4-aminopyridine and has historically been marketed for multiple sclerosis patients with difficulty walking.[12] Because ataxia in EA2 is likely attributed to Purkinje cell dysfunction, inhibition of potassium channels may increase action potential duration, resulting in improved action potential conduction and neurotransmitter release, thereby resulting in fewer episodes of ataxia.[13,14]

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Dalfampridine is generally well-tolerated, although it may rarely trigger seizures, and it is not recommended for use in those with moderate to severe renal impairment.[12] The efficacy and dosing of dalfampridine has not yet been studied in younger pediatric populations.

Case

A young girl was first noted by her caretakers to exhibit nystagmus with a prominent head tilt by 9 months of age as she began sitting on her own. By 12 months, she demonstrated adequate developmental progress, although she did qualify for behavioral interventions for sensory issues and repetitive activities. By 20 months, in addition to intermittent downbeat nystagmus, she had numerous behavioral issues, and a mild baseline ataxia primarily characterized by gait unsteadiness. However, she was also frequently falling out of proportion to her relatively mild ataxia. At age 7, she was confirmed to have a calcium channel *CACNA1A* gene mutation and diagnosed with EA2. Episodic ataxia had not yet been investigated as a cause of her falls. At the time of referral to our office on her initial examination, her physical exam features were similar to what was seen earlier in childhood with downbeat nystagmus and gait ataxia.

Of note this patient's mother had a history of recurring episodes of dizziness, which started in adolescence. Lasting minutes to hours, these episodes were abrupt in onset and involved problems with balance and walking. Between episodes, no issues were reported. In the context of an additional history of intellectual disability with an IQ of 72, mental health diagnoses (bipolar disorder, anxiety, oppositional defiant disorder), and chronic alcohol and drug abuse, her providers had believed these episodes to be functional in nature.

To aid with nystagmus, our patient was initially started on acetazolamide. She experienced no relief in balance or nystagmus, however, so she was weaned off this medication after one month. Her care was ultimately transferred to the institution of the authors for a second opinion, and she was subsequently trialed on dalfampridine 10 mg twice daily. Her weight at the time was 34 kg. After beginning dalfampridine, the patient was noted to have cessation of falling episodes, improvement in gait ataxia, and lessened nystagmus. In retrospect, her daily multiple falls were secondary to episodic ataxia, and the addition of dalfampridine stopped her falls entirely. She initially complained of some associated dizziness with dalfampridine 10 mg twice daily, but this quickly subsided with reduction to a single daily dose of 10 mg. The benefit was sustained at this lower dose, and no other adverse effects were noted. When the patient's family ran short of medication and paused dalfampridine, she resumed having symptoms. Symptoms were again controlled when medication was restarted.

Discussion/Conclusion

Use of dalfampridine for symptomatic management of EA2 has not previously been reported in young children. This case report demonstrates its efficacy and tolerability in an 8-year-old female with EA2 secondary to *CACNA1A* gene mutation, whose symptoms had been previously unrelieved with acetazolamide.

This child's delayed diagnosis and symptom management demonstrates how EA2 could easily go undetected in this age group, with falls being attributed to childhood clumsiness or functional causes. Frequent falls in a patient with a known genetic mutation that can lead to EA2 warrants a medication trial. In a patient with baseline ataxia but without a known genetic mutation, the authors would also recommend considering a medication trial to address unexplained falls.

In a 2011 randomized trial studying the effects of dalfampridine in ten patients with EA2, administration of dalfampridine yielded a significant reduction in attack frequency from 100% to 34.13% as compared to placebo.[3] In addition, patients experienced an improved quality of life and the medication was well-tolerated.[3] A 2004 randomized trial also demonstrated symptoms returning after dalfampridine was stopped, only to attenuate once the medication was resumed.[4] While a 2011 study did include two adolescents receiving a dosage of 5 mg three times daily,[3] the efficacy and dosing of dalfampridine has not yet been studied in younger pediatric populations. EA2 is so rarely diagnosed in this age group that a comparable randomized controlled trial may never be achievable. Therefore, case reports and other anecdotal evidence may be the best that can be achieved to move these patients toward life altering treatment.

A lack of publications and familiarity with dalfampridine for this indication in this age group led to a delay in effective care. We have demonstrated that dalfampridine can be efficacious and well tolerated in elementary school aged children. Our case, combined with previously published cases in adolescents, provides a reasonable starting point for weight-based dosing for dalfampridine in children (approximately 0.3 mg/kg).

Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

Informed Consent

Verbal informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

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