Paroxysmal Kinesigenic Dyskinesia Symptoms Markedly Reduced with Parenteral Vitamins and Minerals: A Case Report

Alisha Bruton1,2,3; Leslie Fuller, ND4

INTRODUCTION

The paroxysmal dyskinesias are a group of rare disorders characterized by attacks of involuntary movements that resolve quickly.1 Paroxysmal kinesigenic dyskinesia (PKD) is the most common type of paroxysmal dyskinesia and is triggered by sudden voluntary movements.2 PKD can be inherited, acquired, or caused by another neurologic disorder.1 Attacks of PKD can occur multiple times per day and have many triggers. The frequency of attacks ranges from once a year to hundreds of time per day. Common triggers include voluntary movements such as getting in and out of a car or moving from sitting to standing.3 Dyskinesias are commonly diagnosed from a clinical history, as most patients have normal neurologic findings between attacks.1 Although the etiology of primary PKD is not fully understood, the disorder responds to treatment with levodopa, flunarizine, and tetrabenazine, suggesting that hyperexcitability in the basal ganglia may play a role.4 Other treatment options include anticholinergic agents or antiseizure medication.5 Genetic studies have revealed that autosomal-dominant mutations in the PRRT2 gene (proline-rich transmembrane protein 2) may be responsible for some cases of inherited PKD. PRRT2 acts to inhibit vesicular release of neurotransmitters, and its gene mutation may lead to excess neurotransmitter release into the synapse.6,7 PRRT2 inhibits the release of multiple neurotransmitters, perhaps explaining why PKD can respond to many classes of medications, including dopamine precursors, sodium channel blockers, and calcium channel blockers.

To the best of our knowledge, this is the first case report examining PKD treated successfully with parenteral vitamin and mineral therapy. This case report was written following the CARE (CASE REPORT) guidelines.7

CASE PRESENTATION

Presenting Concerns

A 61-year-old woman presented to the clinic with PKD, which was so severe she was not ambulatory and had difficulty with activities of daily living. Thirteen years earlier, in 2002, she had experienced her first attack, after which she was evaluated in the hospital, where stroke and myocardial infarct were ruled out. Brain magnetic resonance imaging findings were normal, and although multiple laboratory tests were done (antinuclear antibodies, lupus anticoagulant panel, vitamin B6 glycoprotein, and cardiolipin antibodies), the results were remarkable only for increased high-sensitivity C-reactive protein and erythrocyte sedimentation rate. Later that year, she received the diagnosis of PKD from a neurologist on the basis of her symptoms and history. Genetic testing consistent with the clinical diagnosis of PKD was not available in 2002.

The patient had a previous diagnosis of chronic fatigue syndrome/myalgic encephalomyelitis. She had no family history of PKD, chorea, Parkinson disease, multiple sclerosis, tremors, seizure disorders, or stroke. Her family history did include systemic lupus erythematosis. For 13 years, she had repeated daily episodes of PKD that incapacitated her, limiting her ability to perform activities of daily living and causing her to be nonambulatory. The neurologist managing her case offered her antiseizure medication to manage the PKD symptoms, but she refused because of concerns about exacerbation of her fatiguen caused by chronic fatigue syndrome.

Previous genetic testing, before this episode of care, revealed the patient was homozygous for the C variant of the NBPF3 gene, which is associated with low absorption and use of pyridoxine (vitamin B6). She also was heterozygous for both the A1298C and the C677T MTHFR mutations, suggesting a reduced ability to convert precursors into active folate (vitamin B9). Additionally, she...
was homozygous for the glutamate decarboxylase-1 (GAD1) mutation, which could interfere with conversion of \( \gamma \)-aminobutyric acid from glutamate.

**Therapeutic Intervention and Treatment**

In 2015, the patient presented to the clinic requesting parenteral therapy with vitamins and minerals to address her episodes of dyskinesia. The patient had an episode in the office in which she experienced dyskinesia that interfered with her ability to move and speak. She was treated at this first office visit (Table 1) and reported immediate symptom relief. At a second office visit 1 week later, she reported that after treatment, she had experienced her first entirely symptom-free period since the onset of her symptoms 13 years earlier. She was able to undertake activities of daily living and reported increased energy and diminished symptoms for 6 days after the initial treatment. She received another identical treatment at this time and continued to receive them weekly for 8 weeks (Figure 1).

Five months after treatment began, she started receiving additional intramuscular injections (Table 2) to further support symptom relief. Several months later, she also began receiving additional intramuscular injections to take home and self-administer. She reported greater resolution of her symptoms when pyridoxine was included in the injection. With the injection self-administered 1 week after each round of parenteral therapy, she was able to go 2 weeks between treatments with almost no return of symptoms. In 2017, she began to go 3 weeks between treatments with almost no symptoms.

She tolerated all the treatments well except for one visit when the administration of the vitamin and mineral mix led to an episode of hypotension, muscle spasticity, and inability to move or speak for 20 minutes. She had recently initiated isosorbide dinitrate therapy for angina pectoris. Isosorbide dinitrate forms nitric oxide, leading to vasodilation and increased blood flow. It is unclear why this episode was triggered, but the stacked vasodilatory effects of magnesium from the vitamin/mineral mix and nitric oxide from isosorbide dinitrate may have been the cause. The magnesium dose was decreased from 3 mL to 1 mL after this incident, with no further episodes.

**Follow-up and Outcomes**

At this time, the patient can care for herself and engage in activities of daily living. She receives parenteral therapy every 3 to 4 weeks, has discontinued the intramuscular injections, and reports that between office visits she experiences minimal to no symptoms of dyskinesia.

The patient shared her perspective:

*Parenteral vitamin and mineral therapy has been like a miracle drug for me and has significantly improved my quality of life. Without [it], I present as if I have cerebral palsy and Parkinson disease, and my speech is affected. Although the parenteral therapy is not curative, it is keeping the movement disorder under control and providing an almost-instant relief when symptoms are flaring. At my worst times it has felt like life was being infused back into my body when getting a round of treatment. The transformation is incredible: A true Jekyll-and-Hyde type of experience. Of the 16 years I have been living with this disorder, it has only been the last few years that my quality of life has improved, thanks largely to parenteral therapy. I am grateful to have found this.*

<table>
<thead>
<tr>
<th>Table 1. Parenteral therapy ingredients</th>
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<tr>
<td>Ingredient</td>
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<tr>
<td>Sterile water, mg/mL</td>
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<tr>
<td>Vitamin B12/dexpanthenol, mg/mL</td>
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<tr>
<td>Vitamin B12/pyridoxine, mg/mL</td>
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<td>Vitamin B12, hydroxycobalamin/methylcobalamin</td>
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<td>Vitamin B complex*</td>
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<td>Vitamin C NC, mg/mL</td>
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<tr>
<td>Calcium gluconate, %</td>
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<td>Magnesium sulfate, mg/mL</td>
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<tr>
<td>Selenium, μg</td>
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<tr>
<td>Sodium bicarbonate, %</td>
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<td>Total volume</td>
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*Thiamine hydrochloride, 100 mg/mL; riboflavin-5-phosphate, 2 mg/mL; pyridoxine hydrochloride, 2 mg/mL; dexpanthenol, 2 mg/mL; and niacinamide, 100 mg/mL.

b Reduced to 1 mL after episode of paroxysmal kinesigenic dyskinesia was triggered during treatment.

NC = noncorn source.
DISCUSSION

Research on animal models of PKD is consistent with the theory of hyperexcitability in the basal ganglia as a cause of symptoms. Hamster models of PKD have dopaminergic overactivity in the striatum, and both glutamate and dopamine receptor antagonists reduce symptoms. This increase in dopamine may be mediated by nitric oxide, which enhances striatal dopamine release and is synthesized by the enzyme nitric oxide synthase. Nitric oxide synthase inhibitors reduced the severity of dystonia in animal models of PKD for several hours after administration. There is also a link between nitric oxide and glutamic acid decarboxylase (GAD); autoantibodies to the GAD enzyme are involved in cerebellar ataxia. The administration of these antibodies to animals increased excitability of motor neurons and reduced the production of nitric oxide. The bilateral injection of the GAD enzyme into the subthalamus of patients with advanced Parkinson disease resulted in a reduction of symptoms over 6 months, suggesting that a deficiency of GAD plays a role in some parkinsonian symptoms. Lack of cerebral blood flow may also contribute to episodes of PKD. One theory is that vascular insufficiency may lead to hypoxic episodes in the basal ganglia, leading to increased production of excitatory amino acids such as glutamate, causing neuronal hyperexcitability. There are cases of PKD secondary to vascular insufficiency in which no structural abnormalities were found on brain imaging, although hypoxia was noted. This theory about reduced blood flow is supported by the induced episode of PKD in the patient when she was given parenteral treatment after recently initiating isosorbide dinitrate therapy for angina. The administered parenteral treatment included magnesium sulfate, which has been shown to modulate the function of acetylcholine receptors. Acetylcholine can activate nitric oxide synthase, increasing nitric oxide concentrations and contributing to vasodilation. Isosorbide dinitrate also forms nitric oxide, and the combined effects of it and magnesium sulfate may have decreased blood pressure, leading to hypoxia in the basal ganglia and a subsequent episode of PKD.

Genetic testing in this patient seemed to support the role of glutamate and GAD in her symptoms of PKD. This patient’s genetic testing revealed a GAD1 mutation. GAD catalyzes the conversion of glutamate to γ-aminobutyric acid, requiring pyridoxal 5′-phosphate (vitamin B6) as a cofactor. This genetic polymorphism could have allowed glutamate to accumulate, contributing to PKD attacks. The patient was also found to have a MTHFR polymorphism, reducing the ability to convert precursors to active folate, as well as an NBPF3 polymorphism, reducing use of pyridoxine. Vitamin and mineral therapy was chosen to promote enzyme-cofactor binding and restore the rate of these reactions. To the best of our knowledge, no research exists on parenteral therapy with vitamins and minerals in paroxysmal dyskinesia.

Limitations of this case report include the short duration of action of the treatments, the limited research on the interventions, and the challenges associated with making this diagnosis. The patient’s diagnosis of PKD was complicated by a diagnosis of CFS, confounding both symptom presentation and treatment response (Table 3). Diagnostic guidelines, published 2 years after this patient’s diagnosis, bring her diagnosis into question. The parenteral vitamin and mineral treatment has little research, and these treatments decreased the patient’s symptoms for only days to weeks. In this case, the patient experienced near-resolution of her symptoms with periodic parenteral therapy, and with 1 minor treatment-related episode of PKD symptoms. Because effective treatments for movement disorders are multidisciplinary, parenteral therapy may be appropriate as adjunctive therapy in some patients.

CONCLUSION

This case suggests that parenteral vitamin and mineral administration may be safe in some patients with paroxysmal dyskinesia, although caution must be taken to avoid adverse interactions with medications.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

CLINICAL MEDICINE

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