Lisdexamfetamine Therapy in Paroxysmal Non-kinesigenic Dyskinesia Associated with the KCNMA1-N999S Variant

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Abstract: Background: KCNMA1-linked channelopathy is a rare movement disorder first reported in 2005. Paroxysmal non-kinesigenic dyskinesia (PNKD) in KCNMA1-linked channelopathy is the most common symptom in patients harboring the KCNMA1-N999S mutation. PNKD episodes occur up to hundreds of times daily with significant morbidity and limited treatment options, often in the context of epilepsy.

Cases: We report 6 cases with the KCNMA1-N999S variant treated with lisdexamfetamine (0.7–1.25 mg/kg/day), a prodrug of dextroamphetamine. Data were collected retrospectively from interviews and chart review. Parent-reported daily PNKD episode counts were reduced under treatment, ranging from a 10-fold decrease to complete resolution.

Conclusion: Our findings suggest that lisdexamfetamine is an effective therapy for PNKD3 (KCNMA1-associated PNKD). Treatment produced dramatic reductions in debilitating dyskinesia episodes, without provocation or exacerbation of other KCNMA1-associated symptoms such as seizures.
| Case | A | B | C | D | E | F |
|------|---|---|---|---|---|---|
| **KCNMA1 Genotype** (all heterozygous) | N999S (rs886039469) | N999S (rs886039469) | N999S (rs886039469) | N999S/R1128W<sup>a</sup> (rs886039469/rs747029218) | N999S/R1128W<sup>a</sup> (rs886039469/rs747029218) | N999S (rs886039469) |
| Other known variants (all heterozygous) | RNF31-Q622LRNF31-V1036L TNXB-R38Q TNXB-G2846L | none | none | none | GRIN2A-E1256K | none |
| Age of dyskinesia onset | 12 mo | 24 mo | 7 mo | 12 mo | 18 mo | 11 mo |
| Estimated pre-treatment dyskinesias per day | 50–200 | 2 to dozens | 50–200 | 200–300 | 300+ | 10–45 |
| Dyskinesia duration (s) | 5–30s | 5–20s | 5–120 s | 1–20s | 15–30s | 30–120 s |
| Time to onset of medication effect (min) | 30–45 m | 30 m | 30–60 m | 60 m | 20 m | Not known |
| Duration of effect (hr) | 11 hr | 12 hr | 13 hr | 12 hr | 8 hr | Not known |
| No. of spells per day during lisdexamfetamine effect | 0/day | 0/day | 0/day | 5/day | 0–3/day | 1–3/day |
| Weight (kg) | 28 kg | 16 kg | 61 kg | 20 kg | 18 kg | 26 kg |
| Current dose (mg) | 20 mg<sup>b</sup> | 20 mg<sup>c</sup> | 30 mg<sup>b</sup> | 15 mg am<sup>b</sup> / 5 mg pm<sup>d</sup> | 15 mg<sup>b</sup> | 30 mg<sup>b</sup> |
| Dose by weight (mg/kg/day) | 0.71 | 1.25 | 0.5 | 1 | 0.8 | 1.1 |
| Highest total daily dose tried (mg) | 20 mg | 20 mg | 40 mg | 20 mg | 15 mg | 30 mg |
| Age lisdexamfetamine started (yr) | 8 yr | 3 yr | 9 yr | 5 yr | 4.5 yr | 7 yr |
| Current age (yr) | 9 yr | 4 yr | 20 yr | 6 yr | 5 yr | 7 yr |

*KCNMA1* variants were identified via commercial diagnostic genetic testing through clinical exome sequencing or genetic epilepsy panels and confirmed as a condition of participation.

<sup>a</sup>*KCNMA1-R1128W* is designated benign<sup>2,3</sup> (and ALM unpublished data).

<sup>b</sup>Capsule form.

<sup>c</sup>One 10 mg capsule and one 10 mg chewable tablet.

<sup>d</sup>Chewable tablet.

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| CASE SERIES |  |  |  |  |  |  |
| Case                                                                 | A         | B                                           | C                                         | D                                           | E                                           | F                                           |
|----------------------------------------------------------------------|-----------|---------------------------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| Reported negative effects (subjective parental report)               | None      | Initially “less happy” (resolved)           | Mild anorexia and insomnia, both resolved. Persistent personality changes “less laughing, more serious” | Severe mood swings, aggressions             | Diminished appetite                         | Diminished appetite                         |
| Non-PNKD benefits (subjective parental report)                       | Improved attention and academic performance | Improved speech                            | None                                      | Improved social skills, improved academic performance, “excelling” | Improved speech, concentration and cognitive function, newly potty trained | Acetazolamide***                           |
| Other current medications                                             | Melatonin | Melatonin                                   | None                                      | Docosahexaenoic acid                         | Levetiracetam, medical cannabis             | None                                        |
| Medication trials with partial effectiveness of PNKD                 | Dextroamphetamine (one dose), mixed amphetamine salts | Acetazolamide, docosahexaenoic acid         | Clobazam, clonazepam                       | None                                        | None                                        | Acetazolamide***                           |
| Ineffective medication trials                                        | Acetazolamide, clonazepam, ethosuximide*, imipramine, levetiracetam, oxcarbazepine, zonisamide | Levetiracetam, topiramate, valproate        | Acetazolamide, carbamazepine, levetiracetam, phenobarbital | None                                        | Acetazolamide, carbamazepine** docosahexaenoic acid, lacosamide, levetiracetam, medical cannabis, valproate | None                                        |
| History of Seizures                                                  | Yes       | Uncertain                                   | Yes                                       | No                                          | Yes                                         | No                                          |
| Seizure types                                                        | Single GTC at 24 mo. Atypical Absence Epilepsy Age 6 yr. | No confirmed seizures                      | Two lifetime seizures in the setting of febrile illness (age 5 and 6 yr) | None                                        | Isolated mild myoclonic jerks observed only on video EEG | None                                        |
| Pre-lisdexamfetamine seizure frequency                               | 100+ per day (EEG confirmed) | None                                        | Two lifetime                              | None                                        | Very rare, unnoticed by mother observed only during video EEG | None                                        |
| Case                        | A                               | B                               | C                               | D                               | E                               | F                               |
|-----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Post-lisdexamfetamine seizure observations | Subjective decrease | None reported | None reported | None reported | None reported | None reported |
| Summary of EEG findings     | Age 1–4: Generalized + multifocal discharges. Age 6: Absence or atypical absence seizures. Normal background. | Rare multifocal sharp waves. Occasional generalized polyspikes. | Age 2 yr: Normal. Age 7 yr: Continuous multifocal spikes in sleep. Age 15: Normal | Normal | Normal background. Spike and wave with bilateral central foci. Generalized multi-spike and wave discharges. | Age 5: diffuse posterior slowing. Multifocal (maximal bi-occipital) and generalized atypical spike-wave discharges activated with photic stimulation |
| MRI findings               | Normal                          | Normal                          | Normal                          | Normal                          | Normal                          | Very mild dilatation of ventricles and CSF spaces |

*Worsened absence seizures.
**Worsened PNKD.
***Diurnal enuresis.
dystonic- or atomic-appearing loss of control of most skeletal muscles, (see Heim et al. for video examples). Some rudimentary voluntary muscle control is preserved, but there is difficulty maintaining posture. Many have rhythmic, stereotyped mouth-gaping movements. Individuals may slump forward or backwards and may fall if standing. Full consciousness is preserved, and patients may answer questions that were asked during the event, after the episode resolves. PNKD episodes tend to be consistent in phenomenology across individuals and can occur dozens of times per day, lasting from a few seconds to several minutes. Although chest wall muscles are affected, the eyes and the diaphragm remain under voluntary control (SK/MCK personal observations and physical examination during PNKD), with few experiencing hypoxia even during prolonged events. Like familial PNKD and other monogenic non-kinesigenic dyskinesias, episodes are commonly triggered by excitement or joy, and tactile stimuli such as cold (eg, after bath, stepping into cold air). Due to phenomenological overlap with cataplexy, these events have also been referred to as cataplexy without narcolepsy. PNKD is often the earliest presenting symptom of KCNMA1-linked channelopathy and typically starts before the age of 24 months. In the authors’ experience, PNKD episodes are frequently mistaken for seizures due to background epileptiform activity on EEG or co-morbid epileptic seizures, which are also prevalent in KCNMA1-linked channelopathy, despite the lack of confirmatory abnormalities on scalp EEG during the dyskinesias. Treatment options in PNKD3 are limited. Episodes are refractory to a wide range of anticonvulsants, although acetazolamide can reduce but not eliminate the dyskinesias in some patients.

In 2019, the family of a young adult reported to one of the authors a 10-year history of daytime remission of dyskinesias after starting lisdexamfetamine, a prodrug of dextroamphetamine. The episodes were phenotypically similar to those in PNKD3 and subsequent genetic testing revealed a KCNMA1–N999S variant. In addition, a prior case report presented in abstract form at the 2018 American Epilepsy society meeting described an individual with a different KCNMA1 variant (N536H, also a GOF mutation) whose PNKD3 were successfully treated with dextroamphetamine. These anecdotal observations were shared with neurologists and families via the patient advocacy group KCNMA1 Channelopathy International Advocacy Foundation (KCIAF; www.kciaf.org), social media, and news media. Several affected individuals were subsequently started on lisdexamfetamine by their treating physicians, with consistent, though anecdotal, reports of reduction or remission of PNKD. Here we provide our experience with lisdexamfetamine-responsive PNKD in the setting of KCNMA1–N999S. Study objectives were to describe the efficacy, dosage range, duration of effect, and side effects.

Case Series

Data from six cases treated with lisdexamfetamine were collected in 2020–2021. All cases were previously known to the authors as having reported a reduction in PNKDs after initiation of lisdexamfetamine. Data were obtained retrospectively via combination of chart review of medical records and from family interviews (Tables 1 and 2). Specifically, data on dyskinesia duration, daily frequency, and time of onset and duration of medication responses were obtained from interviews and based on estimates and approximations from parental recollection in an open manner. Subjects’ dyskinesias started between 7 and 24 months of age. Lisdexamfetamine (0.71 to 1.25 mg/kg daily) led to a reduction of parentally-observed PNKD in all cases (Table 1). The reported onset of this effect across cases ranged from 20 to 60 minutes after taking an oral dose, with a duration of 8 to 13 hours. This reported time of onset and duration is consistent with the known pharmacokinetic profile of the active metabolite of lisdexamfetamine, dextroamphetamine. In three cases (Cases A, B, C), there were no observed dyskinesias during this therapeutic time window, down from a baseline of up to 300 daily events. Although most subjects take lisdexamfetamine once daily in the morning, one child (Case D) takes an additional dose of lisdexamfetamine immediately before bed, which led to cessation of previously prolonged, severe nocturnal events.

Side effects, including appetite suppression, insomnia, and irritability were reported (Table 2). These adverse effects did not result in discontinuation of lisdexamfetamine but in most cases prevented further increases in dosage. In four of the six cases, parents reported improvement in one or more non-motor related areas, such as speech, academic performance, concentration, or social skills, based on subjective family observation. PNKD did not resolve with commonly used anti-epileptic medications. Two cases had a partial response to acetazolamide, and one case partially responded to a benzodiazepine.

Notably, none of the cases reported new-onset seizures after starting lisdexamfetamine (Table 2), including those with a prior history of seizures or myoclonic jerks. One case with active daily absence seizures (Case A) reported a subjective decrease in observed absence seizures.

Discussion

This case series suggests that lisdexamfetamine is well-tolerated and effective for PNKD3 in children as young as 3 years old. Our observation of the successful use of stimulants in KCNMA1-linked channelopathy corroborates the previously reported case treated with dextroamphetamine. Although the long-term effects of using stimulants in PNKD patients is not yet known, stimulants are routinely used for the long-term management of ADHD in children. Dextroamphetamine is FDA-approved for ADHD and narcolepsy in children age 3 and older. At present, lisdexamfetamine is approved for the treatment of ADHD in patients 6 and older. While the patients in our series experienced some of the expected side-effects for stimulant therapy, such as insomnia and anorexia, none were severe enough to discontinue treatment. In addition, no subject had exacerbation of existing conditions, notably there was no worsening or new development of seizures. Due to the severe neurodevelopmental consequences of PNKD3 at the frequency of up to hundreds of episodes per day, the risk to benefit ratio may be favorable for this treatment option. This data provides
support for initiation of a clinical trial to further characterize the efficacy of this treatment regime, which would include a control group that was not possible in this retrospective case series study.

While the mechanism remains to be determined, almost all observations of PNKD3 episodes express as hypokinetic movement. Interestingly, attacks of familial PNKD can be triggered by stimulants such as caffeine. Of note, neither lisdexamfetamine nor dextroamphetamine alter KCNMA1-encoded BK channel activity in heterologous systems (and ALM unpublished data), suggesting that drug effects on motor control may be mediated indirectly and not via specific modulation of BK channel activity. There is superficial similarity to freezing episodes in Parkinson’s disease, in that PNKD3 patients have difficulty initiating lower limb movement such as walking, and which suggests a hypothesis that PNKD3 could be linked to basal ganglia dysfunction.

This case series is retrospective and relies on post hoc parental recall of pre- and post-treatment PNKD counts. However, all the individuals in our series had high-frequency, persistent symptoms that were consistent with other individuals harboring KCNMA1-N999S variants and other pathogenic KCNMA1 variants. In all cases, the reported decrease in PNKD events was robust and matched the expected pharmacokinetics for lisdexamfetamine, arguing against reporting bias significant enough to invalidate the key observation. Despite the overall effectiveness of lisdexamfetamine, debilitating dyskinesias often continue to occur in the morning prior to medication onset and in the evenings when effectiveness wanes as blood concentrations decrease. As also seen with stimulants used to treat ADHD, insomnia and appetite suppression essentially prevents around-the-clock use of lisdexamfetamine in most cases, and thus alternative treatments are needed.

KCNMA1-linked channelopathy is also associated with mild to severe developmental delay and intellectual disability. Several parents reported improvements in school, speech, or social interactions co-occurring with reductions in PNKD attacks. This may in part reflect treatment of a co-morbid deficit in executive function, or may provide evidence that the frequent motor pauses from PNKD attacks directly interfere with development. However, a more global beneficial effect of lisdexamfetamine on neurological function cannot be excluded.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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M.C.K.: 1C, 3B
Z.G.: 1B, 3B
A.L.M.: 1A, 1B, 1C, 3A, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the Institutional Review Board of the Weill Cornell Medical College (protocol 20-07022352) and Phoenix Children’s Hospital (protocol 15-080) in accordance with all applicable national guidelines and laws. Written consent for participation in this study was obtained from all participants (or legal guardians when appropriate). All authors confirm they have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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References

1. Bailey CS, Moldenhauer HJ, Park SM, Keros S, Meredith AL. KCNMA1-linked channelopathy. *J Gen Physiol* 2019;151(10):1173–1189.
2. Miller J, Moldenhauer HJ, Keros S, Meredith AL. An emerging spectrum of variants and clinical features in KCNMA1-linked channelopathy. *Channels (Austin)* 2021;15(1):447–464.
3. Moldenhauer HJ, Matychak KK, Meredith AL. Comparative gain-of-function effects of the KCNMA1-N999S mutation on human BK channel properties. *J Neurophysiol* 2020;123(2):560–570.
4. Harvey S, King MD, Gorman KM. Paroxysmal movement disorders. *Front Neurol* 2021;11(12):659064.
5. Heim J, Vemuri A, Lewis S, et al. Cataplexy in patients harboring the KCNMA1 p.N999S mutation. Mov Disord Clin Pract 2020;7(7):861–862.

6. Pennick M. Absorption of lisdexamfetamine dimesylate and its enzymatic conversion to d-amphetamine. Neuropsychiatr Dis Treat 2010;24(6):317–327.

7. Gibson R, Galentine W, Gunduz MT, et al. Novel phenotype of paroxysmal spells due to KCNMA1 de novo gene mutation mimicking epilepsy and responding to stimulant therapy. Abst. 3.446. In: American Epilepsy Society Meeting. Washington, DC; 2018.

8. Zhang G, Gibson RA, McDonald M, et al. A gain-of-function mutation in KCNMA1 causes dystonia spells controlled with stimulant therapy. Mov Disord 2020;35(10):1868–1873.

9. Sanders L. DIAGNOSIS: The boy slumped to the floor. Could these be seizures? The New York Times. 2020 June 3, 2020.

10. Dolder PC, Strajhar P, Vizeli P, Hammann F, Odermatt A, Liechti ME. Pharmacokinetics and pharmacodynamics of Lisdexamfetamine compared with D-amphetamine in healthy subjects. Front Pharmacol 2017;Sep;7(8):617.