

Paroxysmal Nonepileptic Events in Glut1 Deficiency

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Abstract: Movement disorders are a major feature of Glut1 deficiency. As recently identified in adults with paroxysmal exercise-induced dystonia, similar events were reported in pediatric Glut1 deficiency. In a case series, parent videos of regular motor state and paroxysmal events were requested from children with Glut1 deficiency on clinical follow-up. A questionnaire was sent out to 60 families. Videos of nonparoxysmal/paroxysmal states in 3 children illustrated the ataxic-dystonic, choreatiform, and dyskinetic-dystonic nature of paroxysmal events. Fifty-six evaluated questionnaires confirmed this observation in 73% of patients. Events appeared to increase with age, were triggered by low ketosis, sleep deprivation, and physical exercise, and unrelated to sex, hypoglycorrhachia, SLC2A1 mutations, or type of ketogenic diet. We conclude that paroxysmal events are a major clinical feature in Glut1 deficiency, linking the pediatric disease to adult Glut1D-associated exercise-induced paroxysmal dyskinesias.

Glut1 deficiency (Glut1D) represents a rare metabolic encephalopathy with many faces. A defect in the facilitated glucose transporter, GLUT1, at the blood–brain barrier and in brain cells impairs glucose transport into the brain. This is reflected by hypoglycorrhachia, the diagnostic hallmark of this entity. Approximately 80% of patients carry mutations in the SLC2A1 gene.¹ The resulting cerebral energy deficit is treatable and potentially curable by means of ketogenic diets (KDs) providing ketones as an alternative fuel.² Patients present with epilepsy, a range of developmental disorders, and movement abnormalities or a complex combination of these features. Recently, paroxysmal events (PEs) were recognized in Glut1D children and SLC2A1 mutations detected in adults with paroxysmal exercise-induced dystonia (PED), linking this entity to the Glut1D spectrum.^{3–7} Here, we provide video examples of normal and paroxysmal state in 3 children with Glut1D and investigated incidence, type, and potential associations of PEs in 56 children

with Glut1D with and without SLC2A1 mutations by questionnaire.

Patients and Methods

Video

Three children from outpatient clinics (authors J.K. and C.E.) with confirmed Glut1D (for details, see the Video Case Reports section below) described PEs on regular follow-up. Families were asked to provide representative videos of the normal motor state (video part A), and of PEs (video part B). Consent for video publication was obtained in all cases.

Questionnaire

Sixty patients with a diagnosis of Glut1D confirmed by hypoglycorrhachia and/or molecular testing were contacted by

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phone, e-mail, parent support groups, and in follow-up clinics and were asked to complete a questionnaire (see Supplemental Questionnaire 1). Parents were asked to provide information and videos on paroxysmal events that were clearly different from seizures. Response to KD was defined as (1) adequate seizure control (>50% seizure reduction) on introduction of a KD and/or (2) significant clinical improvement of motor disorders as observed by parents/caretakers and stated on clinical follow-up by the treating physician. A total of 56 of 60 families answered; 27 of 56 patients, including the 3 index cases, were on regular clinical follow-up by two of the authors (J.K. and C.E.).

Results

A total of 56 of 60 questionnaires were completed (Table 1). Glut1D was diagnosed by hypoglycorrhachia (15 of 56; 27%), SLC2A1 mutations (12 of 56; 21%), or a combination (29 of 56; 52%). Twenty-seven patients were followed clinically by two of the authors (J.K. and C.E.)—the genetic diagnosis was backed by multiplex ligation-dependent probe assay (MLPA) analysis in all patients of this subgroup. A total of 13 of 56 (23%) patients presented with isolated movement disorders, 4 of 56 (7%) exclusively with epilepsy, and 2 of 56 (4%) with cognitive/behavioral disturbances only. A total of 37 of 56 (66%) patients combined all three features.

All patients were treated with KD. A total of 37 of 56 patients (66%) received a classical diet, whereas 6 of 56 (11%) changed to a modified Atkins diet (MAD) regime. A total of 2 of 56 patients were exclusively treated with MAD. In 11 of 56 patients (20%), the diet could not be specified. Duration of KD at the time of the survey was ≤ 2 years (16 of 56; 29%), 3 to 4 years (14 of 56; 25%), 5 to 6 years (6 of 56; 11%), and >6 years (20 of 56; 36%), respectively. Mean time on KD was 4.7 years.

PEs were reported in 41 of 56 patients (73%). Clinical features were impairment of motor control (35 of 56; 63%), muscle tone (31 of 56; 55%), speech (17 of 56; 30%), vigilance (16

of 56; 30%), and unclassified individual features reported in free text. Episodes lasted from seconds to several minutes. Common triggers were physical exercise (21 of 56; 38%), low ketosis (13 of 56; 23%), and sleep deprivation (12 of 56; 21%). A total of 27 of 56 patients reported PEs before dietary treatment. The KD terminated PEs in 19 patients, but proved ineffective in 8. A total of 14 of 56 patients developed PEs while on the KD. PEs were unrelated to duration of KD, sex, age, or hypoglycorrhachia. No significant differences in these parameters or of PEs were observed when comparing SLC2A1-positive and SLC2A1-negative patients (Table S1).

Video Case Reports

Case 1

This 8-year-old boy developed global developmental delay, grand mal epilepsy, and severe PEs in infancy. Pregnancy and birth history were uncomplicated, and family history for neurological disease was negative. Seizures started at the age of 6 months with staring spells and cyanotic attacks, evolving into grand mal seizures. Valproate aggravated symptoms, whereas topiramate achieved incomplete seizure control. Movement abnormalities, apparent in infancy, developed into daily PEs with loss of motor control, wobbly, broad-based ataxic “drunken” gait, and falls (Video 1). Attacks lasted 3 to 5 minutes without apparent triggers. Consciousness was unimpaired, and in intervals, no neurological abnormalities were present. MRI imaging of the brain was normal. At the age of 6 years, Glut1D was diagnosed based on hypoglycorrhachia (cerebrospinal fluid [CSF]/blood glucose ratio: 0.37; CSF glucose: 33 mg/dL) and SLC2A1 mutation (c.138_141dupGACA het). A 2:1 KD achieved full seizure control and topiramate was discontinued. PEs stopped within 2 weeks of KD with dramatic improvement of muscle tone and coordination—the boy learned to cycle within a month. Only two episodes of PEs associated with loss of ketosis have occurred since while on a 2:1 KD.

TABLE 1 Summarized questionnaire data

Sex (%)	Male 24/56 (43)	Female 32/56 (57)		
Age (%)	Infant 4/56 (7)	Preschool 9/56 (16)	School 14/56 (25)	Adolescent 29/56 (52)
Diagnosis by (%)	Hypoglycorrhachia 15/56 (27)	SLC2A1 mutation 12/56 (21)	Combination 29/56 (52)	
Phenotype (%)	Movement disorder 13/56 (23)	Epilepsy 4/56 (7)	Combination 37/56 (66)	None 2/56 (4)
KD (%)	Classical diet 37/56 (66%)	Classical => MAD 6/56 (11%)	MAD 2/56 (3%)	Unspecified 11/56 (20%)
Time on KD (%)	0–2 years 16/56 (29)	3–4 years 14/56 (25)	5–6 years 6/56 (11)	>6 years 20/56 (36)
PE features ^a	Motor function 35	Muscle tone 31	Speech 17	Vigilance 16
PE triggers ^a	Physical exercise 21	Low ketosis 13	Sleep deprivation 12	Other 27
PE duration (&)	0–2 minutes 15/56 (27)	3–5 minutes 15/56 (27)	6–9 minutes 12/56 (21)	>10 minutes 24/56 (43)

Numbers are given in absolutes and in percentages where feasible.

^aSummarized data given in absolute numbers and percentage where feasible.

Case 2

This 13-year-old girl was born after an uneventful pregnancy and delivery. Family history for neurological disease was negative. Motor and language milestones were delayed. Parents described her as slow and unsteady compared to peers. She was particularly weak and wobbly on fasting. In early childhood, she experienced two PEs with loss of motor control, abnormal leg movements involving both legs, and retained responsiveness lasting around 5 minutes. In addition to ongoing PEs, she presented with a seizure characterized by loss of awareness, eye deviation, lip cyanosis, and drooling at 5 years of age. Idiopathic generalized epilepsy was suggested by interictal EEGs demonstrating runs of 2/s bilateral frontally dominant spike-wave complexes enhanced in sleep, but physicians questioned the epileptic nature of these episodes. On carbamazepine, PEs appeared exacerbated with sudden head extension backward and falls in clusters of several per hour. After withdrawal of carbamazepine, a bilateral convulsive seizure lasting 15 minutes with loss of responsiveness and mild limb jerking occurred and valproate was commenced. Seizures were controlled, but PEs were ongoing with abnormal leg movements and retained awareness triggered by longer periods of walking. Further episodes with behavioral change, disturbed awareness, and twitchy movements occurred. At 8 years, Glut1D was diagnosed by lumbar puncture (CSF glucose: 40 mg/dL) and SLC2A1 mutation (c.998G>A; p.Arg333Gln het.). Clinical examination and brain MRI were entirely normal. A 2.5:1 KD achieved full seizure control with adequate ketosis and valproate was withdrawn. However, physical exercise continued to trigger choreatiform PEs, as shown in Video 2. Subsequently, compliance difficulties with KD and low ketosis were associated with recurrence of PEs despite attempts to adjust the KD regimen.

Case 3

This 13-year-old girl, a monozygotic twin, developed PEs at the age of 12 years. Pregnancy, delivery, and infancy were uneventful. At the age of 13 months, delay of motor milestones was noted (walking without support at 19 months), followed by ataxia and dysarthria. No clinical seizures occurred despite epileptic EEG discharges. MRI brain imaging was normal except for delayed myelination of U-fibers. At the age of 4 years, Glut1D was diagnosed by lumbar puncture (CSF glucose: 26 mg/dL) and a SLC2A1 mutation (p.R153L het.).⁸ A 4:1 KD was initiated and gradually reduced to 3:1. She remained seizure free with normal development and attended regular schooling with good results. There were no neurological signs on regular follow-up. At age 10 years, the 3:1 KD was gradually weaned from MAD to low glycemic index treatment and eventually discontinued at 11 years of age. The first PEs developed at age 12 years, anticipated by an aura of “loss of control of feet and legs.” They were dyskinetic-dystonic in character, often painful, and triggered by exercise like walking the dog, walking home from school, or after stressful days, as shown in Video 3. PEs

lasted 5 to 8 minutes and gradually faded. The patient was unable to comply with a restart of a KD. Interestingly, her monozygotic twin sister shares the R153L SLC2A1 gene and developed similar, but somewhat milder, PEs.

Discussion

Classical Glut1D (MIM 606777) features global developmental delay, intractable childhood epilepsy, and complex movement abnormalities. In our study, 37 of 56 patients displayed this phenotype. Isolated epilepsy (4 of 56) was rare, whereas isolated persistent nonparoxysmal movement abnormalities (13 of 56) were rather frequent. A total of 15 of 56 patients were negative for SLC2A1 mutations, but were diagnosed by hypoglycorrhachia (no absolute values determined) and responded to KD treatment, indicating that the absence of SLC2A1 mutations does not always exclude Glut1D.⁹ Of note, MLPA analysis could only be verified in 41 of 56 patients followed by the authors, indicating that SLC2A1 mutational frequency in patients enrolled may be underestimated.

PEs are well-recognized clinical features of Glut1D (for detailed descriptions of movement disorders, see⁴). Pons et al. reviewed video recordings and charts of 57 patients with Glut1D and identified nonepileptic PEs in 28% of cases. Poor dietary compliance and low ketonuria appeared to trigger PEs in some patients.⁴ Individual reports of paroxysmal exercise-induced dyskinesia in Glut1 include 2 monozygotic twins and 2 adults.^{5,10} Published videos of movement disorders in Glut1D are rare and reported in adults only.^{7,11}

Video sampling was initiated by parental reports that PEs were very different from seizures, but not reproducible at clinical follow-up. Videos 1, 2, and 3 (Parts B) backed these reports and the paroxysmal nature of events, especially when compared to regular movements (Parts A). The different types of PEs in Glut1D, for example, ataxic-dystonic, choreatiform, and spastic-dystonic PEs, were also observed in additional video data (not shown) and repeatedly confirmed in the free text part of the questionnaire. We are aware of the shortcoming that PEs in the questionnaire were defined and rated as nonepileptic by parents only. However, parents distinguished the different character of PEs and epileptic seizures in their children very well, in particular, the different nature of predictability, responsiveness, and distress of PEs.

Given that PEs are major clinical features in Glut1D, this entity is part of the spectrum of primary paroxysmal dyskinesias, a group of episodic abnormal involuntary movements that are usually autosomal-dominant genetic conditions. For instance, clinical features of case 2 are similar to ADCY5-related dyskinesia, a childhood-onset disorder with a wide range of hyperkinetic abnormal movements.^{12,13}

Pathophysiological mechanisms of PEs in Glut1D remain elusive. It has been postulated that PEs may reflect intermittent basal ganglia dysfunction resulting from exertion-induced energy deficit and/or nutrient deficiency during brain development.⁶ The response to treatment for PED is usually poor, posing a substantial burden to many families (see Video 2).

Acetazolamide has been described as effective in a single Glut1D patient,¹⁴ but has failed in others.¹⁵ At this point, treatment remains experimental.

We conclude that PEs are major features in both pediatric and adult Glut1D. Further studies, especially toward potential treatment of PEs, are required. The recent establishment of a Glut1D patient data bank (www.G1DRegistry.org) will provide further data on PEs incidence, character, and mechanisms in this entity.

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.

J.K.: 1A, 1B, 3A, 3B

B.L.: 1B, 3B

C.E.: 1B, 3B

N.H.: 1B, 1C, 3B

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Supporting Information

Videos accompanying this article are available in the supporting information here.

Table S1. Analysis of means of diagnosis vs. sex, presence of PEs, and Glut1D phenotype.

Video 1. Part A: normal gait of a 6-year-old boy with Glut1D while on a KD. Part B: ataxic-dystonic PEs at the age of 3 years occurring daily before the diagnosis of Glut1D was made and a KD initiated.

Video 2. Part A: normal gait of a 13-year-old girl with Glut1D. Part B: choreiform PEs—the patient was unable to rest in the hotel lobby after a walk through town on a winter day. She was clearly distressed, but unable to stop the PEs while hugging her mother for support. Ketosis at the time of PEs was not determined.

Video 3. Part A: mildly impaired gait of a 13-year-old girl with Glut1D. KD was discontinued 1 year before the occurrence of PEs. Part B: dyskinesic-dystonic PEs. The patient was on her way back from school. Episodes were painful, triggered by exercise, and required a period of rest for symptoms to resolve.

Data S1. Supplemental Questionnaire 1