Atypical Manifestations in Glut1 Deficiency Syndrome

V. De Giorgis, MD1, C. Varesio, MD2, C. Baldassari, MD2, E. Piazza, MD1, S. Olivotto, MD2, J. Macasaet, MD3, U. Balottin, MD1,2, and P. Veggiotti, MD1,2

Abstract
Glucose transporter type 1 deficiency syndrome is a genetically determined, treatable, neurologic disorder that is caused by an insufficient transport of glucose into the brain. It is caused by a mutation in the \textit{SCL2A1} gene, which is so far the only known to be associated with this condition. Glucose transporter type 1 deficiency syndrome consists of a wide clinical spectrum that usually presents with cognitive impairment, epilepsy, paroxysmal exercise-induced dyskinesia, acquired microcephaly, hemolytic anemia, gait disturbance, and dyspraxia in different combinations. However, there are other clinical manifestations that we consider equally peculiar but that have so far been poorly described in literature. In this review, supported by a video contribution, we will accurately describe this type of clinical manifestation such as oculogyric crises, weakness, paroxysmal kinesigenic and non-kinesigenic dyskinesia in order to provide an additional instrument for a correct, rapid diagnosis.

Keywords
GLUT1DS, \textit{SCL2A1}, oculogyric crises, paroxysmal kinesigenic dyskinesia, paroxysmal nonkinesigenic dyskinesia, fatigue

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Glucose transporter type 1 deficiency syndrome (OMIM 606777) is a genetically determined, treatable, metabolic, neurologic disorder leading to an insufficient transport of glucose into the brain, which is its main energy source. It is caused by a mutation in the \textit{SCL2A1} gene, on chromosome 1p35-31.3, which is, so far, the only gene known to be associated with this condition.

GLUT1 deficiency syndrome is a rare disease; in literature, no more than 300 cases have been described. A real incidence has not been well elucidated in recent years, and in 2006 the estimated birth incidence was about 1 in 90,000, with an estimated prevalence of 3000 to 7000 in the United States. However, in 2013 Arsov et al demonstrated that 1.4% of their population of “idiopathic” epilepsies had a functionally validated mutation in \textit{SLC2A1}; thus, GLUT1 deficiency syndrome incidence may be higher but it is still an underdiagnosed disease.

The clinical manifestations of GLUT1 vary. Because this condition was first described by De Vivo, who reported an infantile-onset epileptic encephalopathy associated with delayed neurologic development, acquired microcephaly, ataxia, and spasticity, the Glut1DS phenotypes have been widely expanded.

Methods
This is a retrospective descriptive study done between 2006 and 2015 among 35 patients with a genetic diagnosis of GLUT1 deficiency syndrome with both typical and atypical manifestations. With the aid of video contributions taken from our series, we described these atypical and rarely reported symptoms that may aid for a quicker and more precise clinical diagnosis.

Informed consent for video recording was obtained from all patients in accordance with national guidelines.

Detailed information regarding family history, pre- and perinatal events, age of seizure onset, psychomotor development, neurologic examination, electroencephalographic (EEG) and neuroimaging findings are described elsewhere.

Results
Our cohort of 35 patients with \textit{SLC2A1} mutations is composed of 24 girls and 11 boys.

At the time of diagnosis, patients presented a combination of “common” signs and symptoms of GLUT1 deficiency syndrome, 37.1% (13/35) of patients had acquired microcephaly, 71.4% (25/35) had mild to severe mental retardation, 71.4% (25/35) had mild to severe mental retardation,
82.8% (29/35) had epilepsy, 14.3% (5/35) had continuous movement disorder, and 54.3% (19/35) had paroxysmal exercise-induced dyskinesia.

Two patients (patients 1 and 2, Table 2) showed paroxysmal kinesigenic dyskinesia which is less associated GLUT1 deficiency syndrome. They experienced dyskinesic attacks that were either myoclonic (patient 1) or dystonic (patient 2) on lower limbs precipitated by a sudden voluntary movement (patients 1 and 2), for example, getting up quickly to answer the doorbell or the telephone, or by a sudden increase in speed, amplitude, or strength (patient 2). These episodes usually lasted between 1 and 4 minutes and appeared sporadically. In both patients, this kind of movement disorder well responded to ketogenic diet.

Patients 3 and 4 in Table 2 presented a different type of paroxysmal movement disorder as shown in Videos 3 and 4. At the diagnosis, they had “common” clinical manifestations characterized by mild cognitive delay, epilepsy, and paroxysmal exercise-induced dyskinesia. After introduction of ketogenic diet in both patients, epilepsy and paroxysmal exercise-induced dyskinesia resolved, but they developed a focal, painful, distal toes dystonia, lasting from a few minutes to an hour, with a weekly frequency that we diagnosed as paroxysmal nonkinesigenic dyskinesia.

Nine of 35 patients (25%) of our series experienced generalized body weakness described as persistent fatigue throughout the day that worsened in the afternoon or during fasting. It is a very disabling symptom more common in young patients (mean age of onset 10 years, range 6-20 years) and improves over time. Although poorly detailed in the literature, this symptom is very disabling. As far as our experience, weakness has a great response to ketogenic diet (100% in our sample) with a prompt improvement after its introduction.

Abnormal eye movement occurred as sporadic, paroxysmal, and self-limiting episodes often occurred within the first years. We refer to them as “oculogyric crises.” They are characterized as episodes of sustained upward, lateral, or downward deviation of the eyes, recurrent eyelid retraction without loss of consciousness, episodes of tonic deviation of the gaze upward and/or sideways lasting a few seconds, and uncoordinated horizontal left and right slow eye movements. Table 2 describes in detail the clinical characteristics of our patients. The above-mentioned observations were seen in around 20% (7/35) of our population. EEG was not performed during the occurrence of the symptoms, these episodes were often sporadic and brief, and they usually were described retrospectively. During these attacks, the patients do not have alteration of sensorium or behavioral changes.

In Video 1, we present the paroxysmal attacks of eye movement in a 6-year-old GLUT1 deficiency syndrome girl (patient 11 in Table 1) who showed a darting involuntary, conjugate rolling movement of her eyes culminating in a deviation upward and laterally tonic eye movement lasting about 120 seconds. Video 2 showed a 6-month-old GLUT1 deficiency syndrome male (patient 12 in Table 1) who presents a sudden convergent squint with rolling movements, he tries to correct the abnormal movement with little head movements lasting about 3 minutes.
absence of hypoglycemia, in combination with a low to normal lactate in the CSF.\textsuperscript{10} GLUT1-DS is suspected on clinical grounds, and the diagnosis is confirmed by means of a controlled lumbar puncture.\textsuperscript{11} Based on our results, CSF-to-blood glucose ratio is below 0.6,\textsuperscript{2} with a mean ratio of 0.43 (ranges between 0.33 and 0.56).

The molecular analysis of the \textit{SLC2A1} gene became the gold standard for the diagnosis of GLUT1-DS, but only 70\% to 80\% of patients carry a \textit{SLC2A1} mutation. Among patients with negative results of genetic testing, presence of hypoglycorrhachia plus presence of highly suggestive clinical manifestations prove the presence of a functional problem in glucose transport in the brain which is also sufficient to confirm the diagnosis.\textsuperscript{12}

Hence, GLUT1 deficiency syndrome diagnosis is highly suspected among patients who present with microcephaly, continuous movement disorders, paroxysmal exercise-induced dyskinesia, and epilepsy. However, there are clinical manifestations that we consider atypical but important to be recognized by the physicians.

Given the results and observations in 35 patients genetically diagnosed with GLUT1 deficiency syndrome, we propose to classify it into 2 groups based on clinical manifestations that could be helpful for early diagnosis: (a) common and (b) uncommon manifestations.

These signs could either be persistent or paroxysmal. Persistent manifestations are present since birth or may appear progressively with the evolution of the disease with different levels of severity. These symptoms usually do not respond to ketogenic diet. Paroxysmal manifestations are really peculiar and characteristic of GLUT1 deficiency syndrome. They only appear when there is relative depletion of substrates for brain metabolism, such as exertion, stress, starvation, or sleep deprivation. These are alleviated by eating sugar or glucose and rest.\textsuperscript{13} Ketogenic diet furnishes an alternative energetic substrate and guarantees in the long term a better performance and better result, especially if we consider paroxysmal movement disorders.

### Common Manifestations

- \textit{Microcephaly:} It is not always present at birth. This may manifest late and become evident in early childhood as deceleration of head circumference.
- \textit{Cognitive impairment} of variable severity. In most cases, it is proportional to the severity of the disease.\textsuperscript{9}
- \textit{Continuous movement disorders:} gait disturbance like ataxia, spasticity, or dyspraxia\textsuperscript{5,6,12} are the most commonly described.
- \textit{Epilepsy:} starting from early infancy\textsuperscript{14} is present in approximately 90\% of the subjects.\textsuperscript{15} Absence and generalized tonic seizure are the most common types followed by partial, myoclonic, and astatic seizures.\textsuperscript{16}
- \textit{Paroxysmal exercise-induced dyskinesia} is now considered the predominant feature of the phenotype spectrum.

### Table 2. Clinical Description of the Ocular Phenomenology in Our GLUT1 Deficiency Syndrome Patients.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Birth date</th>
<th>Mutation</th>
<th>CSF ratio</th>
<th>Onset (mo)</th>
<th>Episode duration (mo)</th>
<th>Frequency</th>
<th>Disappearance (mo)</th>
<th>Clinical description</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>March 29, 1987</td>
<td>Q283X; exon 6; nonsense</td>
<td>0.33</td>
<td>3</td>
<td>Few seconds</td>
<td>Daily</td>
<td>12</td>
<td>Brief upward deviation of eyes</td>
<td>MR, EOE, PED, A, DS</td>
</tr>
<tr>
<td>6</td>
<td>September 28, 1986</td>
<td>R249A; exon 4; missense</td>
<td>0.38</td>
<td>4</td>
<td>Few seconds</td>
<td>Weekly</td>
<td>6</td>
<td>Eyeball revulsion</td>
<td>MR, EOE, PED</td>
</tr>
<tr>
<td>7</td>
<td>March 22, 2012</td>
<td>R249A; exon 13; nonsense</td>
<td>0.37</td>
<td>2</td>
<td>5-6 s</td>
<td>Sporadic</td>
<td>10</td>
<td>Sustained upward deviation of eyes</td>
<td>MR, EOE, PED</td>
</tr>
<tr>
<td>8</td>
<td>June 16, 2005</td>
<td>R153C; exon 4; missense</td>
<td>0.51</td>
<td>6</td>
<td>Few seconds</td>
<td>Weekly</td>
<td>73</td>
<td>Episodes of tonic deviation of gaze</td>
<td>MR, EOE, PED, A, DS</td>
</tr>
<tr>
<td>9</td>
<td>September 4, 1999</td>
<td>R400C; exon 4; nonsense</td>
<td>0.44</td>
<td>1</td>
<td>2 months</td>
<td>Weekly</td>
<td>2</td>
<td>Right eye convergence and fixed gaze</td>
<td>MR, EOE</td>
</tr>
<tr>
<td>10</td>
<td>March 2002</td>
<td>R400C; exon 4; nonsense</td>
<td>0.38</td>
<td>2</td>
<td>Few seconds</td>
<td>Daily</td>
<td>9</td>
<td>Right eye convergence</td>
<td>MR, EOE</td>
</tr>
<tr>
<td>11</td>
<td>December 24, 2007</td>
<td>L124W; exon 1; nonsense</td>
<td>0.36</td>
<td>13</td>
<td>60-120 s</td>
<td>Weekly</td>
<td>72</td>
<td>During conjugate rolling eye movements, upward and laterally tonic deviation</td>
<td>MR, EOE, PED, A, DS</td>
</tr>
<tr>
<td>12</td>
<td>December 24, 2007</td>
<td>R153C; exon 4; nonsense</td>
<td>0.39</td>
<td>5</td>
<td>12-180 s</td>
<td>Monthly</td>
<td>10</td>
<td>Mono/bilateral convergent paroxysmal squint, rolling eye movements</td>
<td>MR, EOE</td>
</tr>
</tbody>
</table>

Abbreviations: A, ataxia; C, choreoathetosis; CSF, cerebrospinal fluid; DS, dysarthria; E, epilepsy; EOE, early-onset epilepsy; MR, mental retardation; PED, paroxysmal exercise-induced dyskinesia.

\*After introduction of ketogenic diet.
of GLUT1 deficiency syndrome\textsuperscript{13,15,17} which may manifest solely or be associated with epilepsy. Paroxysmal exercise-induced dyskinesia is characterized by sudden, transient, involuntary dyskinetic movements classified as dystonia and/or chorea and/or ballism triggered by exercise, physical exertion, and less frequently by exposure to cold and stress.\textsuperscript{18}

**Uncommon Manifestations**

**Paroxysmal kinesigenic and nonkinesigenic dyskinesia.** In literature, precise references to movement disorders other than paroxysmal exercise-induced dyskinesia are poor. “Complex movement disorder” is widely used to disclose the presence of a continuous movement disorder (ataxia, spasticity, etc.) associated with a paroxysmal kinesigenic dyskinesia / paroxysmal nonkinesigenic dyskinesia, or others (dysarthria, dysmetria, writer’s cramp, total body paralysis, etc.).

Authors described the presence of “paroxysmal movement disorders”\textsuperscript{19} or paroxysmal or persistent dystonia / dyskinesia / ataxia\textsuperscript{20,21} to describe the presence of paroxysmal events other than paroxysmal exercise-induced dyskinesia without a precise description and classification of these events. Other terms commonly used are unsteady gait, fluctuating gait disorders, and abnormal gait with dystonic posturing.\textsuperscript{22} Few citations of paroxysmal kinesigenic dyskinesia and paroxysmal nonkinesigenic dyskinesia associated with GLUT1 deficiency syndrome were reported.\textsuperscript{2,22,23}

In paroxysmal kinesigenic dyskinesia, dyskinesias are precipitated by voluntary movements and it usually lasts less than 5 minutes. Typically, an attack is induced by a sudden voluntary movement, an example of which is getting up quickly to answer the doorbell or the telephone. Furthermore, even a sudden increase in speed, amplitude, force, or even the sudden additions of new actions during ongoing steady movements may induce an attack. The most common involuntary movement is dystonia; however, chorea, ballismus, or a combination of these may occur. Typically, attacks affect limbs unilaterally but it may be bilateral or even generalized. Paroxysmal kinesigenic dyskinesia and paroxysmal exercise-induced dyskinesia have overlapping clinical manifestations but they have different triggers. Paroxysmal exercise-induced dyskinesia is provoked by prolonged exercise whereas paroxysmal kinesigenic dyskinesia is elicited by sudden movements. In our population,\textsuperscript{2} 2 patients (Table 2) were affected by paroxysmal kinesigenic dyskinesia who responded well to ketogenic diet.

On the other hand, PNKD has a longer duration compared with paroxysmal kinesigenic dyskinesia and is not induced by sudden movement. Triggers are alcohol, coffee, fatigue, or strong emotions but it may occur spontaneously in GLUT1 deficiency syndrome.\textsuperscript{13} In this form, the attacks typically lasted minutes to 4 hours. Our experience showed that this kind of movement disorder has a poor response to ketogenic diet than paroxysmal exercise-induced dyskinesia and paroxysmal kinesigenic dyskinesia.

Both paroxysmal kinesigenic dyskinesia and paroxysmal nonkinesigenic dyskinesia are specifically associated with mutations in PPRT2 and MR-1 genes respectively, but presence of those involuntary movements should not exclude a possibility of GLUT1 deficiency syndrome. Paroxysmal exercise-induced dyskinesia is often associated with SLC2A1 mutation but it is difficult to differentiate the semiology and the genetic origin. For this reason, various authors in the presence of a paroxysmal dyskinesia suggest further comprehensive diagnostic workup in order to search for the more relevant gene mutations that correlates with paroxysmal dyskinesia.\textsuperscript{18,23}

In our population, PNKD appeared after the introduction of ketogenic diet. In these patients, ketogenic diet was followed correctly as well as daily monitoring of ketones, which were maintained at about 3.4 mmol/L. The implementation of the said therapy was done in a short period (around 6 months duration) and it corresponds to the onset of PNKD. The semiology and the frequency of paroxysmal movement disorders

\begin{center}
\includegraphics[width=\textwidth]{figure1.png}
\end{center}

**Figure 1.** Evolution of GLUT1 deficiency syndrome symptoms and its frequency according to age. Symptoms shaded in dark to lighter color corresponds to the frequency of occurrence of symptoms and were placed from top to bottom.
remained stable and with no noted improvement. Thus, given the above patients, we can hypothesize that the ketogenic diet itself may have an unmasking effect on movement disorders that are not previously reported.

GLUT1 deficiency syndrome is a relatively newly discovered disease, and the clinical course is not yet well established. The movement disorder is known to appear in teenage years or in early adulthood (Figure 1) but nothing has yet been reported on the various types of paroxysmal movement disorders.2,19,20

A possible explanation for the limited effects of the ketogenic diet in these kinds of movement disorders is the fundamental difference between glucose and ketones as metabolic fuels. Glucose passes through the glycolytic pathway whereas ketones are converted in the mitochondria directly to acetyl-CoA, so glycolytic intermediates are affected only by glucose, not ketones. For example, methylglyoxal, a byproduct of glycolysis and γ-aminobutyric acid (GABA) receptor agonist is known as a modulator of seizure susceptibility.24 Other metabolic intermediates, replenished only by glucose as the substrate precursor, can be enumerated, and these intermediates may play critical roles in the brain development. There may be critical regional and cellular differences in the equivalence of ketones as a substitute for glucose.20

Ketones cannot be a fully substitute for glucose in more vulnerable regions like thalamus, cerebellum, basal ganglia, and their associated connections and circuits responsible for the genesis of movement disorders.25,26 Although ketones are the only brain fuel alternative to glucose, it is not an absolute substitute.20

**Other paroxysmal movement disorders.** GLUT1 deficiency syndrome patients can also present with various involuntary movements such as dystonia, chorea, cerebellar intention tremor, myoclonus, or combinations of these.1,4,27 In addition, there can also be dysarthria, dyssynergia, dysmetria, writer’s cramp, truncal incoordination,27,28 and total body paralysis.6 But these symptoms are mainly reported in isolated cases; hence, they cannot be considered pathognomonic of GLUT1 deficiency syndrome.

**Fatigue.** Fatigue, weakness, lethargy, somnolence, and sleep disturbance are a common feature described in the medical history of these patients, especially in those with carbohydrate responsive GLUT1 deficiency syndrome,8,19,29 where symptoms are accentuated in the case of fasting or hours after meals. Often the description of the event is not immediately reported by the patient but it must always be investigated in a suspected GLUT1 deficiency syndrome considering its discrete frequency of appearance. Although it is not a highly specific symptom, this could be considered a useful warning sign for the diagnosis in patients who have less “typical” symptoms like epilepsy or cognitive delay. Generalized weakness and somnolence have a good response to ketogenic diet, which is 100% in our population, with early improvement after the introduction of the therapy.30

**Oculogyric crises.** Since the first report,5 the presence of early-onset, paroxysmal “peculiar eye movements” was a characteristic early sign of many patients described in the literature, but no author has ever accurately described the semiology, and no video contribution has yet been widespread.

Until now, this abnormal paroxysmal eye movement has been described in an approximate manner as opsoclonus,29 conjugate movements of the eyes in all planes,21 right convergent squint and horizontal jerk nystagmus,31,32 eye rolling,33 nystagmus-like eye movement,34 rotatory nystagmus, paroxysmal attacks of abnormal eye movement.32 Usually it lasts from a few seconds to 10 to 15 minutes and is recurrent, and this is a clinical observation with no ancillary procedures needed. It could be the very first sign of the GLUT1 deficiency syndrome, which may occur in the first months of age. These findings were congruent with 7 of our patients (20%) and were described in the previous section.

Pons et al (2010)27 referred these manifestations as an ocular dyspraxia. We hypothesize that this kind of paroxysmal eye movement is a dystonic manifestation of the disease that in our sample presents within the first few years of life as one of the early signs that occur intermittently, lasting for a few seconds and resolving spontaneously. Its pathophysiology is not yet well established but we interpret the clinical characteristics and origin as oculogyric crises of dystonic origin, comparable to the other paroxysmal dystonic manifestations typical of GLUT1 deficiency syndrome patients.

The similar semiology with structural lesions impinging on the upper brain stem indicates disturbance of midbrain tectum. However, the intermittent nature of the ocular movement disturbance and the absence of any demonstrable pathologic lesion by imaging suggests that the disturbance could be due to immaturity or depletion of a neurotransmitter or in the case of GLUT1 deficiency syndrome could be energy depletion.

Differential diagnosis with other abnormal paroxysmal eye movements35 to be considered are tonic up gaze caused by a structural lesion of the brain stem; parkinsonian oculogyric crises or drug-related crises (phenothiazines, l-dopa, risperidone, maxolon); opsoclonus typical of opsoclonus-myoclonus syndrome, ocular flutter observed in encephalitis, paraneoplastic syndromes, drug intoxications (eg, lithium, organophosphates) and abnormal metabolic states (eg, hyperosmolar coma); retinal disease preserving the lower visual fields; epilepsy and ocular tics or with the dysconjugate eye movements typical of Joubert syndrome and the other related disorders (Senior-Løken syndrome, Bardet-Biedl syndrome, Meckel syndrome).

Based on our experience, we cannot conclude on the efficacy of ketogenic diet30 on abnormal eye movements because they already disappeared before the course of therapy. In literature, there are no reports of possible effectiveness of the diet toward these symptoms.

Regardless of the success of this therapy, we stress that recognizing such a symptom is an important aid for a more rapid diagnosis of GLUT1 deficiency syndrome.
Conclusion

GLUT1 deficiency syndrome is a relatively new and under-diagnosed neurologic disorder with a wide spectrum of clinical evolution of the symptoms and with varying age of onset (Figure 1). Currently the various clinical manifestations and the real pathophysiology has not yet been established. But the continuous and progressive energetic deficit in the brain is the primary candidate for the whole semiology of GLUT1 deficiency syndrome.

The diagnosis of GLUT1 deficiency syndrome is challenging because of the lack of a distinctive GLUT1 manifestation, and a variety of symptoms appear and change over the years. These clinical manifestations of GLUT1 deficiency syndrome are to be considered age-dependent. Considering that the evolution of the disease is variable with age, physicians must be driven by age-related symptoms.

Therefore, besides the “common” clinical manifestation often described (mental retardation, epilepsy, paroxysmal exercise-induced dyskinesia), other symptoms should be considered equally peculiar and may be critical for a correct and rapid diagnosis:

- **Oculogyric crises** in our opinion could be an early, very precise, and unmistakable sign that could speed up the diagnosis of this treatable disease
- **Fatigue**, though not a highly specific symptom, could be considered a useful warning for a close follow-up and eventually further investigations
- In all the forms of **paroxysmal dyskinesias** (paroxysmal exercise-induced dyskinesia, paroxysmal kinesigenic dyskinesia, paroxysmal nonkinesigenic dyskinesia), SLC2A1 mutation identification should be performed, alone or associated with PPRT2, MR-1, along with other panels.

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Author Contributions

Study conception and design: VG, CV, PV. Acquisition of data: VG, CV, PV. Analysis and interpretation of data: JM, SO, EP, CB, PV. Drafting of manuscript: VG, CV, JM. Critical revision: VG, CV, SO, EP, UB, PV.

Declaration of Conflicting Interests

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Fondazione Istituto Neurologico Casimiro Mondino Ethics Committee approved this study.

Supplemental Material

The supplementary videos are available at http://jcn.sagepub.com/supplemental.

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