Case Report

Language regression, hemichorea and focal subclinical seizures in a 6-year-old girl with GLUT-1 deficiency

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ARTICLE INFO

1. Introduction

GLUT 1 is the primary glucose transporter of the brain, and thus the primary bottleneck for energy metabolism of the brain [1]. GLUT1 deficiency is a disorder of glucose metabolism that results in a variety of neurological manifestations. First described in 1991 by De Vivo at al, the classic phenotype includes infantile-onset seizures, delayed neurological development, and acquired microcephaly [2,3]. Since that time, the phenotypes of GLUT 1 deficiency have expanded to include infantile-onset epileptic encephalopathy, paroxysmal exercise-induced dyskinesia and epilepsy, paroxysmal choreoathetosis with spasticity, atypical childhood absence epilepsy, myoclonic astatic epilepsy, intermittent ataxia, paroxysmal dystonia, paroxysmal migraines and alternating hemiplegia [3]. Although these are the broad phenotypic classifications of GLUT 1 deficiency to date, new clinical phenotypes are discovered frequently. Here we present a patient with GLUT 1 deficiency with unique, not previously described features that include global language deficits and nocturnal subclinical focal seizures, further expanding the clinical phenotype.

2. Case Presentation

A 6 year and 3-month-old right-handed girl born to non-consanguineous parents presented with concerns of language regression, right-sided abnormal movements, and repeated falls.

The patient initially began having trouble with speech 2 months earlier with stuttering, hypophonia, repeating herself and had new word-finding difficulty. Parents felt that she knew what she was trying to say but "could not get the words out". As a result, she began pointing more to express herself and make her needs known.

She also began having abnormal movements of her right arm, episodes of 'drunken walking', and increased falls around the same time period. She was usually able to catch herself from falling, however. Her arm movements, described as a twisting, rotatory movement, began affecting her writing and school performance.

Initial neurological exam noted choreiform movements of her face, tongue, and right hemibody chorea with intact cognition for age. She was able to follow 1 and 2 step commands and was fully oriented for age. Finger nose finger, rapid alternating movements, and gait were normal with interrupting choreiform movements of right upper and lower extremities. The choreiform movements affected gait much more than finger nose finger testing.

Brain magnetic resonance imaging (MRI) showed a subtle linear hyperintensity without mass effect running from anterior to posterior involving the claustrum, adjacent to the putamen and abutting the left external capsule but was otherwise normal. Laboratory testing including CBC, CMP, lead levels, CMV titers, ASO titers, Strep Dnase B, ESR, CRP, TSH, T4 and Lyme titers were all normal.

Routine electroencephalography (EEG) revealed focal, subclinical seizures arising exclusively from the right fronto-central, maximally over F4, C4 and F8. The ictal pattern was composed of sharply contoured, rhythmic delta slow waves intermixed with low amplitude spikes and clear evolution with an onset, progression and end to each individual seizure. These EEG findings were not compatible with electrical status epilepticus in sleep (ESES) (Fig. 1). Seizures were present only during sleep beginning immediately after sleep onset without any clinical correlate, with an average frequency of one seizure every 2 min and duration of 60–75 s. EEG was normal during wakefulness.

Initial neuropsychological evaluation suggested a left hemisphere dysfunction related to the impaired dominant hand fine motor dexterity and below average verbal reasoning. Specifically, it showed low average naming but average language comprehension and a suspicion that expressive language was affected by speech or oral motor weakness. Visual and non-verbal functions were low average. This result contrasted with the EEG finding and could not be explained by the MRI findings either.

3. Results

The patient was then started on oxcarbazepine to treat the subclinical seizures. Follow up EEG did not show any improvement in frequency or duration of seizures arising from the right fronto-central region. In fact, rare nocturnal, subclinical seizures arising from the left central region (C3) developed. Furthermore, right centro-frontal interictal

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Fig. 1. MRI: Axial fluid-attenuated inversion recovery (FLAIR) image showing a hyperintense, linear lesion abutting the left external capsule (red circle).

discharges lacking ictal evolution appeared in wakefulness associated with eye closure. The addition of clobazam was also unhelpful in stopping the subclinical seizures.

Clinically, the addition of oxcarbazepine resulted in resolution of choreiform movements and partial improvement in speech. Repeat neuropsychology evaluation 10 months after the onset of symptoms revealed developmentally appropriate gains in verbal and non-verbal intellectual abilities, but with continued difficulties in expressive vocabulary and articulation and impaired right-hand fine motor functions. The profile was still suggestive of a dominant, left hemispheric dysfunction. However, some speech abnormalities remained with mild dysarthria. A repeat brain MRI showed near resolution of the FLAIR hyperintensity seen a year previously.

Due to the ongoing subclinical seizures and partial resolution of speech deficits, a lumbar puncture was then performed. Cerebrospinal fluid (CSF) amino acids, CSF transmitters, pyruvic acid, CSF cell counts, and gram stain were normal. CSF glucose was low at 44 mg/dL, with a normal blood glucose of 94 mg/dL, (0.47 CSF:blood ratio) and normal CSF lactic acid.

That patient's hypoglycorrhachia, normal blood glucose, abnormal and normal CSF:Blood glucose ratio and normal CSF lactate were suggestive of a blood–brain barrier glucose transport anomaly. Clinical *SLC2A1* gene testing via Sanger sequencing did not result in any reported variants. Deletion/duplication analysis of *SLC2A1* was not completed. The patient was subsequently started on the modified Atkins diet, per parental preference. At last clinic follow up six months after starting the modified Atkins diet, parents reported that despite mild dysarthric speech, there was gradual and significant improvement. School performance was reportedly improved as well. There was no chorea or any other abnormal movements and no clinical seizures. A

repeat neuropsychology evaluation was planned, but the family was not able to attend as they had to move out of state. A follow up LP was also not performed for the same reason. Last follow up EEG done seven months after starting the diet showed persistent seizures arising exclusively from the right fronto-central region, with no change in the overall burden. Interestingly, no seizures from the left central region and no interictal discharges during wakefulness were seen.

4. Discussion

GLUT 1 deficiency syndrome is characterized by a CSF glucose level at or below the 10th percentile in combination with a CSF to blood glucose ratio at or below the 25th percentile, and a CSF lactate at or below the 10th percentile. Since the designation of the classic phenotype, infantile-onset seizures, delayed neurological development, and acquired microcephaly, numerous expanded phenotypes have been recognized as part of the clinical syndrome [3]. It is a general consensus that GLUT 1 deficiency is likely underdiagnosed, with the potential for expanded phenotypes to be recognized.

Limited data exist on EEG patterns of Glut 1 deficiency. These are as varied as the phenotypes encompassing the disorder, with the most common interictal EEG finding being a normal EEG, followed by focal epileptiform discharges in infantile GLUT 1 deficiency and generalized 2.5–4 Hz spike–wave and slowing in children older than 2 years of age [4]. In those phenotypes that include seizures, the most common presenting seizure type is generalized tonic clonic or an apneic/cyanotic episode. Our patient had no clinical seizures, but the EEG pattern has a few novel features that are not described before. Focal interictal epileptiform abnormalities and focal seizures are known to occur in GLUT 1 deficiency, but they are found in patients less than 2 years old [5]. Our

patient is the oldest with focal seizures in the setting of GLUT 1 deficiency described thus far. Activation of epileptiform discharges during drowsiness and sleep is common in GLUT 1 deficiency [6] but strict sleep dependent seizures were not previously reported. This finding strongly supports that obtaining awake only EEG can be misleading and may underestimate the true interictal/ictal burden which may have treatment consequences. The morphology of the interictal and ictal epileptiform discharges was quite different from that seen in benign Rolandic epilepsy despite similarity in the location of the phenomenon as seen in Figs. 2 and 3. Initially, the location of the focal seizures remained the same in the right fronto-central region without secondary spread, but over time, the seizure burden increased and a new focus in the left central region appeared and was independent from the right focus. This evolution over time is a new EEG phenotype that was not described previously. The seizures in our patient proved resistant to conventional medical therapy and to modified Atkins diet.

Neuroimaging studies in GLUT 1 deficiency syndrome are nonspecific. MRI scans of patients with GLUT 1 deficiency usually show normal findings or occasionally mild enlargement of CSF spaces [5]. MRI in our patient showed linear hyperintensity involving the claustrum and in close proximity of the putamen and left external capsule. We postulate that there may be a connection between this finding and the clinical presentation with right hemichorea. This is further supported by the clinical resolution of chorea associated with disappearance of the hyperintensity on MRI following treatment with oxcarbazepine. Favorable responses of chorea to oxcarbazepine were reported previously, but not in the setting of GLUT 1 deficiency, which is another novel finding in this case [7]. We conclude that oxcarbazepine may be a useful treatment for chorea in the setting of GLUT 1 deficiency. However, the location of the MRI hyperintensity did not correlate with the location of subclinical seizures on EEG, nor did it correlate with the neuropsychology results suggesting a dominant left hemisphere dysfunction.

The currently known gene responsible for glut 1 deficiency is *SLC2A1*, localized to the short arm of chromosome 1 [3]. Laboratory studies are necessary to rule out the diagnosis due to the much higher sensitivity for disease compared to genetic sequencing for GLUT 1 deficiency. In fact, it is estimated that relying solely on molecular sequencing one would miss approximately 10% of GLUT 1 deficiency cases [8,9]. This is due to the nature of our genetic testing, as most genetic testing examines only exons. Exon sequencing may miss intronic variants, promoter region variants, or epigenetic changes which may lead to dysfunction in the gene [9]. Microdeletions including the SLC2A gene have been described in some GLUT1 deficiency patients, however, copy number variant testing was not performed in this patient [10]. Phenotypic diversity of GLUT 1 deficiency may also result from secondary gene action, somatic mosaicism, protein folding, transport, or activation, and additional unidentified causative genes, in addition to the classic pathogenic variants in *SLC2A1*. The patient presented here had normal genetic testing, but the laboratory results were typical for GLUT 1 deficiency, which in combination with the phenotype were enough to make the diagnosis.

The treatment of GLUT 1 deficiency revolves around providing an alternate energy source to the brain by way of the ketogenic diet. The ketogenic diet uses a 4:1 ratio of fats to carbohydrates and protein, thus mimicking the metabolic state of fasting. Ketones cross the blood brain barrier via facilitated diffusion mediated by the monocarboxylic acid transporter, allowing an alternate source of energy to fuel the brain [11]. Thus, the problems arising from a lack of energy to the brain are attenuated by an alternate energy source. Ketogenic diet was offered to the parents, but they preferred the modified Atkins diet on the basis of tolerance. Since a full trial of the traditional 4:1 diet was not done, it is hard to draw conclusions on the potential efficacy of the ketogenic diet in this patient, especially the effect on the subclinical seizures that did not respond to either traditional anti-epileptic medications or the Atkins diet.

The phenotypic spectrum of non-classic GLUT 1 deficiency continues to expand with the identification of new clinical manifestations. Our patient presented with some unique features not described previously including speech and language regression, focal, subclinical, and strictly nocturnal seizures and the unique MRI finding of deep white matter linear hyperintensity adjacent to the basal ganglia. While the effect of the classical ketogenic diet is not known in our patient, it is interesting that the modified Atkins diet was effective in restoring a near normal speech, and that oxcarbazepine was helpful in treating chorea and subsequently normalizing the MRI, both unique and not previously reported treatment responses in the setting of GLUT 1 deficiency.
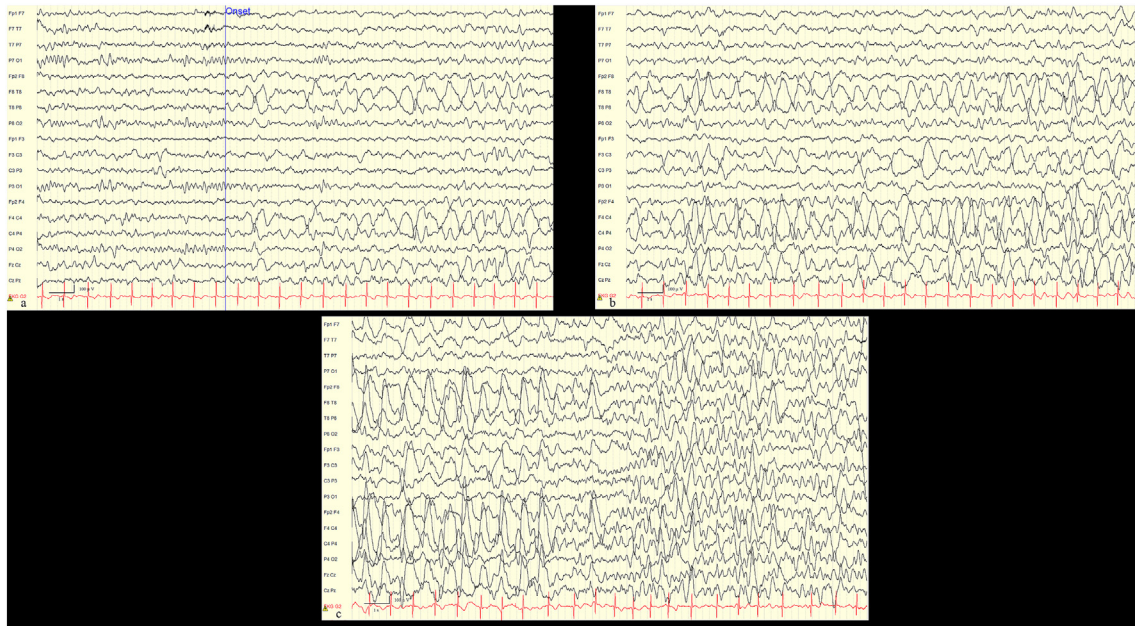
Fig. 2. Ictal EEG: Bipolar, double banana montage during non-REM sleep. (a) A sub-clinical seizure pattern is seen arising from the right fronto-central region at C4-F4 as the patient is transitioning from wakefulness to sleep. (b) Thirty seconds into the seizure, a clear evolution in amplitude, morphology, and frequency of the ictal rhythm occur. (c) End of the seizure after seventy-five seconds. Settings: 15 second page, high frequency filter: 70 Hz, low frequency filter: 1 Hz, gain: 100 microvolts/cm.
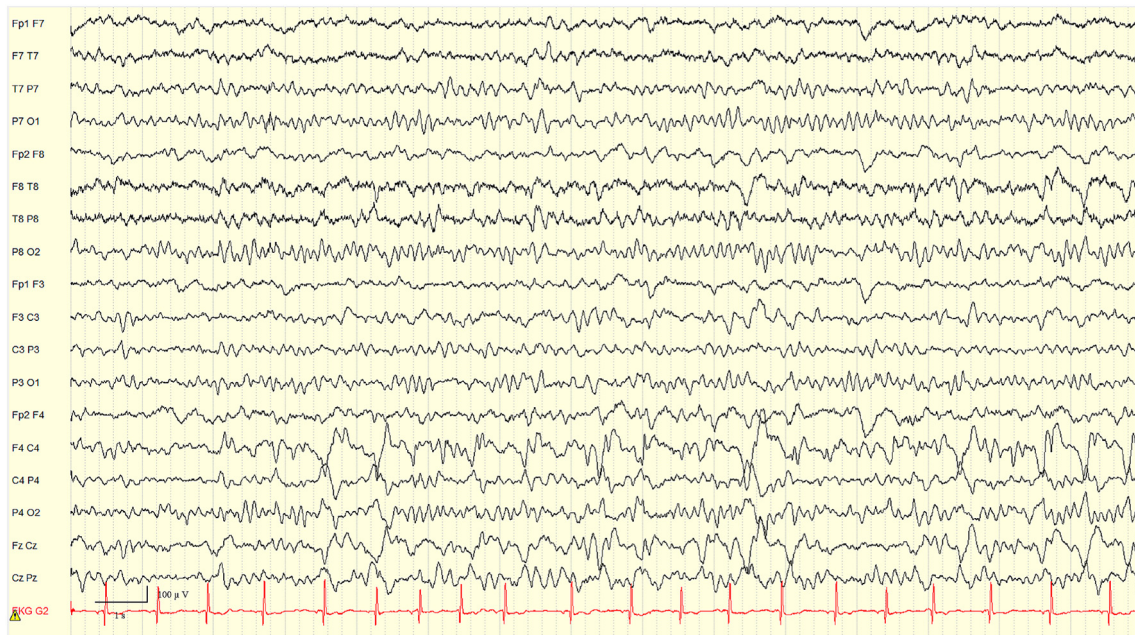
Fig. 3. Interictal EEG: Bipolar, double banana montage during wakefulness with eyes closed. Sharp waves in the right central region (C4) are seen without evolution. Settings: 15 second page, high frequency filter: 70 Hz, low frequency filter: 1 Hz, gain: 100 microvolts/cm.

Many paroxysmal non-epileptic manifestations have been recognized as part of the clinical phenotype of GLUT 1 deficiency, though the language dysfunction thus far characterized, including dysarthria, dysfluency, and decreased receptive/expressive language skills, have not been characterized as a paroxysmal manifestation but rather a long-standing form of impairment, usually alongside severe global developmental delays [3].

Inherent to any single patient case report, there are limitations in the ability to draw clear cut conclusions and in our case, this is especially true for the significance and long-term effects of the persistent subclinical seizures, lack of a full trial of the ketogenic diet and overall long-term outcomes. Our patient's presentation could also be explained by a focal structural lesion (congenital or acquired), metabolic or mitochondrial etiology, though these were ruled out by screening laboratory testing and imaging early in her presentation. Therefore, we conclude our patient represents a new phenotype of variant negative GLUT 1 deficiency.

Author Declaration of Interest

Dr. Alexandra Wood declarations of interest: none.
Dr. Ahmad Marashly declaration of interest: none.
Dr. Gabrielle Geddes declaration of interest: none.

Ethical Statement

The accompanying paper includes a de-identified case report of a patient with GLUT-1 deficiency. Care has been taken to ensure privacy and anonymity of this patient. No informed consent was required as the presentation is completed de-identified.

The aim of publishing this case presentation is to add to the knowledge of phenotypic presentations of GLUT-1 deficiency.

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