Focal non-motor seizures and subsequent focal motor seizures as the main clinical expression of GLUT-1 deficiency

M.E. Santarone a, L.M. Piscitello b, C. Volponi b, F. Vigevano b, L. Fusco b,c

a La Nostra Famiglia, IRCCS MEDEA, Via Don Luigi Monza 20, Bosisio Parini, LC, Italy
b Department of Neuroscience, Bambino Gesù Children’s Hospital, IRCCS, Full Member of European Reference Network EPICARE, Piazza di Sant’Onofrio, 4 – Rome, Italy

corresponding author.
E-mail address: lucia.fusco@opbg.net (L. Fusco).

ARTICLE INFO

The seizure type most frequently described in GLUT1 deficiency is generalized (mainly absence). We report the case of a young boy who, as the main clinical manifestation presented with focal non-motor, and then focal motor seizures.

At the age of 3 months episodes of face pallor/cyanosis and hypotonus lasting about 1 min, occurred. They were initially misdiagnosed as gastroesophageal reflux. These episodes disappeared spontaneously at 6 months of age. At 12 months, episodes similar to the previous ones reappeared. A few months later, a cluster of several episodes manifest as impaired responsiveness and vomiting occurred. The patient initially performed long-term video-EEG monitoring (LTVEM) however, no seizures were captured. During a second hospitalization for LTVEM, a focal to bilateral clonic seizure was recorded. Brain MRI was normal. Next Generation Sequencing (NGS) panel for genes associated with epilepsy showed a de novo mutation of SCL2A1 gene. The CSF showed glucose of 41 mg/dL, and the CSF/serum glucose ratio was equal to 0.46. The ketogenic diet was started with optimal efficacy in seizure control.

Meal-sensitivity in childhood onset focal seizures may be associated with GLUT-1 deficiency syndrome that can be confirmed by biochemical analysis on blood and CSF following diagnostic genetic study.

Introduction

GLUT1 deficiency syndrome is due to brain energy failure caused by impaired glucose transport across the blood-brain barrier. Glucose diffusion across tissue barriers is facilitated by a family of proteins including glucose transporter type 1 (Glut1). An effective therapy for patients with this condition is the Ketogenic Diet (KD) [1].

Key clinical features alerting the onset of the disease are early-onset epilepsy, eye-head movement abnormalities, neurodevelopmental impairment and movement disorders. When these clinical signs are present, the diagnosis is confirmed by cerebrospinal fluid (CSF) analysis to identify the presence of hypoglycorrhachia and genetic analysis revealing pathogenic SLC2A1 mutations [1]. As far as epilepsy is concerned, drug-resistant seizures are frequently observed as the first sign of GLUT1-deficiency. Generalized seizures are most frequently described, but focal seizures (with or without impaired awareness) have been reported [2,3]. Early-onset absence epilepsy (onset before the age of 4 years) and myoclonic-ataxic seizures have been frequently associated with GLUT1-deficiency [4,5]. The initiation of the KD is highly effective in controlling seizures [1]. Because GLUT1-deficiency syndrome and associated clinical features are potentially treatable, early diagnosis even when an atypical presentation occurs is fundamental.

We describe an unusual clinical presentation of epilepsy in a young male patient with GLUT1-deficiency whose sole seizure type was focal in onset.

Case report

At the age of 3 months, a male infant was brought to our emergency room and was subsequently admitted to hospital after presenting with episodes that were characterized by perioral pallor/cyanosis, loss of muscle tone, and impaired responsiveness. These episodes always occurred during or immediately after meals. They lasted a few seconds and were followed by full recovery of awareness and muscle tone.

The infant was born from normal pregnancy and delivery, had a regular perinatal and neonatal period and showed no abnormal neurological or other clinical signs upon medical examination. The events were initially interpreted as symptoms associated with gastroesophageal reflux and the patient was treated accordingly.
The frequency of the episodes was initially once or twice a month but disappeared at the age of 6 months.

However, at 12 months of age, slightly different episodes occurred, once again in association with meals. The first type was more frequent (once a week) and was non-motor. It was characterized by cyanosis, upward gaze deviation, hypotonus and unresponsiveness followed by vomiting. The second type (which occurred only twice) was motor, characterized by rhythmic and repeated movements of left eyelid, sometimes in association with rhythmic jerks of the left hand and foot. Oral automatisms, slight hypotonus, unclear impaired awareness was followed by vomiting.

The child was therefore admitted to the neurological ward of Bambino Gesù Children’s Hospital, where a brain MRI was performed with normal results. A neurological examination showed mild generalized hypotonia. A neuropsychological evaluation showed mild motor delay. Long-term video-EEG monitoring (LTVM) was performed and demonstrated intermittent frontal theta over the right hemisphere during wakefulness and sleep. Consensus was to take a “wait-and-see” approach and the child was discharged without therapy.

For the persistence of the paroxysmal events, although with an oscillating frequency, at the age of 21 months, the child was readmitted to the Neurological Unit at Bambino Gesù hospital. During LTVM that lasted 3 days, no seizures were recorded and interictal EEG trace was inconclusive. Notwithstanding, an anti-seizure therapy with carbamazepine (CBZ) was initiated and the child became seizure-free for 9 months.

At the age of 30 months, further focal non-motor seizures with impaired awareness occurred. One of them evolved to a bilateral tonic-clonic seizure. Two months later, because of a significant increase in seizure frequency (occurring 2–3 times a week), he underwent repeat LTVM, during which a focal motor seizure evolved to a bilateral tonic-clonic seizure (Fig. 1). It occurred during sleep and began with a semiology of right focal tonic posturing (preceded by subtle bilateral vibration/myoclonic jerks that were mainly recorded from deltoid muscles before evolving to a bilateral tonic-clonic seizure. Apparently it was not preceded by other signs (as the onset was during sleep), lasted about one minute and was followed by one minute of reduced responsiveness and therefore awareness during seizure was not assessed. The EEG onset was in the left hemisphere with a discharge of fast activity over left fronto-polar and anterior vertex regions; the discharge spread over parasagittal regions and contra-laterally with spikes and spike-waves activity followed by post-ictal generalized EEG suppression (PGES). The interictal EEG was normal during the first 2 days, while on day 3 and 4 of recording and before a seizure occurred, moderate slowing of the posterior dominant rhythm was observed. In addition, bilateral slowing in the frontocentral and vertex region was seen. At first in isolation, then in long sequences progressing with increased frequency and greater amplitude during wakefulness and sleep (Fig. 2).

Considering the clinical features and the neurophysiological data, metabolic screening on blood and urine was performed. This was composed of amino acid assay on blood and urine, urine organic acids, urine oligosaccharides/Barry’s test, very long chain fatty acids, acylcarnitine, creatine, transferrin, sulfites, oxysterols, lysosphingolipids with normal results. Moreover, NGS panel for genes related to epilepsies was performed. At clinical examination, no further signs were assessed and the new neuropsychological evaluation confirmed the mild developmental delay (the Griffiths Development Scales revealed a global general development quotient of 87, with an age development of 28 months for a chronological age of 32 months. As far as treatment was concerned, phenobarbital (PB) was added to CBZ, with subsequent disappearance of focal to bilateral tonic seizures.

A few months later, the results of NGS panel reported a de novo heterozygous missense variant c.401G > A of gene SCL2A1 (amino acid substitution p.Gly134Asp), not reported in the literature to our knowledge. This was classified as probably pathogenic.

The patient therefore underwent a lumbar puncture: CSF glucose was 41 mg/dL and a CSF: serum glucose ratio was 0.46 confirming the diagnostic hypothesis of GLUT1-deficiency.

The classic KD was started with initial 1:1 ratio, in association with serial measures of ketones and glucose. Side effects were immediately reported including headache and vomiting during a significant rise in ketonemia (higher than 5 mmol/L). Therefore, the KD was stopped with subsequent clinical improvement and resolution of ketonemia. Given excessive ketosis that developed, gene sequencing associated with ketolysis defects was performed. Results showed a variant (c.109 + 2 T > C) of OXCT1 gene.

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Fig. 1. Ictal EEG of the focal to bilateral tonic-clonic seizure (above, demonstrates seizure onset and EEG below the terminal part of the seizure. Note, the end of the seizure is followed by PGES. High frequency filter (HFF) 70 Hz; Low frequency filter (LFF) 0.16 Hz; sensitivity 300 µV/cm.
(Succinyl-CoA acetoacetate transferase deficiency) in a condition of heterozygosity (due to maternal segregation), which was classified as potentially pathogenic, according to the American College of Medical Genetics and Genomics guidelines.

At the age of 3 years, KF was reattempted, targeting a lower ratio of 0.5:1. As this ratio was well tolerated, it was progressively increased until stable ketones between 1 and 2.3 mmol/L was achieved.

One month after the KF was started, laboratory analysis demonstrated good metabolic compensation. The KF ratio was eventually set at 1.7:1 and was well tolerated resulting in stable levels of ketones between 1.5 and 3.5 mmol/L.

At his last follow-up when he was age 3 years and 10 months (November 2021), a repeat EEG was normal and no further seizures were reported. Physiotherapy and speech therapy were continued and he was still taking PB and CBZ.

**Discussion**

The Glut1-deficiency syndrome phenotype includes the clinical features of movement disorders with spasticity, dystonia, and ataxia. Complete seizure control with dietary manipulation may occur in children with drug-resistant epilepsy, those with unexplained paroxysmal events at any age, early-onset absence epilepsy (typically under 4 years of age), and myoclonic-atonic epilepsy [6].

With regard to the epilepsy syndrome associated with GLUT1-deficiency, in 1999, Boles et al. [7] described two affected children with atypical absence seizures whose electrophysiological signature was generalized paroxysmal 2- to 2.5-Hz spike–wave complexes on video-EEG monitoring [7]. GLUT1-deficiency is most likely to be found in Myoclonic-atonic epilepsy and in early-onset Absence epilepsy, while the probability of finding GLUT1-deficiency in other types of idiopathic generalized epilepsies is very low [8]. It appears that presence of slow-waves (<3 Hz) and irregular complexes is an attribute of GLUT1-deficiency syndrome [9]. In a study by Leary et al. [10], the EEG phenotype of a series of patients with GLUT1-deficiency syndrome was described. At all ages, an interictal EEG is often normal. Abnormalities appear more common at certain ages: in infants, focal slowing and epileptiform discharges are more prevalent, whereas in children at age two years or older, the 2.5- to 4-Hz generalized spike-wave pattern is observed. An intriguing feature, when present, is a pre-prandial EEG abnormality that improves with feeding as glucose is replenished [11]. In a study by Von Moers et al. [11], pre- and post-prandial EEG recordings of two children with GLUT1-deficiency syndrome were compared. The fasting background EEG in both children was described as mild to moderately slow, with multifocal and generalized high-amplitude irregular spikes and spike–waves. A significant reduction in epileptiform discharges was noted in the postprandial EEG recordings [11]. As far as seizures are concerned, although most of the patients show generalized seizures (described as generalized tonic and/or clonic, absences, myoclonic, atactic), focal seizures have been reported [2,10]. Therefore focal onset seizures, even if they are the only seizure type, does not exclude GLUT1-deficiency syndrome.

As the main clinical presentation, besides mild hypotonia and motor delay, our patient showed early onset non-motor focal seizures with apparent impairment of awareness and autonomic signs. The initial association between the paroxysmal events and meals was unexpected. We hypothesized that episodes connected with meals in infancy may correspond to the peak of fasting and the effects may last and disappear in a few minutes after the meal.

Only later in life did the patient begin to manifest focal to bilateral tonic-clonic seizures. The seizure recorded in our epilepsy monitoring unit, appeared to be characterized by both a focal tonic-clonic seizure. As the main clinical presentation, besides mild hypotonia and motor delay, our patient showed early onset non-motor focal seizures with apparent impairment of awareness and autonomic signs. The initial association between the paroxysmal events and meals was unexpected. We hypothesized that episodes connected with meals in infancy may correspond to the peak of fasting and the effects may last and disappear in a few minutes after the meal.

Another unexpected electrophysiological feature was the interictal moderate slowing of the posterior dominant rhythm with intermittent brief bursts of irregular delta activity and the concomitant appearance of sequences of focal theta-delta polymorphic slowing over the anterior regions of the frontopolar/frontal and
vertex head regions. The slow activity was not clearly related to fasting as it did not change throughout the day but progressively developed over a few days. This occurred as it seemed to culminate with seizure onset, just as the brain was experiencing metabolic distress (appearing as slow cerebral activity on EEG) that eventually led to a seizure.

As the clinical presentation was atypical, glucose analysis of the CSF was not included within the initial routine diagnostic assessment, and it was performed when we received the result of NGS panel sequencing. After biochemical confirmation of GLUT1-deficiency, the KD was started with efficacy in seizure control and seizure-freedom at the last follow-up.

Conclusion

We conclude that GLUT1-deficiency syndrome should be considered as a possible diagnosis not only in the presence of early onset absence seizures but also when focal non-motor seizures occur in early childhood, especially when associated with other neurological signs (such as mild hypotonia and motor delay).

Meal-sensitivity in childhood onset staring spells may be associated with GLUT-1 deficiency syndrome that can be identified by biochemical analysis comparing blood and CSF glucose and subsequently supported by genetic study.

Moreover, the presence of progressive EEG deterioration involving slowing of the background activity, although non-specific, is an objective sign of dysfunction caused by metabolic distress such as those caused by Glut1-deficiency syndrome.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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