Electroclinical features of a patient with GLUT1 deficiency syndrome and adult onset periodic weakness

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Background

The glucose transporter 1 deficiency syndrome (GLUT1DS) is a heterogeneous neurological disorder due to mutations in the SLC2A1 gene encoding the glucose transport protein 1.

The 'classical' phenotype includes early onset epileptic encephalopathy, cerebellar and pyramidal features, acquired microcephaly and dyskinesia or a variable combination of ataxia, dystonia and chorea [1,2]. In addition, GLUT1DS has been identified in some recognizable conditions including idiopathic generalized epilepsies [3–5], childhood paroxysmal-exercise-induced dyskinesia (PED) and epilepsy [6], isolated PED and PED associated with progressive spastic paraparesis [7,8]. Recently, weakness on awakening or in the fasting state has been reported as an associated clinical sign in GLUT1DS patients [5]. Here, we describe clinical, molecular and electrophysiological correlates of a GLUT1DS patient with mild intellectual disability and adult onset of episodic weakness as unique clinical symptoms.

Case report

A 19-year-old man was referred to the Neurological Clinic at the University of Catania because of a 2-year history of episodic exercise/fasting-induced weakness. He reported weakness at fasting during prolonged physical activity since he was an auto-mechanic and had to lift up heavy weights. As a consequence of the exercise, he reported weakness in his upper limbs impairing his lifting his arms. Sometimes he reported lower limb weakness causing him to fall after a long walk or prolonged standing position. He never reported dyskinesia or hemiplegia. The episodes typically lasted about 10 min or less and were restored by rest and food intake.

The patient had a delay of verbal language development and learning disability. He had two febrile seizures by 2 years of age but he never had epilepsy. The intercritical neurological examination including muscle tone and strength was normal. Cognitive testing showed mild intellectual disability (full scale IQ 68; verbal IQ 77; performance IQ 60). Basal and post-critical electrolyte levels, erythrocyte morphology, blood creatine kinase, thyroid hormones, electrocardiogram and echocardiography were normal. Cerebrospinal fluid/blood glucose ratio was 0.58 (normal values > 0.6). Magnetic resonance imaging of the brain as well as visual, motor and sensory evoked potentials were unremarkable. Nerve conduction studies performed in the upper and lower limbs showed normal compound muscle action potential (CMAP) amplitude, normal motor and sensory conduction velocities and normal F-wave latencies in median, ulnar and peroneal nerves. Repetitive nerve stimulation of ulnar and axillary nerves and electromyographic studies were normal.

Electroencephalography (EEG) recordings performed throughout the day, before and after meals, showed slowed background rhythm with intermittent high voltage theta-delta activity with a widespread distribution over both hemispheres not associated with clinical correlates that diminished in the post-prandial phase (Fig. 1a and b). Based on clinical and EEG findings, GLUT1DS was suspected. Mutation analyses revealed heterozygous 1002G-A transition in the SLC2A1 gene, resulting in an Ala275-to-Thr (A275T) mutation. Familial analyses showed that the mutation was present only in his father. He had experienced similar exercise/fasting-induced muscle weakness as a young adult.

The evidence of episodic muscle weakness triggered by fasting and/or exercise suggested an alteration in muscle membrane excitability and the patient underwent a neurophysiological assessment by a standardized electromyographic protocol known as exercise test (ET) [7]. The ET was aimed to evaluate the capability of the muscle membrane to depolarize and repolarize after a supramaximal electrical stimulation of the nerve following an exercise.

Compound muscle action potential amplitude was recorded from the abductor digiti minimi muscle when the ulnar nerve was stimulated at the wrist before and after a short exercise (10 s) and a long exercise (5 min). CMAPs were checked immediately after cessation of exercise, then every 5 min for 10 min, and finally every 10 min for 50 min. The tests were performed at fasting and after a meal.

In the fasting state (10 h fast), the short time ET did not induce abnormal changes to the CMAP amplitude with respect to the pre-exercise value (+8.2%; normal range from −10% to +20%). However, the long ET (LET) showed an abnormal decrement of CMAP amplitude after 30 min and a persistent decrease up to −42% after 40 min (normal range from −20% to +10%) (Fig. 1c). We re-tested the patient with the LET procedure repeated 120 min after a carbohydrate-rich food intake, and we found an improvement of CMAP (−26%) 40 min after the long exercise (Fig. 1d). Subsequently, the patient modified his daily diet preferring frequent carbohydrate-containing snacks when he was at work, with a sensible reduction of the attacks.

Discussion

Our GLUT1DS patient with p.A275T mutation of the *SLC2A1* gene presented

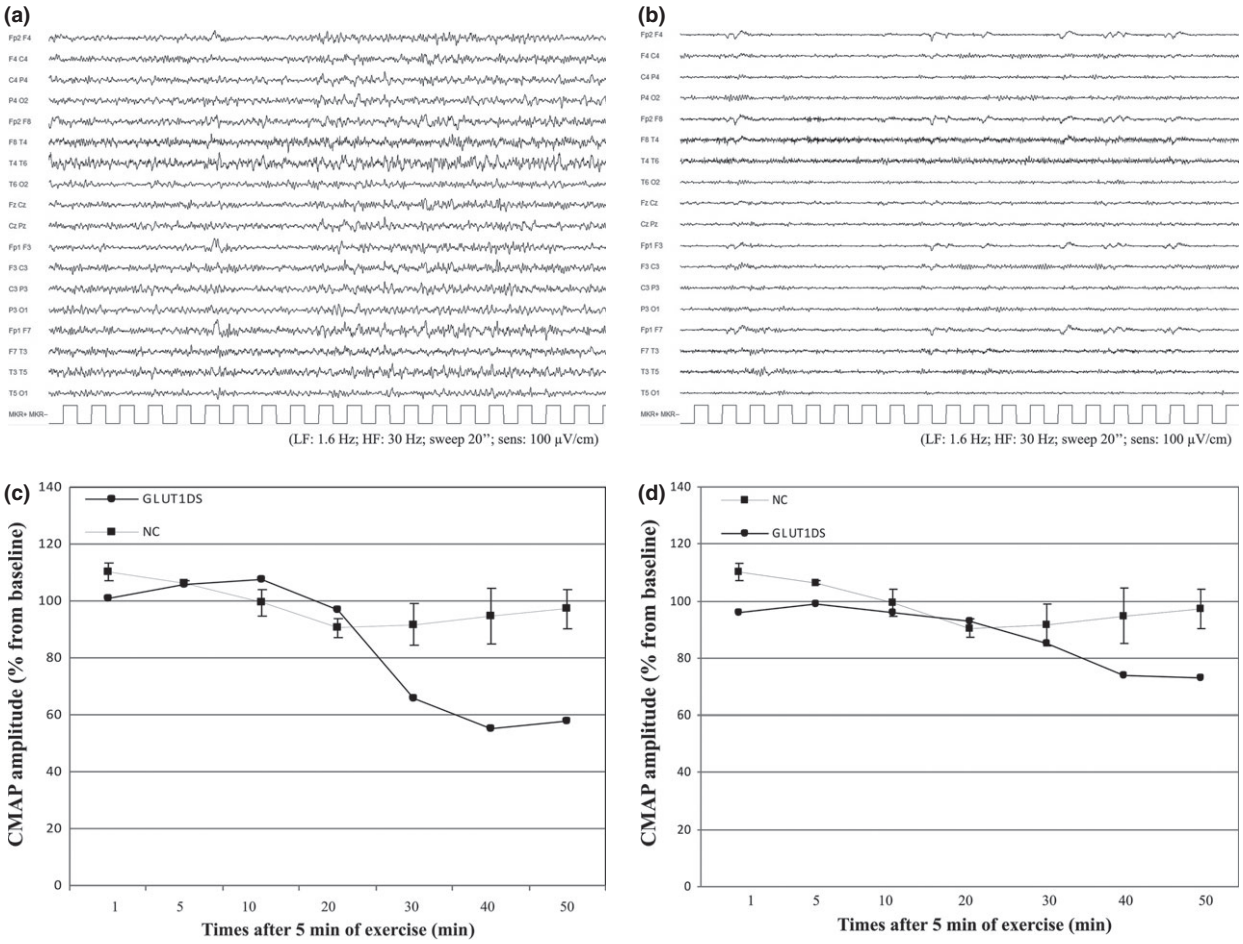

Figure 1 (a) EEG recording performed after prolonged fasting showed a slow background rhythm with intermittent high voltage theta-delta activity with a widespread distribution over both hemispheres. (b) EEG performed post-prandially showed a normalization of the background activity with 10 Hz alpha activity over the parieto-occipital regions and a disappearance of slow rhythms. (c) Long exercise test (5 min) performed during fasting. The CMAP amplitude of the abductor digiti minimi showed an abnormal decrement after 30 min and a persistent decrease after 40 min (−42%). (d) Long exercise test (LET) repeated after carbohydrate-rich food intake. Improvement of CMAP amplitude after 40 min (−26%). NC, normal control values during LET; GLUT1DS, glucose transport 1 deficiency syndrome (p.A275T) patient values recorded during LET.

with episodic weakness triggered by fasting and/or exercise with onset in adulthood. The p.A275T mutation was already reported in a two generation family with juvenile onset PED [8] and in a patient with drug resistant epilepsy and myoclonias [5]. Functional studies revealed that the p.A275T mutant transporters have lost most of their intrinsic ability to transport glucose across the cell membrane thus confirming their pathophysiological significance [3].

The present patient did not have seizures; however, the abnormalities found in the EEG performed after prolonged fasting, including slow background rhythm responsive to food intake, have been associated with GLUT1DS and were interpreted as a marker of the metabolic distress of a brain subjected to chronic glycopenia [2]. The electrophysiological ET was consistent with clinical features suggesting hypo-excitability of the muscular membrane in the fasting state after sustained exercise such as an abnormal CMAP amplitude decrease following LET (>40%) [7]. These findings indicate a reduced sarcolemma excitability with durable membrane hyperpolarization in the fasting state induced by exercise. Likewise it was proposed that chronic neuroglycopenia may lead to developmental alterations in channel expression or function causing abnormal neuronal excitability in GLUT1 deficiency [9]. *In vivo* studies in transgenic mice overexpressing GLUT1 show that glucose uptake into skeletal muscle in the fasting state is regulated by the level of GLUT1 expression in this tissue [10]. Further electrophysiological and functional studies should reinforce this hypothesis. Little is known about the natural history of GLUT1DS and disease manifestations in adulthood. Based on the present family we suggest that in some instances fasting/exercise-induced weakness especially in the presence of intellectual disability may be a clue to the detection of GLUT1DS patients and it may suggest the diagnosis in asymptomatic family members.

The observation is crucial for proper counselling and therapy using diet modifications.

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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

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