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Glut1 deficiency is a rare but treatable cause of childhood absence epilepsy with atypical features

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ABSTRACT

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a rare genetic disorder caused by pathogenic variants in *SLC2A1*, resulting in impaired glucose uptake through the blood-brain barrier. Our objective is to analyze the frequency of GLUT1-DS in patients with absences with atypical features. Sequencing analysis and detection of copy number variation of the *SLC2A1* gene was carried out in patients with atypical absences including: early-onset absence, intellectual disability, additional seizure types, refractory epilepsy, associated movement disorders, as well as those who have first-degree relatives with absence epilepsy or atypical EEG ictal discharges. Of the 43 patients analyzed, pathogenic variations were found in 2 (4.6%). Six atypical characteristics were found in these 2 patients. The greater the number of atypical characteristics presenting in patients with absence seizures, the more likely they have a *SLC2A1* mutation. Although GLUT1-DS is an infrequent cause of absence epilepsy, recognizing this disorder is important, since initiation of a ketogenic diet can reduce the frequency of seizures, the severity of the movement disorder, and also improve the quality of life of the patients and their families.

1. Introduction

Glucose transporter 1 deficiency syndrome (GLUT1-DS) is a rare inborn error of metabolism (1:83.000) caused by impaired glucose transport through the blood-brain barrier due to mutations in the *SLC2A1* gene, which encodes the glucose transporter protein Type 1 (GLUT1). First described in 1991 by Di Vivo et al. (Trifiletti et al., 1991), the classic phenotype was based on 2 patients presenting with epileptic encephalopathy characterized by infantile-onset refractory epilepsy, cognitive impairment, acquired microcephaly, and a complex movement disorder including spasticity, ataxia, and dystonia (Trifiletti et al., 1991).

In recent years, a wide clinical spectrum has been described for GLUT1-DS, including sporadic paroxysmal exercise-induced dyskinesias (Zorzi et al., 2008), mixed movement disorder (Friedman et al., 2006) (dystonia, dysarthria, ataxia, chorea, dystonic tremor), intellectual disability, or epilepsy in different combinations. It has been reported to cause alternating hemiplegia, spastic paraparesis (Weber et al., 2011), hemolytic anemia, migraine, and has even been described in asymptomatic patients (Suls et al., 2008).

Diagnosis of GLUT1-DS is based on presence of a reduced ratio of cerebrospinal fluid to plasma glucose or the identification of a pathogenic variation in *SLC2A1*.

It is important to recognize GLUT1-DS, as initiation of a ketogenic diet can reduce the frequency of seizures, the severity of the movement disorder, and lead to improvements in cognitive functions such as alertness and concentration (Fujii et al., 2016).

Recently, GLUT1-DS has been identified as the cause of different types of epileptic syndromes, such as idiopathic generalized epilepsy including absences with some atypical features (Pong et al., 2012) and myoclonic astatic epilepsy (Mullen et al., 2011).

The aim of our study was to analyze the presence of variants in

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SLC2A1 in patients with absences with atypical features

2. Materials and methods

We recruited a cohort of 43 Spanish patients from several hospitals in Madrid (Spain); all patients presented one or more atypical features, including early-onset absence epilepsy (EOAE) with onset before 4 years of age, psychomotor delay or intellectual disability, additional seizure types (such as tonic-clonic or myoclonic seizures), refractory epilepsy (following administration of 2 appropriate antiepileptic treatments), associated movement disorder, first-degree relatives with absence epilepsy, or atypical EEG ictal discharges (slow or irregular).

Patients' past histories and results from laboratory testing were obtained by face-to-face interviews and by consulting their medical records. The information regarding clinical, developmental, imaging, and neurophysiology data were reviewed by two epilepsy specialists with experience in childhood epilepsy.

All participants or their relatives (in the case of minors) provided signed informed consent, and DNA samples were obtained from peripheral blood lymphocytes using standard procedures. The study was approved by the local ethics committee.

Molecular analysis of *SLC2A1* was performed by Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis (P138 probe mix; MRC-Holland, Amsterdam, The Netherlands).

3. Results

The average age of the 43 patients (53.5% female) was 12.4 years (range, 3–62, median, 9). The most frequent atypical associated characteristic was other associated epileptic seizures (26/43, 62.8%) in the form of generalized tonic-clonic seizures in 20, myoclonic seizures in 13, partial seizures in 5, and atonic seizures in 3. Twenty-six patients (60.5%) needed more than 2 antiepileptic drugs to control their seizures. In 25 patients (58.1%), absence onset occurred before age 4, and nearly half (46.5%) presented psychomotor delay or intellectual disability of varying degrees. Thirteen patients (30.2%) presented movement disorder (tremor, 13; dystonia, 5; paroxysmal dyskinesia, 2), EEG abnormalities were discovered in 11 patients (25.6%) (4 were found to have slow spike-wave complexes (< 3 Hz), and irregular spikes and waves were found in 6) (Table 1).

Sequencing of *SLC2A1* in our cohort led to identification of two point variants in two patients (4,6%). No copy number variation was found in any patient. Patient-1 was a girl who presented an epileptic encephalopathy with seizures of different features (spasms, tonic and focal) since two months of age, severe intellectual disability and a complex movement disorder characterized by chorea, myoclonus and dystonia. GLUT1-DS was confirmed with one *de novo* splice-site variant (c.115-2G > A). Patient-2 was a boy who presented an refractory epilepsy since four months of age characterized by focal and tonic seizures, a moderate-severe intellectual disability and a movement disorder characterized by ataxia and tremor. It was reported an heterozygous variant (c.847C > T, p.Gln283Ter, rs587784397). Parental DNA samples were not available in the this case but the variant has been reported as a pathogenic variant. These two patients with GLUT1-DS presented with all atypical characteristics except for family history of absence seizures (Fig. 1). Only one of these two patients (patient-1) was able to begin a ketogenic diet (3:1 ketogenic ratio). This patient experienced resolution of the tonic-clonic and absence seizures, though the myoclonic seizures persisted. The movement disorder improved partially, especially choreoathetosis. EEG findings were atypical in both, with the two patients exhibiting multifocal epileptiform patterns (spikes). In addition, patient-1 had slow spike-wave complexes (2.5 Hz), and patient-2 had frontal spikes.

Table 1
Characteristics of patients with absence seizures. Early onset absence epilepsy (EOAE), psychomotor delay or intellectual disability (ID), refractory epilepsy (REF), additional seizure types (AS), associated movement disorder (MOV), atypical EEG ictal discharges (EEG) or first degree relatives with absence epilepsy (FDR).

EOAE	ID	REF	AS	MOV	EEG	FDR	Patients	*SLC2A1* pathogenic variants
x							6	0/6
x		x					1	0/1
x			x				1	0/1
x	x		x				1	0/1
x		x	x				2	0/2
x	x	x	x				2	0/2
x	x		x	x			1	0/1
x	x		x			X	1	0/1
x	x	x	x	x			3	0/3
x	x	x	x		x		2	0/2
x	x		x	x	x		2	0/2
x	x	x	x	x	x		3	2/3
		x					4	0/4
		x	x				2	0/2
	x	x	x				2	0/2
	x	x	x		x		3	0/3
	x		x				1	0/1
				x			2	0/2
				x		x	1	0/1
			x	x	x		1	0/1
						x	2	0/2
							43	2/43

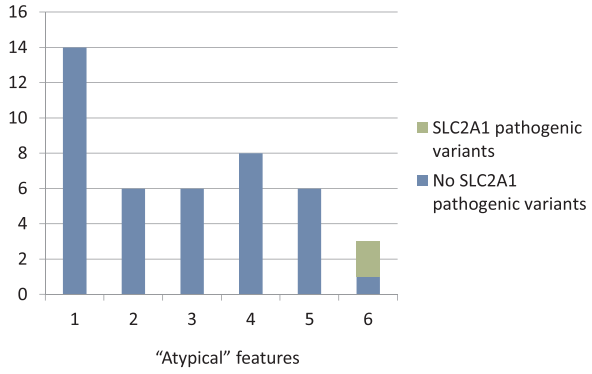

Fig. 1. Number of atypical characteristics in patients with absence seizures.

4. Discussion

GLUT1-DS is not a frequent cause of generalized epilepsy or absence seizures. In a study conducted by Arsov et al. (2012), in 504 patients with idiopathic generalized epilepsy, only 7 of them (1.4%) presented pathogenic variations in the *SLC2A1* gene. In contrast, when the absences are associated with other symptoms, the probability of the epilepsy being secondary to GLUT1-DS is greater. In our series, 2 patients (4.6%) had GLUT1DS. Specifically, these were 2 of the 3 patients (66.6%) who had the highest number of atypical features, presenting with all abnormal features except presence of family history of absence seizures, and both had a variant in *SLC2A1*. In their recent meta-analysis, Lebon et al. (Lebon et al., 2015) recommend performing genetic studies in search of mutations in the *SLC2A1* in patients with EOAE in addition to abnormal developmental or neurological features and other seizure types such as tonic-clonic or atypical EEG

One of the entities in which the relationship between GLUT1-DS and epilepsy has been most intensively studied is that which occurs when onset of absences occurs before 4 years of age. It is generally considered that 5%–10% of patients with EOAE present GLUT1-DS (Suls et al., 2009). Other authors claim that no such relationship is found when

stringent EEG criteria are applied and none of the patients included have atypical EEG (no 3-to-4–Hz symmetrical pattern). Indeed, Agostinelli et al. (2013a) failed to find mutations in *SLC2A1* in 84 patients with absences and onset of these seizures before age 3 years and normal EEG readings. In our series, pathogenic variants in *SLC2A1* were found in only 2 of 25 patients (8%) with EOAE and these cases also had atypical EEG findings. It appears that presence of slow-wave (< 3 Hz) or irregular complexes is an attribute of GLUT1-DS. In another study by Agostinelli et al. (2013b), only those patients with atypical EEG findings presented mutations in the *SLC2A1* (4/77), while none of the cases with a typical EEG revealed presence of the mutation (0/111).

Other characteristics or absences reported to be associated with GLUT1-DS are presence of movement disorders (especially paroxysmal exertion-induced dyskinesia), intellectual disability, other associated types of seizures (e.g. focal, myoclonic, tonic-clonic), or pharmaco-resistant seizures. Although GLUT1-DS has been associated with family history of absences (Striano et al., 2012), our series contains no such cases.

Although onset of epilepsy occurs in the first few months of life, diagnosis is delayed in most cases. In a recent series of French patients (Hully et al., 2015), the median age at diagnosis was 8 years and 5 months. This delay in diagnosis has serious prognostic implications, as the introduction of a ketogenic diet leads to increased control of symptoms such as epilepsy, neurological symptoms including ataxia, spasticity, and dystonia, and cognitive features like alertness, concentration, motivation (apparently there is no significant change in the intelligence quotient) For this reason, specific, early diagnosis and treatment are linked to increased quality of life and improved patient management (Fujii et al., 2016).

Despite the limitations introduced by the small sample size used in the present study and the fact that other variables such as microcephaly or response of seizures to a fasting state, our study shows that the greater the number of atypical patient characteristics, the greater the likelihood that these characteristics are secondary to GLUT1-DS.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

Disclosure

Neither of the authors has any conflict of interest to disclose

References

Agostinelli, S., Traverso, M., Accorsi, P., et al., 2013a. Early-onset absence epilepsy: SLC2A1 gene analysis and treatment evolution. Eur. J. Neurol. 20, 856–859.
Agostinelli, S., Accorsi, P., Beccaria, F., et al., 2013b. Clinical dissection of early onset absence epilepsy in children and prognostic implications. Epilepsia 54, 1761–1770.
Arsov, T., Mullen, S.A., Rogers, S., et al., 2012. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. Ann. Neurol. 72, 807–815.
Friedman, J.R., Thiele, E.A., Wang, D., et al., 2006. Atypical GLUT1 deficiency with prominent movement disorder responsive to ketogenic diet. Mov. Disord. 21, 241–245.
Fujii, T., Ito, Y., Takahashi, S., et al., 2016. Outcome of ketogenic diets in GLUT1 deficiency syndrome in Japan: a nationwide survey. Brain Dev. 38, 628–637.
Hully, M., Vuillaumier-Barrot, S., Le Bizec, C., 2015. From splitting GLUT1 deficiency syndromes to overlapping phenotypes. Eur. J. Med. Genet. 58, 443–454.
Lebon, S., Suarez, P., Alija, S., et al., 2015. When should clinicians search for GLUT1 deficiency syndrome in childhood generalized epilepsies? Eur. J. Paediatr. Neurol. 19, 170–175.
Mullen, S.A., Marini, C., Suls, A., Mei, D., Della Giustina, E., Buti, D., et al., 2011. Glucose transporter 1 deficiency as a treatable cause of myoclonic astatic epilepsy. Arch. Neurol. 68, 1152–1155.
Pong, A.W., Geary, B.R., Engelstad, K.M., et al., 2012. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. Epilepsia 53, 1503–1510.
Striano, P., Weber, Y.G., Toliat, M.R., et al., 2012. GLUT1 mutations are a rare cause of familial idiopathic generalized epilepsy. Neurology 78, 557–562.
Suls, A., Dedeken, P., Goffin, K., et al., 2008. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1. Brain 131, 1831–1844.
Suls, A., Mullen, S.A., Weber, Y.G., et al., 2009. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. Ann. Neurol. 66, 415–419.
Trifiletti, R.R., Jacobson, R.I., Ronen, G.M., et al., 1991. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N. Engl. J. Med. 325, 70370–70379.
Weber, Y.G., Kamm, C., Suls, A., et al., 2011. Paroxysmal choreoathetosis/spasticity (DYT9) is caused by a GLUT1 defect. Neurology 77, 959–964.
Zorzi, G., Castellotti, B., Zibordi, F., et al., 2008. Paroxysmal movement disorders in GLUT1 deficiency syndrome. Neurology 71, 146–148.