Seizure 24 (2015) 28–32

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Sporadic and familial glut1ds Italian patients: A wide clinical variability

Valentina De Giorgis [a], Federica Teutonico [b], Cristina Cereda [c], Umberto Balottin [a,d], Marika Bianchi [c], Lucio Giordano [e], Sara Olivotto [a], Francesca Ragona [f], Anna Tagliabue [g], Giovanna Zorzi [f], Nardo Nardocci [f], Pierangelo Veggiotti [a,d,*]

[a] Brain and Behaviour Department, University of Pavia, Pavia, Italy
[b] Child and Adolescence Neuropsychiatry Unit, "G. Salvini" Hospital, Rho, Italy
[c] "C. Mondino" National Neurological Institute, Pavia, Italy
[d] Department of Child Neurology and Psychiatry, "C. Mondino" National Neurological Institute, Pavia, Italy
[e] Pediatric Neuropsychiatric Division, Spedali Civili, Brescia, Italy
[f] Department of Child Neurology, Fondazione IRCCS Istituto Neurologico "C. Besta", Milan, Italy
[g] Human Nutrition and Eating Disorders Research Centre, University of Pavia, Pavia, Italy

ARTICLE INFO

Article history:
Received 14 August 2014
Received in revised form 19 November 2014
Accepted 20 November 2014

Keywords:
GLUT1 deficiency syndrome
SLC2A1 gene
Epilepsy
Paroxysmal exercise-induced dyskinesia
Cognitive impairment
Ketogenic diet

ABSTRACT

Purpose: GLUT1 deficiency syndrome is a treatable neurological disorder characterized by developmental delay, movement disorders and epilepsy. It is caused by mutations in the SLC2A1 gene inherited as an autosomal dominant trait with complete penetrance, even if most detected SCL2A1 mutations are de novo. Our aim is to present a wide series of Italian patients to highlight the differences among subjects with de novo mutations and those with familial transmission.
Methods: We present clinical and genetic features in a series of 22 GLUT1DS Italian patients. Our patients were classified in two different groups: familial cases including GLUT1DS patients with genetically confirmed affected relatives and sporadic cases with detection of SLC2A1 de novo mutation.
Results: We found remarkable differences in the severity of the clinical picture regarding the type of genetic inheritance (sporadic versus familial): sporadic patients were characterized by an earlier epilepsy-onset and higher degree of intellectual disability. No significant differences were found in terms of type of movement disorder, whilst Paroxysmal Exertion-induced Dyskinesia (PED) is confirmed to be the most characteristic movement disorder type in GLUT1DS. In familial cases the clinical manifestation of the disease was particularly variable and heterogeneous, also including asymptomatic patients or those with minimal-symptoms.
Conclusion: The finding of a "mild" phenotype in familial GLUT1DS gives rise to several questions: the real incidence of the disease, treatment option with ketogenic diet in adult patients and genetic counseling.

1. Introduction

GLUT1 deficiency syndrome (GLUT1DS, OMIM 606777) is a treatable neurological disorder caused by a deficiency of glucose transporter type 1 (GLUT1) at the blood–brain barrier and in brain cells which results in impaired glucose transport into the brain. The clinical manifestations of GLUT1DS include developmental delay, movement disorders, epilepsy and acquired microcephaly.

GLUT1DS was first described in 1991 by De Vivo[1] and seven years later, a molecular basis for the defect in GLUT1-mediated glucose transport was found.[2] GLUT1DS is still an often underdiagnosed condition but it benefits from rapid recognition because an early introduction of the ketogenic diet (KD) could reduce the frequency of seizures, the severity of the movement disorders, and improve patients' behavior and alertness.[3]

GLUT1DS is caused by mutations in the SLC2A1 gene (OMIM 138140) which maps to the short arm of chromosome 1 (1p35-31.3).[4] This is the only gene associated with GLUT1DS so far. The condition is inherited as an autosomal dominant trait with complete penetrance, however most detected SCL2A1 mutations are de novo.[5]

We hereby present the clinical and genetic features in a series of 22 GLUT1DS Italian patients and compare their clinic-genetic characteristics in order to find any difference and significant features.

* Corresponding author at: Department of Child Neurology and Psychiatry, "C. Mondino" National Neurological Institute, Via Mondino 2, 27100 Pavia, Italy. Tel.: +39 0382 380289; fax: +39 0382 380206.
E-mail address: pveggiot@unipv.it (P. Veggiotti).

http://dx.doi.org/10.1016/j.seizure.2014.11.009
1059-1311/

2. Materials and methods

2.1. Patients

56 Italian patients satisfying the clinical criteria for diagnosis of GLUT1DS [6–9] underwent the genetics test from 2006 to 2014 at our Institutes and 22 patients were found positive at SLC2A1 mutation.

Our study was approved by the Ethic Committee of our Institutes.

At recruitment the study sample includes 16 females and 6 males, aged 2–57 (average 21.3) born to non-consanguineous parents.

In some previous papers the clinical, biochemical and genetic features of patients #1, #2, #3 and #7[10–12] and patients #15 and #16[13] have already been described.

In 14/22 patients lumbar puncture (LP) was performed in the fasting state (after 5–6 h of fasting), and the blood sample for glucose measurement was obtained immediately before the procedure to avoid stress-related hyperglycemia.[7] A CSF-to-blood glucose ratio below 0.6 was considered indicative for GLUT1DS.

In the remaining 8 patients, presenting high suggestive clinical signs of the disease (intellectual disability, epilepsy and/or movement disorder), LP was not performed for various reasons (non-compliance, investigation failure, 5 patients were relatives of probands) and they were directly submitted to SLC2A1 mutation analysis.

All the blood and CSF samples were collected, after obtaining written informed consent, from patients and/or the parents. The investigations fulfilled our institution's ethical rules for human studies.

All GLUT1DS patients were subjected to our diagnostic and follow-up protocol including blood tests for the KD monitoring, sleep EEG, neuropsychological assessments.[7]

All patients were classified in two different groups: familial cases including GLUT1DS cases with genetically confirmed affected relatives and sporadic cases due to SLC2A1 de novo mutation.

We compared the two groups in order to identify some possible clinical and genetic peculiarities.

2.2. Mutation analysis of SLC2A1

After obtaining written informed consent to genetic test collected at "C. Mondino" National Neurological Institute, genomic DNA from probands and relatives were extracted from peripheral blood using standard procedures (Maxwell® 16 Blood DNA – Promega, Milan, Italy).

All 10 exons of *SLC2A1* gene were screened for sequence variations by direct sequencing using the Big-Dye Terminator v. 3.1 sequencing kit (Applied Biosystems, Milan, Italy) and ABI 3130 Genetic Analyzer (Applied Biosystems, Milan, Italy). Each fragment was sequenced on both strands. The alignment to reference sequence (NG 008232.1) was performed using Sequencher 4.8 software.

The effect of the newly detected *SLC2A1* mutations on protein structure or function was analyzed with the prediction programs ExPASy (http://www.expasy.org).

3. Results

The clinical signs and laboratory data are presented in Tables 1 and 2.

3.1. Clinical and genetic features in sporadic patients

The age range of sporadic cases (9 females and 2 males) at the time of diagnosis and study enrollment was 2–20 (mean 13.5). Their clinical signs and laboratory data are detailed in Table 1 and summarized below.

Pregnancy, delivery and the neonatal period were uneventful in all. Five patients (45%) had microcephaly (head circumference below or equal to the 25th percentile for age at the time of enrollment). Eight patients (73%) presented intellectual disability, severe in 3 of these; 3 patients (27%) presented a borderline Intellectual Quotient (IQ).

Epilepsy represented a main feature and the first symptom in all patients. Seizure onset was in the first years of life (mean 24.1 months) and 6 patients (55%) developed a drug resistant condition. Seizure types varied and included absence seizures (64%), usually atypical or drug-resistant, dyscognitive seizures (36%), generalized tonic-clonic (27%), myoclonic (27%), focal seizure without dyscognitive features (18%), myoclonic-atonic (9%).

Ten patients (91%) presented a movement disorder (MD) consisting of paroxysmal exercise-/stress-/fasting-induced MD (73%) and/or paroxysmal kinesigenic MD (9%) and/or non-paroxysmal MD (36%). In most cases it began in childhood (age range: 8–168 months; mean 80.4 months) after seizure onset.

Dysarthria, reported to be a common sign in GLUT1DS,[6,8] was present in 55% of the patients, with halting speech, pauses, articulation errors and dropping of word endings. Other associated clinical signs included spasticity (45%), weakness on awakening or in the fasting state (36%), migraine (27%), myoclonias (27%) and prognathism with dental malocclusion (18%).

Table 1
Clinical and laboratory data in GLUT1DS sporadic patients.

Pt	Gender	Age (y)	Ratio	HC (p)	IQ	Spasticity	Seizure	Seizure onset (m)	Seizure type	DR	EEG	MD	MD type	MD subtype	MD onset (m)	Other	KD response
1	F	20	0.33	>50°	<45	Y	Y	6	ABS GTC MS	Y	SB G	Y	C	a	12	Ds Pr W Mi	EEG E MD W
2	F	19	0.33	>50°	<45	Y	Y	3	FS, ABS, GTC MS	Y	SB G F	Y	C	a c	8	Ds	EEG E MD
3	F	20	0.38	25–50°	<45	Y	Y	4	ABS FS MS	Y	SB G F	Y	C	a	18	Ds Pr W Mi	EEG E MD W
4	F	14	0.44	<25°	53	Y	Y	18	DS	Y	SB F	Y	C	a	20	Ds	EEG E MD
5	F	6	0.54	<25°	76	N	Y	11	GTC ABS	N	SB G	Y	PED	d	36	W	E MD W
6	F	10	0.34	<25°	40	N	Y	30	MAS, DS, ABS	Y	SB G F	Y	PED	d	72	Ds W	E MD W*
7	F	13	NA	<25°	84	N	Y	11	ABS	Y	SB G	Y	N	N	NA	M	NA
8	F	17	0.41	>50°	62	Y	Y	72	ABS	N	G	Y	PND	a m	72	Mi	E EEG
9	M	17	0.51	<25°	57	N	Y	72	CFS	N	F	Y	PED	d	168	Ds	E MD
10	M	11	0.51	<25°	82	N	Y	30	CFS	N	F	Y	PED	c d	96	M	MD
11	F	2	0.37	25–50°	50	N	Y	9	MAS	NA	SB G	N	–	–	–	–	E EEG

Abbreviations: Pt, patient; F, female; M, male; Ratio, CSF/blood glucose ratio; NA, not available; Y, yes; N, no; HC, head circumference (percentiles); m, months; DS, dyscognitive seizures; ABS, absence seizure; GTC, generalised tonic-clonic seizure; DR, drug resistance; SB, slow background activity; G, generalised discharges; F, focal discharges; N, normal; MD, movement disorder; C, chronic; PED, paroxismal exertion-induced dyskinesia; PND, paroxysmal non exertion-induced dyskinesia; a, ataxia; d, dystonia; c, choreoatetosis; Mi, migraine; Pr, Prognathism with dental malocclusion and/or supernumerary teeth; W, weakness; M, myoclonias; KD, ketogenic diet.