GLUT-1 DEFICIENCY SYNDROME: PHENOTYPE – GENOTYPE CORRELATIONS
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Glucose transporter type I deficiency syndrome (GLUT-1 DS) is a metabolic encephalopathy, caused by a defect of glucose uptake, mediated by GLUT-1, at the blood-brain barrier and into brain cells. [1;2] GLUT-1 is a membrane-bound glycoprotein that provides base rate glucose transport across blood-tissue barriers. [3] The gene exclusively associated with GLUT-1 is SLC2A1, located on chromosome 1 (1p34.2).[4] It is a relatively small gene and consists of ten exons, spanning 2842 base pairs encoding 493 amino acids. [4; 5] The structure and function of the GLUT-1 protein has been intensively investigated. [4; 5] It has been identified and described for the first time in 1985 by Mueckler. (Figure 1) [2; 5] The amino-acid sequence of the GLUT-1 protein is highly conserved, with 97-98% identity between the human, rat, rabbit, mouse and pig sequences, which implies that all domains of this protein are functionally important. [6] Its structural model contains 12 transmembrane domains, spanning the plasma membrane as alpha-helices with intracellular located amino- and-carboxyl-termini. Helices 6 and 7 are separated by a large intercellular loop. The postulated three-dimensional structure is
characterized by a central channel across the protein, connecting the extracellular and intracellular environments. Crucial domains for transport and pathogenicity are clustered around the central channel and in the long intracellular loop. *(Figure 1)* [2; 5; 7]

GLUT-1 is constitutively expressed in erythrocytes, brain microvessels and astroglia.

In brain, GLUT-1 has been detected in two different isoforms encoded by the same gene and differing only in their extent of glycosylation: the 55 Kda isoform, located in the endothelial cells of brain microvessels and erythrocytes and the 45 Kda isoform, detected in most cells including astrocytes and maybe responsible for basal glucose uptake into these tissues. [8]

Most of SLC2A1 mutations detected occurred de novo as a sporadic autosomal dominant condition, resulting in GLUT-1 haploinsufficiency. [9; 10]

Recently, however, an autosomal dominant mode of transmission was indentified in several unrelated families. [11; 12]

Finally, Klepper et al., for the first time, have shown that GLUT-1 DS can be also transmitted as an autosomal recessive disease. [13]

All mutations are heterozygous and mostly private; infact, homozygous GLUT-1 mutations presumably are lethal in utero, this observation is confirmed in GLUT-1 knockout mice. [14]

To date, about 100 different mutations in the SLC2A1 gene has been described in approximately 200 patients, including large-scale deletions, missense, nonsense, frame shift and splice-site mutations. *(Figure 2)* [15]
All mutations either lead to absence or loss of function of one of the SLC2A1 alleles. Generally, patients with missense mutations often present moderate to mild symptoms, but we noted that the expressivity is variable and the penetrance can be incomplete and so we underline that genotype-phenotype correlation in GLUT-1 DS is complex and it is not yet clearly defined. [16; 17]

Classic clinical phenotype associated to GLUT-1 deficiency was first described by De Vivo et al. in 1991 and it includes a range of complex movement disorders (as ataxia, dystonia, paroxysmal induced dyskinesia, spasticity), epilepsy, often drug resistant, mental retardation, acquired microcephaly, with onset under a year of age. [18]

In recent years, many atypical variants associated with different mutations of SLC2A1 gene have been described. In these atypical phenotypes seizures, movement disorders and mental delay can occur either separately or in different combinations. Particularly, a group of patients can present prominent movement disorders without seizures or exclusively paroxysmal exercise-induced dyskinesia (PED), or exclusively epilepsy, for example early onset absence epilepsy (EOAE) or classic generalized epilepsy (IGE) or childhood absence epilepsy (CAE). (Figure 3) [16; 19; 20; 21; 22]

About epilepsy, no specific seizure type has been identified because GLUT-1 DS is associated with a wide range of epilepsies. Generally, patients develop seizures in infancy and early childhood, that frequently do not respond to anticonvulsivant drugs.
In infants, seizures are described as brief, subtle myoclonic limb jerking with staring alternating with eye-rolling, a sudden onset of pallor, a dazed expression or horizontal roving eye movements, unresponsiveness, and hypotonic as well as head bobbing. [16; 27] Later in childhood, seizures often appear to be myoclonic and generalized. Surprisingly, familial GLUT-1 deficiency has recently been associated with IGE, especially EOAE. [20; 23; 24; 25]

IGE syndromes associated with GLUT-1 DS are usually, but not always, drug responsive and individual cases may be phenotypically indistinguishable from common forms of IGE. In particular, a recent family study has shown that of 15 subjects with SLC2A1 mutation, epilepsy occurred in 12; epilepsy phenotypes varied widely, including IGE with absence, myoclonic-astatic epilepsy and focal epilepsy; furthermore, PED occurred in just under half of the family members and 1 individual PED was present without seizures. So, we think that GLUT-1 deficiency should be suspected where the family history suggest a dominant inheritance of IGE or PED, especially where PED and IGE coexist in the same family. [20; 23; 25]

Previously, the same authors found that GLUT-1 DS accounts for over 10% of EOAE, beginning before 4 years of age; these patients presented milder phenotypes of GLUT-1 deficiency because they had normal development before seizures onset, good AED seizures control, and intellectual outcome range from normal to moderately impaired. Thus, in these patients, the seizure phenotype could not be readily distinguished from CAE, except for the earlier age of onset. Probably, GLUT-1 DS may underline a significant proportion of EOAE, in particular those with atypical features. [26; 27]
Furthermore, it is very important to remember that same patients show prominent movement disorders other than epilepsy. Then, epilepsy and movement disorders can occur either separately or in combination. [16; 19; 28; 29]

Purpose of this study is to research mutations in SLC2A1 gene in a population of patients with early onset epilepsy with or without mental delay and movement disorders; to analyze phenotype-genotype correlations and to study first-degree relatives to evaluate the possible reduced penetrance.

**Figure 1:** Conformational model of GLUT-1 in the cellular membrane.
The GLUT-1 protein shows 12 transmembrane helices with a large intracellular loop connecting helix 6 and 7, the N-glycosylation site in the first extracellular loop, and the amino- and carboxy-termini located in the cytosol. [2]
Figure 2: List of the main pathogenic mutations identified to date [15]
Figure 3: Clinical phenotypes and severity of GLUT-1 disease. Seizures, movement disorders and mental delay can occur either separately or in combination [22].

Fig. 1 – Title: Clinical phenotypes and severity of GLUT1-DS. Seizures and movement disorders can occur either separately or in combination. The most severe phenotype is the classic GLUT1 encephalopathy with intractable infantile seizures, complex movement disorders, developmental delay and acquired microcephaly. Milder nonclassical phenotypes include the paroxysmal exercise-induced dyskinesia, early-onset absence epilepsy and idiopathic generalized epilepsies. MAE = myoclonic-astatic epilepsy; R-IGE = refractory idiopathic generalized epilepsy; EOA = early-onset absence epilepsy; PED: paroxysmal exercise-induced dyskinesia.
Materials and methods

In the first part we have selected a population of 98 patients with:

1. Early onset (within 4 years) epilepsy drug resistant and/or drug responsive;
2. Early onset (within 4 years) drug resistant and/or drug responsive associated with cognitive impairment and/or movement disorders.

All selected patients underwent to neurological evaluation with physical examination and collection of medical history with data concerning pregnancy, child-birth, possible presence of acquired microcephaly and evaluation of psychomotor development. Data were collected on the age of onset of epilepsy, the frequency of seizures and their semiological characteristics and possible triggers of the seizures.

Blood samples obtained from selected individuals were sent at the “Gaslini Institute” of Genoa to search for mutations in the SLC2A1 gene, which was carried out by PCR for the detection of missense mutations and MLPA for the detection of possible deletions and/or translocations.
Furthermore, we have submitted all selected patients to neuroimaging examinations (brain MRI and brain PET). Each of the patients with mutations on SLC2A1 gene was followed serially in a quarterly checks. During each follow-up visit the patient proceeded:
- Neurological examination pre- and post-prandial;
- Video-EEG long-term pre- and post-prandial;
- EEG monitoring in long-term sleep;
- Neuropsychological study with evaluation of the IQ by Wischler stairs:
  • WISC-R for children between 6 and 16 years old;
  • WAIS for patients with more than 16 years.
- research and study of potential specific learning disabilities.

In addition, the genetic study was extended to all family members. In the end, for each family member with a mutation of SLC2A1 gene was collected clinical history, was performed a neurological examination and a video-EEG recording long-term pre- and post-prandial.
Results

Following the analysis of 98 selected patients 4 subjects were identified with 4 different mutations in the SLC2A1 gene.
All 4 patients presented heterozygous missense mutations, never previously described, which determined an aminoacid substitution in an exon of the SLC2A1 gene.

Below we will analyze in detail the individual cases with clinical insights performed on individual patients and their family and with the results obtained.

The first case that we want to describe is the case of A.M., ♀ 49 yo., born at term by vaginal delivery, after a normal pregnancy.
Her family history is negative for epilepsy and febrile seizures.
She has presented a normal psycomotor development until the age of 21 months, when she has showed a cognitive delay and presented the first seizures, before infantile spasms and after, at the age of 36 months, myoclonic seizures. About interictal/ictal EEG of that time the documentation in our possession is very poor. We have only a few old interictal EEG that, however, show generalized spikes, polispikes and polispikes-waves complex. (Figure 4)
Over the years, A.M. has taken many different therapies, often with the association of more drugs (for example: valproic acid, ethosuximide, clobazam and clonazepam).

Actually A.M. have no seizures from the age of 40 years and her current therapy is a valproic acid (500 mg/die) and clobazam (10 mg/die) association.

Her neurological examination shows an awkward and slightly unstable gait, with lightly enlarged base and her neuropsychological study shows a moderate mental delay (WAIS-R: VIQ: 55; PIQ: 61; TIQ: 53).

We have performed serial fasting and after meal EEG, all with normal results.

Furthermore we have submitted our patient to brain MRI and brain PET.

There are not reported alterations in Brain MRI, instead Brain PET shows a reduction of tracer distribution in the cerebral cortex in relation to the striated, appearing preserved/hypermetabolic. The more evident reduction is in the temporal, particularly in mesial/hippocampal , regions bilaterally, in both thalamus, in brainstem and cerebellum (hemispheres and worm). (Figure 5)

In the end, the analysis of the SLC2A1 gene shows a mutation c.844 C> G in exon 6 in the heterozygous state, that determines a substitution of Glutamine in position 282 with a Glutamnic acid (p.Gln282Glu).

This mutation is not present in the mother; instead we could not study the father who had died.
Figure 4: A.M., ♀ 49 yo., interictal EEG that shows generalized spikes, polispires and polispires-waves complex.
Figure 5: A.M., ♀ 49 yo., BRAIN PET that shows a reduction of tracer distribution in the temporal lobe, particularly in mesial/hippocampal regions bilaterally, in both thalamus, in brainstem and cerebellum (hemispheres and worm).
The **second case** we have identified is that of **A.S., ♀, 15 yo.**

This patient was born at term by vaginal delivery, after a normal pregnancy.

She has a cousin in paternal line that suffers of epilepsy.

She has presented a normal psycomotor development until the age of 15 months, when appeared episodes such benign paroxysmal vertigo and gradually revealed a cognitive delay associated with dysgraphia, dyslexia and dyscalculia.

Later appeared atypical absences with myoclonic component and rare tonic-clonic generalized seizures (CTGS).

We have recorded an atypical absence with a critical EEG that shows long sequences of slow spikes/waves complex in bi-frontal areas (> left) of 2-2.5 Hz, with a tendency to a diffusion. *(Figure 6)*

The intercritical EEG were characterized initially by generalized spikes/waves and spikes/waves complex in bi-frontal areas asynchronously; later, by slow spikes/waves complex in bi-frontal areas (> left) and rare spikes/waves complex in right parietal paramedian area. *(Figure 7)*

By the age of 12 yo seizures are disappeared and after meal EEG are normal instead all fasting EEGs show small sporadic isolated wave-sharp/slow-wave complex on the left frontal and temporal regions. *(Figure 8)*

Actually A.S. takes a combination of 3 drugs: valproic acid (500 mg/die); etosuximide (500 mg/die) and lamotrigine (75 mg/die).

Her current neurological examination shows disharmonious gait with light ataxia and a moderate difficulty in fine movements.
The neuropsychological study evinces a light mental retardation (WISC-R: QIV: 78; QIP: 45; QIT: 59) associated with dysgraphia, dyslexia and dyscalculia.

Our patient has performed a brain MRI resulted normal and a brain PET that shows a slight reduction of the distribution of the tracer in the frontal cortex and in the upper part of the thalamus, bilaterally. *(Figure 9)*

Molecular genetic analysis of SLC2A1 gene showed a mutation c.667 C>T in exon 5 in the heterozygous state, that determines a substitution of Arginine in position 223 with a Tryptophan (p.Arg223Trp).

The same (new) mutation is present in her father (*F.S.*, ♂, 55 yo), who never presented clinical seizures, but whose fasting EEG shows the presence of a widespread slowdown in hyperpnea and sporadic bifrontal wave-sharp/slow-wave complex. *(Figure 11)*

Furthermore, we submitted this patient to a brain MRI resulted normal and to a brain PET that, instead, highlights some alterations: a reduction of the tracer in left parietal, temporal, occipital and cerebellar cortex. *(Figure 10)*

In this family we have studied even the mother of our patient that has not mutations in the SLC2A1 gene and the cousin of the paternal line that presents a form of epilepsy similar to that of our patient but drug responsive. In this child, the onset of seizures was at the age of 4 yo with seizures of benign paroxysmal vertigo, as our patient. However he doesn’t show movement disorders and mental delay but he has presented only an acquisition delay of the language. Even for this patient we have researched mutations on SLC2A1 gene, but no mutations was found.
Figure 6: A.S., ♂, 15 yo. - an atypical absence with a critical EEG with a sequence of slow spikes/waves complex in bi-frontal areas (> left) of 2-2.5 Hz, with a tendency to generalization.
Figure 7: A.S., ♀, 15 yo. - intercritical EEG characterized by slow spikes/waves complex in bi-frontal areas (> left).
Figure 8: A.S., ♀, 15 yo. - actual fasting intercritical EEG characterized by small, sporadic and isolated wave-sharp/slow-wave complex on the left frontal and temporal regions.
Figure 9: A.S.,♀, 15 yo. - BRAIN PET characterized by a slight reduction of the distribution of the tracer in the frontal cortex and in the upper part of the thalamus, bilaterally.

Figure 10: F.S.,♂, 55 yo - BRAIN PET characterized by a reduction of the tracer in left parietal, temporal, occipital and cerebellar cortex.
Figure 11: F.S., ♂, 55 yo - after meal EEG: normal; fasting EEG with sporadic bifrontal wave-sharp/slow-wave complex that are increased during hyperpnea.
The third case that we have identified is that of V.E.B., ♂, 21 yo. He was born at term by vaginal delivery after a normal pregnancy. His family history of epilepsy and/or febrile seizures is negative. His psychomotor developmental is reported normal. He presented seizures from the age of about 8 months before as infantile spasms and later as absences seizures. By the age of 13 yo he is seizures free but he still takes levetiracetam to a low dosage (500 mg/die). Currently he presents episodes of paroxysmal dyskinesia fasting. His actual neuropsychological studies, his IQ and his brain MRI are normal.

On the contrary his brain PET shows a reduction of the tracer bilaterally in the frontal cortex, thalamus and cerebellum than in striated hypermetabolic.

Molecular genetic analysis of SLC2A1 gene shows a mutation c.443 C> T in the heterozygous state, that determines a substitution of Leucine in position 148 with a Serine (p.Leu148Ser). This mutation was researched in his parents but no mutations are identified.
In the end, the fourth case we have identified and studied is the case of D. L., ♂, 13 yo. He was born at term by vaginal delivery after a normal pregnancy. He has a family history of epilepsy. His psychomotor developmental is reported normal. The onset of the seizures was at the age of three years with the appearance of typical absences with an EEG pattern of typical spikes/waves complex to 3 Hz. (Figure 13) Currently he has no seizures from the age of 12 yo and he takes lamotrigine to low dosage. His neuropsychological studies with IQ and brain MRI are normal. On the contrary, brain PET evinces a relative reduction of the tracer in the cerebellum (vermis and hemispheres) and, less markedly, in the thalamus bilaterally. (Figure 12)

We have executed a molecular genetic analysis of SLC2A1 gene that showed a mutation c.694 C> T in the heterozygous state, that causes a substitution of Arginine at position 232 with a Cysteine (p.Arg232Cys).

We have studied all members of this family and we have identified the same mutation in all 8 living affected individuals and in 4 adult healthy carriers (II-4, II-5, III-3 and III-4). (Figure 14) The family comprises 9 individuals (8 living) across 3 generation affected by IGE with variable phenotypes. None of the affected individuals had other neurologic manifestations, including movement disorders. All subjects had generalized seizures, mainly typical absences, with variable age at onset (early childhood to 23 years). During childhood, patients II-7, III-5, III-7 and III-8 had daily, frequent (up to hundreds each day) episodes of sudden, brief impairment of consciousness and
interruption of the ongoing activity. Patient III-8 had also occasional tonic-clonic seizures. In these patients, ictal EEGs showed regular and symmetric generalized discharges of 3-3.5 Hz spike wave complexes on normal background activity, as typically observed in childhood absence epilepsy. *(Figure 15)* Seizures remitted within 2-5 years from onset. However, patient II-7 started experiencing myoclonic jerks after awakening and generalized tonic-clonic seizures precipitated by sleep deprivation in his midteens, as seen in juvenile myoclonic epilepsy. His EEGs showed regular and symmetric generalized discharges of 3-3.5 Hz spike wave complex and polyspike wave complex on normal background activity. Patients III-1 and III-2 experienced weekly, long-lasting (up to 10 minutes) absences starting around age of 10 years. Their EEGs showed generalized discharges of 3.5-4 Hz spike wave complexes on normal background activity. Patient II-2 was “asymptomatic” at the age of 23 years but a video-EEG revealed typical 3-3.5 Hz spike wave discharges accompanied by subtle impairment of consciousness during hyperventilation (phantom absences in adult-onset absence epilepsy). She accepted treatment only after a generalized tonic-clonic seizure. *(Figure 16 and 17)*

Patient III-11 has presented absence seizures starting from 3 years of life. His EEGs showed frequent, spontaneous bursts of generalized irregular spike-wave discharges, occasionally accompanied by atonic components and head drop. Although all affected member of the family had normal neurologic examination and showed excellent response to pharmacologic therapy, individual III-11 showed borderline intellect and was drug resistant, despite add-on of ethosuximide and levetiracetam. A ketogenic diet was not tolerated because of severe diarrhea and nausea.
EEGs were normal in 7 healthy subjects (II-4, II-5, III-3, III-4, III-9 and III-10).
All these patients have done a brain MRI resulted normal but, unfortunately, at the moment, all these family members of our patient have refused to make a brain PET.

**Figure 12:** D. L.,♂, 13 yo - Brain PET evinces a relative reduction of the tracer in the cerebellum (vermis and hemispheres) and, less markedly, in the thalamus bilaterally.
Figure 13: D. L., ♂, 13 yo - a typical short absence with a critical EEG pattern of typical spikes/waves complex to 3 Hz.
Figure 14: D. L., female, 13 yo - genealogical tree with all members of family: 8 living affected individuals and in 4 adult healthy carriers (II-4, II-5, III-3, III-4). Table with the clinical features of the members with mutations: the family comprises 9 individuals (8 living) across 3 generation affected by IGE with variable phenotypes.
Pt. III-8 D. L., ♂, 13 yo - ictal EEG with regular and symmetric generalized discharges of 3-3.5 Hz spike wave complexes on normal background activity, as typically observed in childhood absence epilepsy.
**Figure 16:** Pt. II-2 - EEG that reveals typical 3-3.5 Hz spike wave discharges
Figure 17: Pt. II-2 - another intercritical EEG with typical 3-3.5 Hz spike wave discharges.
Discussion and Conclusions

GLUT-1 deficiency syndrome is a metabolic encephalopathy whose classical phenotype, described for the first time by De Vivo in 1991, includes a clinical picture of extreme gravity characterized by: early onset epilepsy, usually drug-resistant, mental delay, acquired microcephaly and a large group of movement disorders (ataxia, choreoathetosis, dystonia, paroxysmal exercise-induced dyskinesia, spasticity). [2; 18] Over the years, about 200 cases have been described, many of which constitute atypical variants where seizures, movement disorders and mental delay can occur either separately or in different combinations. [15; 16]

To date, genotype-phenotype correlations are poor. Leen et al., in 2010, have attempted to delineate a possible correlation phenotype/genotype for this syndrome. They say that severe mutations resulting in complete loss of one allele are typically associated with the classic GLUT1-DS phenotype, whereas heterozygous missense mutations with a residual function are more often found in milder phenotypes. [15]

In our study, we have identified in 16 different subjects 4 different missense mutations never described in literature and associated with atypical phenotypes, often not so “mild”.

GLUT-1 Deficiency Syndrome: phenotype-genotype correlations
Particularly, we have found a missense mutation in a patient with a rather severe phenotype, with an association of moderate mental delay, epilepsy and slight movement disorder. Moreover we have identified another missense mutation, never described in literature, in a patient with a phenotype not so mild, that presented epilepsy associated with movement disorder and a light mental delay, and in her father, that, instead, presented a very mild phenotype with only instrumental but apparently not clinical signs. Also we have found a patient with an IGE and a missense mutation in SLC2A1 gene, and we have found the same mutation in 11 his family members including 4 healthy subjects.

In light of everything, we have noted a big clinical variability, even evident in neuroimaging (brain PET), where both patients with the same mutation that patients with different mutations presented a different panel of brain PET, often not correlated with the patient's clinical panel, as shown in the recent literature by Akman in 2015. [30; 31]

Unlike what reported in the literature, these observations demonstrate that mild mutations (missense mutations) are found both in severe phenotypes that in milder phenotypes. So, we can say that these results highlight the fact that other modifying genetic and/or acquired environmental factors may influence the underlying pathophysiology and clinical expressivity. Novel genetic methods may be able to detect the underlying reason for this phenomenon.

Another important aspect is the treatment of this syndrome. In the literature the treatment of choice for GLUT-1 DS is a ketogenic diet.
GLUT-1 Deficiency Syndrome: phenotype-genotype correlations

(KD). It is a high-fat, carbohydrate-restricted diet that mimics the metabolic state of fasting; so, the KD relies on exogenous rather than body fat for ketone production, thus maintaining ketosis without weight loss. [32] In GLUT-1 DS, the ketone bodies generated from dietary fatty acid oxidation in the liver readily penetrate the blood-brain barrier and provide an alternative fuel for brain metabolism. As developing brain requires substantially more energy in young children, the ketogenic diet should be started as early possible whenever GLUT-1 DS is suspected and should be continued at least until adolescence. [33]

To date, in literature, it seems that, particularly epilepsy, but also movement disorder are positively affected by ketogenic diet, while, the impact of KD on developmental delay appears less prominent. [15; 28] Recently, also the modified Atkins Diet has been used successfully in patients with GLUT-1 DS and it may offer a good alternative in schoolchildren and adolescents, with difficulties maintaining a classical KD. [34]

We must underline that some pharmacological agents impair GLUT-1 function and should be avoided; these substances include: ethanol, methylxanthines, caffeine, androgens, dioxine, tricyclic antidepressant and anticonvulsivants such as Phenobarbital, diazepam and valproic acid. [35]

The patients in our study taking antiepileptic drugs, especially valproic acid, with often the disappearance of seizures. None of the patients tolerated the ketogenic diet and the attempt to replace the drug did not bring changes in the patient, but only, in some patients, the recovery of seizures. For this reason it was decided to leave
unchanged the therapy, also because the majority of our patients with GLUT-1 DS are adults, in which the diagnosis has come too late.

So, we underline that the early identification of children with GLUT-1 DS is important to prevent treatment with anticonvulsivants that may be ineffective or potential detrimental, and to initiate an alternative energy source during a time of increased cerebral metabolism.

In conclusion, we emphasize that the identification and the description of new patients and families affected by syndrome of deficiency of GLUT-1 and the characterization of the phenotype, as well as the exact correlation with the genotype is essential to better delineate this syndrome and its clinical spectrum, for genetic counseling, for the possible therapeutic implications and for prognostic information.

In the future, we hope that studies are carried out aiming the identification and functional characterization of novel mutations in the SLC2A1 gene in order to contribute to better knowledge about the functions of this gene in the epileptogenesis and more generally on the pathophysiological mechanisms underlying this syndrome and its symptoms.


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