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Review

The glucose transporter type 1 (Glut1) syndromes

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ABSTRACT

The glucose transporter type 1 (Glut1) is the most important energy carrier of the brain across the blood–brain barrier. In the early nineties, the first genetic defect of Glut1 was described and known as the Glut1 deficiency syndrome (Glut1-DS). It is characterized by early infantile seizures, developmental delay, microcephaly, and ataxia. Recently, milder variants have also been described. The clinical picture of Glut1 defects and the understanding of the pathophysiology of this disease have significantly grown. A special form of transient movement disorders, the paroxysmal exertion-induced dyskinesia (PED), absence epilepsies particularly with an early onset absence epilepsy (EOAE) and childhood absence epilepsy (CAE), myoclonic astatic epilepsy (MAE), episodic choreoathetosis and spasticity (CSE), and focal epilepsy can be based on a Glut1 defect. Despite the rarity of these diseases, the Glut1 syndromes are of high clinical interest since a very effective therapy, the ketogenic diet, can improve or reverse symptoms especially if it is started as early as possible. The present article summarizes the clinical features of Glut1 syndromes and discusses the underlying genetic mutations, including the available data on functional tests as well as the genotype–phenotype correlations.

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1. Introduction

Glucose is the most important energy carrier of the brain. Glucose transporter type 1 (Glut1) is located at the blood–brain barrier and assures the energy-independent, facilitative transport of glucose into the brain [1]. Twelve transmembrane segments of the protein and an intracellular N- and C-terminus (Fig. 1A) are forming the protein pore (Fig. 1B) [5]. The original name of Glut1 was HepG2/erythrocyte/brain transporter since it also expressed at the surface of red blood cells [6]. The protein is encoded by *SLC2A1*, a gene on chromosome 1p34.2 which contains 10 exons and spans 35 kb [2].

2. The clinical phenotypes associated with Glut1 defects

2.1. Glucose transporter type 1 deficiency syndrome (Glut1-DS)

The glucose transporter type 1 deficiency syndrome (Glut1-DS) was initially described in 1991 [7]. The first mutations detected in *SLC2A1* were published in 1998 by Seidner and coworkers [8]. Most of the described cases are sporadic. Early onset seizures in the first year of life up to status epilepticus especially in fasting state are the most common initial features. Atypical absences and atonic seizures as "nodding attacks" were described as the classical semiology, but generalized tonic–clonic seizures and hemiclonic seizures can also occur. Additionally, mental retardation and regression of neurodevelopmental development as well as ataxia and microcephaly are common features. Therefore, the disease is fitting into the diagnostic criteria of the developmental and epileptic encephalopathies (DEE) [9]. In the electroencephalography (EEG) findings, focal and generalized epileptiform discharges are described, but the EEG findings can also be completely normal. In general, anticonvulsant medications do not influence seizure activity [7].

2.2. Paroxysmal exertion-induced dyskinesia (PED)

A second syndrome associated with *SLC2A1* mutations is the paroxysmal exertion-induced dyskinesia (PED, DYT18). Paroxysmal exertion-induced dyskinesia belongs to the group of paroxysmal dyskinesias which can be symptomatic/lesional, e.g., in the case of an inflammatory lesion in the basal ganglia or of genetic origin [10]. They are characterized by sudden choreatic, athetotic, and dystonic ballistic movements. In PED, the dyskinesias are triggered by continuous voluntary movements over at least 15 min and often occur only in the extremities that were used before, for example in the legs after a longer period of walking [3]. Other forms are the kinesigenic (paroxysmal kinesigenic dyskinesia, PKC, PKD, DYT10) and the nonkinesigenic (paroxysmal non-kinesigenic dyskinesia, PNKD, PDC, DYT8) paroxysmal dyskinesias. The onset for all three entities is very variable between 1 and 40 years of age, and most of the described cases are sporadic. In PKD, the dyskinetic movements are induced by sudden and short voluntary movements such as running; in PNKD,

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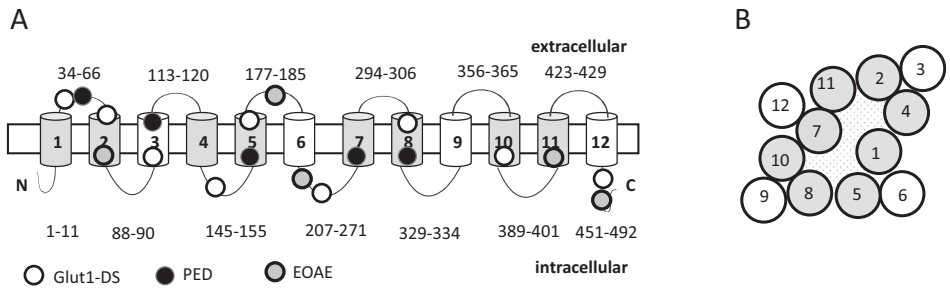

Fig. 1. (A) Presentation of the transmembrane glucose transporter type 1 (Glut1) with twelve transmembrane segments and an intracellular N- and C-terminus. The figure is modified by Wang and coworkers [2] and others [3, 4]. The dots represent selected variants found for the different phenotypes Glut1-DS (glucose transporter type 1 deficiency syndrome), PED (parxoysmal-exertion induced dyskinesia) and EOAE (early-onset absence epilepsy). The figure shows that the location of the variations in Glut1 does not predict the associated syndrome. (B) The figures show an overview of Glut1 with the pore formed by the transmembrane segments marked in gray.

movement triggers are not necessary, but other triggers are known such as caffeine, alcohol, or stress.

For PED, first mutations in *SLC2A1* were described in 2008, and one mutation with a severe electrolyte pore deficiency resulted in deformation of the erythrocytes and anemia in one family [3]. Up to 80% of patients with PKD are carrying a mutation in (gene encoding proline-rich transmembrane protein 2) *PRRT2*, a gene relevant for the vesicular synaptic cycle [11], and much more rarely in *SCN8A*, a sodium channel subtype expressed in the brain [12]. Up to 40% of patients with PKD also suffer from BFIS (benign familial infantile seizures), a benign syndrome with clusters of seizure in the first year of age with a benign outcome concerning psychomental development and rare seizures in adulthood. Treatment is very uncomplicated since several tested anticonvulsant drugs, such as carbamazepine, levetiracetam, or oxcarbazepine, are very effective. The dyskinetic attacks in patients with PNKD last from minutes to hours and can occur several times a day, very often as hemiclonic attacks. Treatment is difficult since only benzodiazepines may reduce frequency of the attacks. For PNKD, two genes were described: *MR1* (myofibrillogenesis regulator-1) and *KCNMA1*. The function of *MR1* remains only poorly understood [13, 14], but Shen and coworkers hypothesized that the long isoform of *MR1* may be involved in a pathway to detoxify an alpha-ketonaldehyde product using glutathione as a cofactor in neuronal cells. Since glutathione is essential for maintaining proper cellular redox status, reduced glutathione levels in cells with a mutation in *MR1* may render them more susceptible to oxidative stress [15]. *KCNMA1* is coding for a calcium-activated potassium channel. Mutations in this gene lead to increased excitability and to generalized epilepsy in the described family [16].

2.3. Early onset absence epilepsy (EOAE)

The pathophysiological association of paroxysmal dyskinesia and epilepsy was described before, e.g., for PKD and BFIS (see Section 2.2). Up to 23% of patients with PKD suffer from seizures, and mutations were described in a Ca^{2+}-activated potassium channel in patients with paroxysmal dyskinesia and generalized epilepsy [14]. The early onset absence epilepsy (EOAE) belongs to the genetic generalized epilepsies and is characterized by absences with onset before 3 years of age. Compared with patients with the classical childhood absence epilepsy (CAE), patients with EOAE are more difficult to treat and show a slowing of the psychomotor development leading to mental retardation. The EEG findings show the classical 3-Hz spike–wave pattern [4]. In the original description, 12% of patients with EOAE carry a mutation in *SLC2A1*, but in bigger cohorts, the rates are lower [17–19].

2.4. Childhood absence epilepsy (CAE)

Childhood absence epilepsy is one of the classical genetic generalized epilepsy (GGE) syndromes and characterized by (i) high frequent absences with an onset from 4 to 10 years of age, (ii) rare seizures in adulthood, and (iii) rare generalized tonic–clonic seizures in general. In 2012, first mutations in patients with CAE were described in *SLC2A1* [20]. The mutation rate in the general cohort with CAE seems to be low [19]. Mutations in *SLC2A1* were also found in other forms of GGEs, but the frequency is very low with approximately 1% in this cohort [19].

2.5. Myoclonic astatic epilepsy (MAE)

Myoclonic astatic epilepsy (MAE) is characterized by early up to middle childhood onset myoclonic, myoclonic–astatic, and generalized tonic–clonic seizures and absences. The EEG shows generalized spike- or polyspike–wave activity above 2.5 Hz. First mutations in *SLC2A1* were described in 2011 with a frequency of 5% in a cohort with MAE [21]. The frequency was confirmed later on [19].

2.6. Episodic choreoathetosis and spasticity (CSE)

To our knowledge, only two families have been described with predominant spastic paraparesis associated with episodic dyskinesia, and *SLC2A1* mutations were described in 2011 [22]. One of these families was clinically described in 1996 for the first time [23] and showed a permanent spastic paraparesis and additional PED attacks.

2.7. Focal epilepsy

Rarely, focal epilepsy was described in patients with *SLC2A1* mutations [24]. Most of the cases suffer from a Glut1-DS with predominant focal seizures, but patients are also known to have focal epilepsy associated with PED.

3. Phenotype–genotype correlations

The reason for the broad clinical spectrum associated with *SLC2A1* mutations is unclear. Special genetic features of mutations and their functional consequences are discussed as the main reasons, but they cannot explain all phenotypic variations.

3.1. Mutations in SLC2A1

Most mutations found in *SLC2A1* are heterozygous missense mutations with an autosomal dominant effect, but frameshift mutations, deletions, insertions, intronic, promotor, and splice-site mutations were also described. Most cases are sporadic; only rare families with *SLC2A1* mutations were described with an autosomal dominant mode of inheritance. Neither the location of the mutation in the gene nor the severity of, e.g., deletions is associated with the disease course (Fig. 1A) [25, 26].

Table 1
Comparing maximum transport velocity (Vmax) for different glucose transporter type 1 (Glut1) variants with phenotype performed in the *Xenopus laevis* oocytes expression system.

Variant in Glut1	Transport velocity (Vmax: mutation/wildtype in %)	Phenotype	Reference
0p.R232C	70	CAE	[20]
p.R126C	51	EOAE	[4]
p.R223P	54	EOAE	[4]
p.S324L	54	EOAE	[4]
p.Q282_S285del	17	PED	[3]
p.G314S	23	PED	[3]
p.A275T	23	PED	[3]
p.R126H	10	Glut1-DS	[29]

CAE: childhood absence epilepsy, EOAE: early onset absence epilepsy, PED: paroxysmal exertion-induced dyskinesia, Glut1-DS: glucose transporter type 1 deficiency syndrome.

3.2. Functional analysis

3.2.1. Glucose uptake analysis in erythrocytes or Xenopus laevis oocytes

Beside cerebrospinal fluid (CSF)/serum level measurements (see Section 4.1), glucose uptake measurement in erythrocytes of patients with Glut1-DS is an additional test to evaluate the pathophysiological relevance of the detected *SLC2A1* mutation [27]. For this test, fresh blood specimens are necessary and must be analyzed in a specialized laboratory which might be too far away for the patients. The advantage of the expression of wildtype and mutated Glut1 in *Xenopus laevis* oocytes is that the test is patient-unrelated, but this can only be performed in a specialized laboratory since radioactivity is required [3]. Recently, a novel test was published which tests Glut1 expression in red blood cells using flow cytometry analysis [28]. Summarizing the measurements in the *Xenopus laevis* oocyte system, the reduction in the maximum velocity of glucose uptake showed a correlation with the phenotype (see Table 1).

3.2.2. Cerebral magnetic resonance imaging (cMRI)

Cerebral magnetic resonance imaging (cMRI) of patients with Glut1-DS mostly depicts either normal findings or occasionally mild enlargement of inner and outer CSF spaces [25]. In addition, white matter abnormalities were described in patients with Glut1-DS [27] and hypointensities in the basal ganglia of patients with PED [20].

3.2.3. Cerebral fluoro-deoxy-glucose positron emission tomography (FDG-PET)

Fluoro-deoxy-glucose positron emission tomography (FDG-PET) in patients with classic Glut1-DS revealed a global decrease in glucose uptake in the cortex [30]. Comparable results were obtained in patients with PED but with a predominant reduction of glucose uptake in the basal ganglia [31].

4. Diagnostics

4.1. Clinical work-up

In summary for the broad spectrum of clinical phenotypes in Glut1-associated syndromes, the clinical history should include the assessment of the association of seizures (mainly absences and myoclonic astatic seizures) or dyskinesia to fasting states or motor activity and/or the improvement after meals. These features are suspicious for a Glut1 defect syndrome, but can also be absent. Therefore, all patients with early onset absences, other forms of absence epilepsies, and GGEs associated with mental retardation and paroxysmal dyskinesias should undergo a Glut1 evaluation. The clinical work-up includes a detailed medical history, a neurological examination, as well as a neuropsychological testing, an EEG (see Section 4.3), a cMRI to exclude symptomatic reasons, a lumbar puncture (see Section 4.2), and a *SLC2A1* sequencing (see Section 4.4).

4.2. Glucose ratio cerebrospinal fluid/serum

The glucose ratio CSF versus serum should be measured in patients with a suspected Glut1 defect syndrome after a fasting period of at least 4 h [32]. The ratio is dramatically reduced in patients with Glut1-DS (<0.4) compared with normal parameters (0.62–0.68) [25]. Patients with less severe phenotypes such as PED have been reported with CSF-to-blood glucose ratios of 0.39 to 0.59 [3, 33]. In EOAE, CSF/serum ratios were higher compared with patients with Glut1-DS: 0.44 to 0.57 [17, 34]. To our knowledge, all described patients carrying a *SLC2A1* mutation also have a reduced CSF/serum glucose ratio, but not all cases underwent a lumbar puncture. We would, therefore, support the indication of sequencing in parallel with the other diagnostic steps.

4.3. Electroencephalography (EEG)

Variable generalized 2.5- to 4-Hz spike–wave pattern and slowing were described during ictal and interictal periods [35] up to EEG status epilepticus in fasting state and a marked improvement after food intake or glucose infusion [3]. Electroencephalographic recording during intravenous glucose administration may represent a helpful screening test for identifying a subset of patients with Glut1-DS with carbohydrate-responsive phenotype.

4.4. SLC2A1 sequencing

Sequencing of *SLC2A1* coding for Glut1 should be performed in patients with EOAE, MAE, absence epilepsies, and GGEs with mental retardation and in patients with DEE as well as paroxysmal dyskinesias even when the attacks are not associated with fasting states (see Section 4.1). Since the early epilepsies fitting into this definition cannot be clinically differentiated in all cases and phenotypes are not leading to one single gene, *SLC2A1* should be integrated in standard panel/exome analysis in these cases especially in patients with DEE.

5. Therapy

The ketogenic diet (KD) as a therapy for patients with epilepsy was proclaimed for the first time in the early twenties [36]. Ketogenic diet is defined as a high-fat and calorie-reduced diet which produces ketone bodies that bypass the Glut1 defect by diffusing across the blood–brain barrier facilitated by a monocarboxylic acid transporter. Ketone bodies serve as an alternative energy source for brain metabolism. For the other forms of epilepsies, the anticonvulsant effect of ketone is still unclear but may reduce seizure activity significantly in pharmacoresistant epilepsies in up to 50% of cases [37, 38]. For patients with Glut1 defect, the KD is a precision medicine therapy and should be started early in the disease stage. We know from case reports that children respond very well to KD, which help in the prevention of mental retardation and in the restoration from mental decline [39]. In our own hands, patients with Glut1 deficiency benefit also from late onset KD in adulthood (unpublished observation). In classical KD, the serum ketones should be 3–4 mg/dl, but very often at that level, side effects such as diarrhea or fatigue occur and are intolerable. Especially for adult patients with Glut1, the classical KD is not compatible with daily life. In our hands, modified KD with lower ketone serum levels (e.g., 1–2 mg/dl) such as the Atkins diet can be better tolerated and is similarly effective (unpublished observation). For the future, gene therapy might be an option for patients with Glut1 defect [40].

6. Conclusions

Glucose transporter type 1 defect syndromes are rare but should be diagnosed early since a precision therapy via the KD is available and should be started as soon as possible. Characterizing history features

are episodic seizures induced by fasting state or permanent voluntary movement. Laboratory diagnostics include CSF/serum glucose ratio, EEG, and *SLC2A1* sequencing coding for Glut1.

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Conflict of interest

The authors report no conflict of interest related to this work.

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