ORIGINAL ARTICLE

Phenotypic and Genotypic Spectrum of Glucose Transporter-1 Deficiency Syndrome

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ABSTRACT: ***Background:*** Glucose Transporter-1 (GLUT1) Deficiency Syndrome (GLUT1DS) is caused by defective transport of glucose across the blood–brain barrier into brain cells resulting in hypoglycorrhachia due to the heterozygous pathogenic variants in *SLC2A1*. We report on the phenotypic spectrum of patients with pediatric GLUT1DS as well as their diagnostic methods from a single center in Canada. ***Methods:*** We reviewed patient charts for clinical features, biochemical and molecular genetic investigations, neuroimaging, treatment modalities, and outcomes of patients with GLUT1DS at our institution. ***Results:*** There were 13 patients. The most common initial symptom was seizures, with the most common seizure type being absence seizures (85%). Seventy-seven percent of the patients had movement disorders, and dystonia and ataxia were the most common movement disorders. Fifty-four percent of the patients did not have a history of developmental delay during their initial presentation, whereas all patients had developmental delay, intellectual disability, or cognitive dysfunction during their follow-up. All patients had a pathogenic or likely pathogenic variant in *SLC2A1* and missense variants were the most common variant type. ***Conclusion:*** We present 13 patients with GLUT1DS in the pediatric patient population. Atypical clinical features such as hemiplegia and hemiplegic migraine were present in an infant; there was a high prevalence of absence seizures and movement disorders in our patient population. We report an increased number of patients with GLUT1DS since the introduction of next-generation sequencing in the clinical settings. We believe that GLUT1DS should be included in the differential diagnosis of seizures, movement disorders, and hemiplegic migraine.

RÉSUMÉ : Spectre phénotypique et génotypique du syndrome du déficit en transporteur du glucose de type 1. ***Contexte*** **:** Le syndrome du déficit en transporteur du glucose de type 1 (SD-GLUT 1) est causé par un transport défectueux du glucose à travers la barrière hémato-encéphalique (BHE) pour atteindre les cellules cérébrales, ce qui entraîne une hypoglycorachie attribuable à des variants pathogènes hétérozygotes dans le gène *SLC2A1*. Au sein d'un établissement hospitalier du Canada, nous avons voulu nous pencher sur le spectre phénotypique du SD-GLUT 1 qui affecte les enfants et sur les méthodes pour le diagnostiquer. ***Méthodes*** **:** Pour ce faire, nous avons passé en revue les dossiers de jeunes patients en portant attention à leurs caractéristiques cliniques, aux résultats consécutifs à des analyses biochimique, à des tests de génétique moléculaire et à des examens d'IRM mais aussi aux modalités des traitements offerts et à l'évolution de leur état de santé. ***Résultats*** **:** Au total, ce sont 13 jeunes patients qui ont été retenus. Le symptôme initial le plus courant était des crises convulsives, le type le plus fréquent étant les crises dites « d'absence épileptique » (85 %). De plus, 77 % des patients étaient atteints de troubles du mouvement, la dystonie et l'ataxie étant cette fois les deux troubles les plus courants. Précisons que 54 % des patients n'avaient pas d'antécédents de retard du développement au moment de se présenter pour la première fois dans notre établissement tandis que tous donnaient à voir des signes d'un tel retard, mais aussi de déficience intellectuelle ou de dysfonction cognitive, lors d'un suivi médical. Enfin, tous les patients avaient un variant pathogène ou fort probablement pathogène dans le gène *SLC2A1*. À ce sujet, les variants faux-sens étaient les types de variants les plus répandus. ***Conclusion*** **:** Nous avons présenté 13 jeunes patients atteints du SD-GLUT 1. Des aspects cliniques atypiques comme l'hémiplégie et la migraine hémiplégique ont été notés initialement chez un enfant. Qui plus est, une forte prévalence de crises d'absence épileptique et de troubles du mouvement a été observée au sein de notre groupe de patients. Nous sommes par ailleurs en mesure de signaler une augmentation du nombre de patients atteints du SD-GLUT 1 depuis l'introduction, dans les milieux cliniques, des techniques de séquençage de prochaine génération. À cet égard, nous estimons que le SD-GLUT 1 devrait être inclus dans le diagnostic différentiel des crises convulsives, des troubles du mouvement et des migraines hémiplégiques.

Keywords: Glucose Transporter-1 (GLUT1) Deficiency Syndrome, Epilepsy, Movement disorder, The ketogenic diet

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Introduction

Glucose Transporter-1 (GLUT1) Deficiency Syndrome (GLUT1DS) is caused by defective transport of glucose across the blood–brain barrier into brain cells, resulting in hypoglycorrhachia.[1] The GLUT1 protein is encoded by *SLC2A1* (Gene/Locus MIM#138140). Heterozygous pathogenic or likely pathogenic variants in *SLC2A1* result in GLUT1DS. In the majority of patients, GLUT1DS is the result of a *de novo* variant in *SLC2A1*.[2] The phenotypes range from infantile-onset epileptic encephalopathy to adult-onset paroxysmal exercise-induced dyskinesia. The infantile-onset epileptic encephalopathy phenotype is the most commonly reported phenotype (~90%) and is characterized by global developmental delay (GDD), infantile-onset (1–6 months) drug-resistant epileptic encephalopathy, progressive microcephaly, and movement disorder (e.g. ataxia, spasticity, dystonia, chorea, tremor, myoclonus, and paroxysmal dyskinesia) (MIM#606777).[3,4] Mild or atypical presentations (~10%) include paroxysmal movement disorders, cognitive dysfunction, alternating hemiplegia, and epilepsy and those symptoms may be triggered by exercise, fasting, or stress (MIM#612126; MIM#601042).

Low cerebrospinal fluid (CSF) to blood (collected within 30 minutes prior to lumbar puncture) glucose ratio or low CSF glucose levels suggest GLUT1DS. In a systematic review, CSF glucose levels were reported between 0.9 and 2.8 mmol/L and CSF to blood glucose ratio was between 0.19 and 0.59 in patients with GLUT1DS.[5] The ketogenic diet is the gold standard treatment of GLUT1DS. Early diagnosis and initiation of the ketogenic diet will likely improve seizures, neurodevelopmental disorder, and movement disorder.[6]

The objective of the present study is to report the phenotypic spectrum of pediatric presentations in GLUT1DS as well as their diagnostic methods from a single center in Canada.

Methods

The Research Ethics Board at the Hospital for Sick Children approved this retrospective cohort study (Approval#1000064305). We included all patients with a molecular genetically confirmed GLUT1DS followed in a single neurometabolic clinic. We reviewed patient charts for clinical features, biochemical investigations, molecular genetic investigations, neuroimaging, treatment modalities, and treatment outcomes.

Results

There were 13 patients. Their phenotypic description and investigations are presented in Table 1. Patients 1, 2, 4, 8, 10 were previously published.[1,7–9] The mean age of symptom onset was 1.6 years (range 1 month–4 years). The mean age of diagnosis was 8 years (range 2–16 years). The mean time between symptom onset and the diagnostic confirmation was 6.4 years (range 0 months–11.5 years). The most common initial symptom was seizure ($n = 9$). Seven patients had no history of GDD or cognitive dysfunction at the time of symptom onset or initial presentation.

All patients demonstrated various degrees of developmental delay, intellectual disability, or cognitive dysfunction during their follow-up. The most common seizure type was absence seizures ($n = 11$) (presented between the ages of 6 months and 8 years). Ten patients (77%) presented with movement disorders in their first decade of life. Dystonia and ataxia were the most common movement disorders (each $n = 5$). Nearly half (46%) of the patients had more than one type of movement disorder. Microcephaly (head circumference <2nd centile) was present in 3 patients (23%). None of the patients had eye–head movement abnormalities during their follow-up in the neurology clinics or in the neurometabolic clinic.

Only two patients had CSF glucose measurement, and both patients had low CSF glucose levels (2.1 mmol/L equals to 37.8 mg/dl), which were below the lower limit of normal CSF glucose of 3.3 mmol/L equals to 60 mg/dl in the post-absorptive state for glucose. None of the patients had blood glucose measurements prior or after the lumbar punctures.

All patients had a pathogenic or likely pathogenic variant in *SLC2A1* identified by direct Sanger sequencing and deletion duplication analysis of *SLC2A1* ($n = 3$), next-generation sequencing panel for epilepsy ($n = 4$), next-generation sequencing panel for hemiplegic migraine ($n = 1$), positive family history with familial variant testing ($n = 1$), and whole-exome sequencing ($n = 4$). Missense variants were the most common variant type (62%). In four patients with asymptomatic parents, the parental segregation was not performed due to the unavailability of the parents.

Twelve patients were started on the ketogenic diet. Detailed treatments and outcomes are summarized in Table 1 and Supplementary Table 1. One patient was not a suitable candidate for the ketogenic diet therapy due to severe vomiting and gastroesophageal reflux disease despite gastro-jejunal tube feeding and the high risk of aspiration. Patient 11 was initially treated with phenobarbital and her seizures were progressed to infantile spasms, which was switched to vigabatrin. Phenobarbital did not improve seizures in Patient 12, which was switched to levetiracetam and resulted in better seizure control.

Discussion

We present 13 patients with GLUT1DS followed in a single neurometabolic clinic at our institution. In our study cohort, absence seizures were the most common seizure type (85%). Movement disorders were present in 77% of the patients in the first decade of life in our study cohort. Interestingly, nine patients had their symptom onset at or before the age of 2 years, but the age of diagnosis was at or less than 3 years of age in only three patients. It seems that despite the application of next-generation sequencing panel for epilepsy or whole-exome sequencing, there are still delays in the diagnosis of GLUT1DS in our study cohort. We report variable phenotypes in presumed monozygotic twins including alternating hemiplegia in one and GDD in another one. Generalized tonic–clonic seizures are the most common seizure type in GLUT1DS[10,11], whereas in our study, absence seizures were the most common seizure type.

International consensus guidelines recommend characteristic clinical features (movement disorders; paroxysmal events; early-onset absence epilepsy, mycolonic-atonic epilepsy), AND hypoglycorrhachia AND a pathogenic variant in *SLC2A1* for the definite diagnosis of GLUT1DS.[6] If the characteristic clinical features were present, pathogenic variants in *SLC2A1* is sufficient for the diagnosis of GLUT1DS. All of our study patients had

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Table 1: Clinical features, EEG, brain MRI, genotypes, and treatments of patients with GLUT1DS

Patient ID/age of diagnosis/ sex/current age[reference]	Age at onset/initial presentation	Seizure types (age)/other clinical features (age)/HC percentile	EEG/MRI	CSF glucose/Molecular genetic results (type of genetic testing)	Current treatment (age started)/ Outcome/current AED
1/10yrs/17yrs/M[8]	2yrs/AbsS	AbsS (2yrs), GTCS (8yrs), FS (8yrs)/ ID, tremors, dyskinesias, OCD, depression, anxiety/50th	3–3.5 Hz Spk/N	2.1 mmol/L/Htz *de novo* c.823G>A (p.Ala275Thr) in *SLC2A1* (direct sequencing)	KD (40% MCT) (10yrs)/improved cognition, dyskinesia, decreased seizures/none
2/14yrs/23yrs/F[1]	4yrs/GDD, hypotonia, ataxia, morning headache	AbsS (4yrs), GTCS, AS/ID, paroxysmal hemiplegia, ataxia, hypotonia/10th	2.5–3 Hz Spk/N	NP/Htz *de novo c.*988C>T (p.Arg330*) in *SLC2A1* (direct sequencing)	LGI diet, glycosade, (18yrs) (noncompliant)/CLB
3/3yrs/6yrs/F	3yrs/seizures (head drops), language delay	AbsS, AS/GDD, dystonia, ataxia/26th	3–4 Hz Spk/N	NP/Htz presumed *de novo* c.940G>A (p.Gly314Ser) in *SLC2A1* (epilepsy panel)	KD (35% MCT) (4yrs) (noncompliant)/LVT, CLB
4/8yrs/11yrs/M[6]	9m/seizures	AbsS, GTCS, FS/speech delay, AD, tremor/46th	NA/N	NP/Htz *de novo* c.624_625delinsGT (p.Glu209Valfs21*) in *SLC2A1* (WES)	KD (15% MCT) (8yrs) noncompliant)/ none
5/16yrs/20yrs/M	5yrs/AbsS	AbsS (5yrs)/ID, ADD, ADHD/<2nd	3 Hz Spk/ND	NP/Htz presumed *de novo* c.854C>T (p.Ser285Phe) in *SLC2A1* (direct sequencing)	KD (16yrs) (noncompliant)/LVT
6*/8yrs/10yrs/M	1yrs/GDD	AbsS (8yrs)/GDD, dyskinesia, dystonia, HA, ASD/96th	3.5–4 Hz Spk/bilateral (frontoparietal) nonspecific T2/FLAIR hyperintensity in subcortical cerebral WM	NP/Htz *de novo* c.971C>T (p.Ser324Leu) in *SLC2A1* (targeted variant testing)	KD (46% MCT) (8yrs)/improved arm dystonia/none
7*/8yrs/10yrs/M	1.5yrs/alternating hemiplegia	AbsS (7yrs), GTCS/GDD, dyskinesia, dystonia, paroxysmal hemiplegia and migraine, ASD/86th	3 Hz Spk/(frontoparietal increased T2/ FLAIR signal in WM	NP/Htz *de novo* c.971C>T (p.Ser324Leu) in *SLC2A1* (hemiplegic migraine panel)	KD (49% MCT) (8yrs)/decreased migraines, HA, improved memory, decreased dystonia/none
8/8yrs/10yrs/M[7]	1.5yrs/regression	FS, AbsS (5yrs)/ID, bradykinesia, dystonia, ADHD/91st	1.5–2 Hz Spk/N	NP/Htz *de novo* c.457C>T (p.Arg153Cys) in *SLC2A1* (epilepsy panel)	LGI diet, glycosade (10yrs) (noncompliant with KD)/improved behavior/none
9/8yrs/11yrs/F	8m/GTCS	GTCS (8m), AbsS (2yrs)/ID, migraines (7yrs), ataxia/91st	2.5–3 Hz Spk/ND	NP/Htz *de novo* c.458G>A (p.Arg153His) in *SLC2A1* (direct sequencing)	KD (40% MCT) (8yrs)/decreased seizures by 90%/none
10/5yrs/8yrs/M	1m/GTCS	GTCS (1m), AbsS, GS/GDD, dystonia, ataxia, tremor, paroxysmal dyskinesia/<2nd	3 Hz Spk/N	NP/Htz *de novo* c.808C>T (p.Gln270*) in *SLC2A1* (epilepsy panel)	KD (33% MCT) (5yrs) CLB/decreased seizures, improved ataxia, increased vocabulary
11/2yrs/3yrs/F	10m/GDD, IS, hypotonia	IS (10m), MS/GDD, hypotonia, FTT, SNHL/<2%	1–5 Hz (multiple rhythms)/CA, heterotopia (*SON* disease)	NP/Htz presumed *de novo* c.680-11G>A IVS5-11G>A in *SLC2A1* (WES)	LGI diet, glycosade (3yrs)/CLB
12/3yrs/4yrs/M	5m/GTCS	GTCS/GDD, hypotonia/NA	Slowing left-frontal/N	NP/Htz *de novo* c.656delA p.Asn219fs*10 in *SLC2A1* (WES)	KD (MCT) (4yrs)/LVT (95% seizure reduction)
13/12yrs/13yrs/M	6m/GDD, seizures	AbsS, AS, GTS/ID, ADD, ASD, aggression episodic ataxia/13th	1.5–2 Hz Spk/Increased signal in T2 frontal WM	2.1 mmol/L/Htz *de novo* c.940G>A p.Gly314Ser in *SLC2A1* (WES)	KD (MCT) (13yrs)/CLB and VPA (90% reduction in seizures)

Abbreviations: AbsS = absence seizures;AD(H)D = attention deficit (hyperactivity) disorder; AED = antiepileptic drugs;AS = atonic seizures;ASD = autism spectrum disorder; CA = cerebral atrophy; CLB = clobazam; CMPZ = carbamazepine;CSF = cerebrospinal fluid;ETS = ethosuximide; F = female; FS = focal seizures; FTT = failure to thrive; GTCS = generalized tonic-clonic seizures; GDD = global developmental delay; GS = gelastic seizures; GTS = generalized tonic seizures; HC = head circumference; Htz = heterozygous; ID = intellectual disability; IS = infantile spasms; KD = ketogenic diet; LAC = lacosamide; LGI = low glycemic index; LMT = lamotrigine; LVT = levetiracetam; M = male; m = months; MCDK = multicystic dysplastic kidney; MCT = medium chain triglyceride; MRS: magnetic resonance spectroscopy; MS = myoclonic seizures; N = normal; NA = not available; ND = not done; NP = not performed; OCD = obsessive compulsive disorder; P5P = pyridoxal-5'-phosphate; PHB = phenobarbital; PrevReport = previously reported; PYR = pyridoxine; SNHL = sensorineural hearing loss; Spk = spike(s); TPM = topiramate; VGB = vigabatrin; VPA = valproic acid; VUS = variant of unknown significance; WES = whole exome sequencing; WM = white matter; yrs = years.
*Twin brothers.

Reference ranges: CSF glucose reference range as per our chemistry laboratory = 2.1–3.6 mmol/L equals to 37.8–64.8 mg/dl; CSF glucose reference range in most diagnostic laboratories = ≥3.3 mmol/L equals to 60 mg/dl; Blood glucose reference range 2.8–6.1 mmol/L.

characteristic clinical features and pathogenic variants in *SLC2A1* confirming the diagnosis of GLUT1DS. Despite hypoglycorrhachia is the metabolic hallmark of the GLUT1DS, only two of our patients had low CSF glucose levels to fulfill all three required features. In the remaining 11 patients, the diagnosis was confirmed by characteristic clinical features and pathogenic variants in *SLC2A1*.

The prevalence of GLUT1DS ranged from 0.9 to 2.4% in our previous studies.[8,9,12] Prior to 2015, there were two patients diagnosed with GLUT1DS, known to us at our institution. Since the availability of targeted next-generation sequencing panels and whole-exome sequencing in clinical settings, we have confirmed the diagnosis of GLUT1DS in more than 10 patients at our institution. Next-generation sequencing technologies have also expanded the phenotypic spectrum of the GLUT1DS in our clinical practice. In about 10–15% of the patients, targeted next-generation sequencing and whole-exome sequencing will likely not identify variants in *SLC2A1*, and deletion/duplication analysis should be performed.[6] One of the characteristic clinical features is good response to the ketogenic diet with decreased seizure frequency. Ten patients had the ketogenic diet with improved seizure control.

Ataxia, dystonia, chorea, and paroxysmal dyskinesia may occur individually or in combination. Movement disorders can be permanent or intermittent, often precipitated by infections or prolonged fasting.[4,13] The spectrum of movement disorders has been reported in 57 patients with GLUT1DS previously.[4] There is wide variability in the age of onset ranging from 3 months to 42 years. Dystonia was the most common movement disorder in 86% of the patients. Gait disturbances, in the form of ataxia or in combination with spasticity, were observed in 70% of the patients. Chorea, tremor, and myoclonus were also reported. Only 28% of the patients had paroxysmal movement disorders; unfortunately, the age of onset for the paroxysmal events was not reported in that study.[4] In our study, we only included pediatric patients (up to 18 years of age) at our center. The frequency of movement disorders was 77%, and ataxia (50% of patients) and dystonia (50% of patients) were the most common movement disorders in our study cohort. Alternating hemiplegia has been reported as one of the clinical features of nonclassical GLUT1DS with a milder phenotype.[13–15] Weller and colleagues sequenced *SLC2A1* in 42 patients with hemiplegic migraine.[15] They identified one patient (2.4%) with an overlapping phenotype of atypical hemiplegic migraine and atypical alternating hemiplegia of childhood due to GLUT1DS.[15] We identified alternating paroxysmal hemiplegia in two patients in our study population; in one of the patients, this was the presenting symptom at the age of 1.5 years. It seems that our study cohort has a higher prevalence and earlier onset of movement disorders.

We present the phenotypic and genotypic spectrum of patients with childhood-onset GLUT1DS from a single neurometabolic clinic. We report absence seizures as the most common seizure type and early onset movement disorders in this pediatric patient population. We also report on the increased diagnostic rate of GLUT1DS since the application of next-generation sequencing in the clinical setting. We propose that GLUT1DS should be considered as an underlying cause for a broad variety of neurological phenotypes and should be included in targeted next-generation sequencing panels for epilepsy, movement disorders, developmental delay, intellectual disability, and atypical migraines. We think that more patients with rarer phenotypic presentations will be diagnosed at an earlier age in the near future, which will likely improve neurodevelopmental outcomes due to early initiation of the ketogenic diet.

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Disclosures

The authors disclose no conflicts of interest.

Statement of Authorship

GAMN, DKB: Reviewed charts, generated the database, drafted the manuscript, read, and approved the final manuscript.

DC: Reviewed charts, generated the database, read, and approved the final manuscript.

JK: Diagnosed some of the patients and applied the ketogenic diet, read, and approved the final manuscript.

SM-A: Planned, designed the study, supervised GAMN, DKB, and DC and revised and finalized the manuscript.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.3.

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