The Effects of Ketogenic Diet on Seizures, Cognitive Functions, and Other Neurological Disorders in Classical Phenotype of Glucose Transporter 1 Deficiency Syndrome

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Abstract

Objectives The purpose of this study was to characterize patients who were diagnosed with glucose transporter protein 1 deficiency syndrome (Glut1D), and also to assess the efficacy of ketogenic diet (KD) therapy on seizure control, cognitive functions, and other neurological disorders.

Patients and Methods We studied six unrelated patients with the classical phenotype of Glut1D, focusing on clinical and laboratory features, the KD therapy and outcome over the 25-month follow-up period.

Results Five patients became seizure-free with the onset of ketosis, and anticonvulsants were discontinued. Other neurological features such as ataxia, spasticity, and dystonia showed a less striking improvement than seizure control. There was no significant change in the intelligence quotient (IQ) level or microcephaly. In all patients, alertness, concentration, motivation, and activity resulted in a moderate improvement of variable degree. The early-onset adverse effects of KD were observed in five patients. The KD regimen failed in one patient, therefore, his diet was changed with an alternative to KD.

Conclusions Treatment with KD resulted in a marked improvement in seizures and cognitive functions but its effect appeared to be less striking on the other neurological disorders of the patients. When the classic KD is not tolerated, an alternative to KD may be helpful.

Keywords
- glucose transporter protein 1 deficiency syndrome
- ketogenic diet
- cognitive functions
- seizures
- children

Introduction

Glucose is the essential substrate for cerebral energy metabolism. Glucose transporter 1 (Glut1), which is expressed in the endothelial cells of erythrocytes and the blood–brain barrier (BBB), is responsible for glucose transport into the brain. Glut1 deficiency syndrome (Glut1D) is predominantly an autosomal dominant disorder, but it can be transmitted as an autosomal recessive.[1] It results from impaired glucose transport into the brain.[2] Glut1D was first described by De

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Vivo et al[3] in 1991 in two children with infantile seizures, developmental delay, acquired microcephaly, and hypoglycorrhachia. To date, the complex clinical phenotype includes an epileptic encephalopathy with complex movement disorders in variable combinations, paroxysmal events, specific seizure types, and adult manifestations.[2,4–8] The "classic" clinical phenotype is a form of early-onset epileptic encephalopathy characterized by seizures, developmental delay, spasticity, acquired microcephaly, and ataxia.[4–8] Nevertheless, several variants of Glut1D have been recognized recently. Patients with atypical presentations such as mental retardation and intermittent ataxia without seizures, or movement disorders characterized by choreoathetosis and dystonia, have also been described.[4,6–13] The clinical signs and symptoms originate from a defect in glucose transport across the BBB as shown by the finding of low cerebrospinal fluid (CSF) glucose in the absence of hypoglycemia. A defect in glucose transport across the BBB is caused by heterozygous *SLC2A1* gene mutations[14]; the gene encoding the Glut1 protein is located on the short arm of chromosome 1 (1p34.2).[15] However, pathological mutations of the *SLC2A1* gene cannot be detected in approximately 12.5% of patients with Glut1D.[16]

The clinical symptoms of Glut1D are usually early-onset seizures which are unresponsive to anticonvulsants. Glut1D has gained importance as a treatable metabolic disease which responds well to the ketogenic diet (KD).[11,12,17] The neurological outcomes can be improved by the timely initiation of the KD; therefore, early diagnosis is crucial.[6,12,17]

In this study, we have evaluated the clinical heterogeneity, laboratory and genetic features, and efficacy of KD therapy on seizure control and cognitive functions and other neurological disorders in pediatric patients who were diagnosed with Glut1D.

Patients and Methods

Patients were evaluated at Erciyes University Medical Faculty, Department of Pediatric Neurology and Pediatric Endocrinology and Metabolism. The study was approved by the Local Ethics Committee of Erciyes University. All the patients and their relatives gave informed consent for further investigations in the clinical study. Laboratory investigations included blood, urine, and CSF biochemistry. Laboratory investigations of blood and urine included serum lactate, pyruvate, ammonia, plasma amino acids concentrations, TANDEM mass, urine amino acid, and organic acid screening, respectively.

Cranial magnetic resonance imaging, abdominal ultrasounds, visual and auditory-evoked potentials, and video electroencephalographic (EEG) monitoring were performed in all patients. Lumbar punctures were performed after fasting for 4 to 6 hours, to allow for the different glucose changes in the blood and CSF in the absence of acute seizures, hypoglycemia, and infection of the central nervous system. Blood glucose determination was obtained immediately before the lumbar puncture to avoid stress-related hyperglycemia. The CSF was analyzed for total cells, protein, glucose, and lactate concentrations. The diagnosis was confirmed by the finding of molecular mutational analysis in only one of the six patients because of technical insufficiencies. The time from the first seizure attack and/or movement disorder until age at diagnosis was defined as delay in diagnosis. The cognitive ability of patients was assessed by parents' reports and neurological presentations, and the Wechsler Intelligence Scale for Children (4th edition) was also used in children aged 6 years and over.[18] If children were younger than 6 years, the Stanford–Binet Intelligence Scale (4th edition) was used.[19] The intelligence quotient (IQ) levels were categorized according to DSM-IV criteria.[20] The provisional diagnosis of "unspecified intellectual developmental disorders" was used in children younger than 4 years of age because of the lack of reliable cognitive assessment.[21] The cognitive functions of patients were evaluated by intelligence scale tests within the last 2 weeks before KD initiation, and they were reassessed after a minimum of 6 months on the diet in four patients. Two patients parents did not agree to the evaluation of neuropsychological tests during follow-up. All the patients were treated with the classic 4:1 KD with the only modification being that the initial fast was replaced by a gradual increase in calories. The fat ratio of KD was provided by olive oil. The KD is relatively deficient in terms of L-carnitine content[7]; therefore, L-carnitine (50 mg/kg/d), multivitamins, calcium, minerals, and trace element supplementations were recommended for all the patients. When the patients refused the classic 4:1 KD, it was changed to the modified Atkins diet. The establishment and follow-up of ketosis was checked twice daily with urine dip sticks. We avoided the use of caffeine, phenobarbital, diazepam, chloral hydrate, and tricyclic antidepressants because of their negative effects on Glut1 functions.[6,7]

Molecular Analysis

White blood cells were used to extract genomic DNA from patient. We amplified and sequenced all the coding exons and intron–exon boundaries of the *SLC2A1* gene of the patient by polymerase chain reaction (PCR), as described previously.[14] The PCR conditions were optimized to eliminate produce spurious amplification products as assessed by 2.0% agarose gel electrophoresis. The PCR products were purified and forwarded to automated DNA sequencing. Genetic analysis showed a heterozygous R153H (p.Arg153His) missense mutation in exon 4 of the *SLC2A1* gene.

Results

The study included six patients (four boys and two girls). The mean age at seizure onset was 5.7 ± 4.4 months (range, 0.5–12 months). The mean age at diagnosis was 7.7 ± 4.1 years (range, 2.5–13 years). The mean time of delay in diagnosis was 86.3 ± 48.5 months (range, 29–148 months). Average follow-up duration was 12.7 ± 7.0 months (range, 6–25 months). The demographic, clinical, and laboratory findings are summarized in ►**Table 1**. All the patients had seizures starting in the first year of life. The clinical presentation of seizure type was as follows: myoclonic in three patients, partial seizure in two patients, and absence seizure in one patient, respectively. The seizures did not respond to anticonvulsant medication. Neurological examination showed a variable combination of

Table 1 Demographic, clinical, and laboratory findings of the patients with GLUT-1 DS

Patients	1	2	3	4	5	6
Age at diagnosis	11.5 y	13 y	8 y	7 y	2.5 y	4 y
Gender	M	F	M	M	M	F
Follow-up duration	6 mo	13 mo	14 mo	12 mo	6 mo	25 mo
Age at seizure onset	5.5 mo	8 mo	7 mo	0.5 mo	1 mo	12 mo
Delay in diagnosis	132.5 mo	148 mo	89 mo	83.5 mo	29 mo	36 mo
Initial seizure type	Partial seizure	Myoclonic seizure	Myoclonic seizure	Myoclonic seizure	Partial seizure	Absence seizure
Ataxia	+	+	+	+	+	+
Spasticity	+	+	++	++	+	+
Microcephaly	–	+	+	+	–	–
EEG findings	Focal epileptiform activity	Focal epileptiform activity	Generalized epileptiform activity	Generalized epileptiform activity	Focal epileptiform activity	Slow background activity
MRI	Normal	Normal	Cortical atrophy, corpus callosum dysgenesis	Normal	Normal	Normal
Mutation analysis	NE	p.Arg153His	NE	NE	NE	NE
Movement disorder	Dystonia	–	–	–	Dystonia	PED

Abbreviations: –, absent; +, present; DS, deficiency syndrome; EEG, electroencephalography; GLUT-1, glucose transporter protein 1 deficiency syndrome; MRI, magnetic resonance imaging; NE, not examined; PED, paroxysmal exercise-induced dyskinesia.

ataxia, spasticity, dystonia, paroxysmal exercise-induced dyskinesia (PED), microcephaly, and mental retardation (►**Table 1**). All patients had global developmental delay, particularly, in speech and gait. The degree of mental impairment remained highly variable, with prominent deficits in speech development and a particular strength in acquiring social skills. The intelligence level of patients was affected from a mild-to-moderate degree.[20] The mean IQ levels were found as 58.4 ± 7.4 (range, 48–66). In kindergarten and school, all patients required special support. Routine laboratory investigations and a full metabolic work-up were unremarkable. The blood glucose concentration was normal in all patients, so that hypoglycemia was ruled out as the cause of hypoglycorrhachia. The mean blood glucose concentration (fasting) was 5.23 ± 0.63 mmol/L (range, 4.75–6.49 mmol/L [normal range, 3.33–5.88 mmol/L]). Lumbar puncture demonstrated a low CSF/blood glucose ratio in all patients. The mean CSF glucose was 1.59 ± 0.18 mmol/L (range, 1.28–1.86 mmol/L [normal > 2.2 mmol/L]). The mean CSF/blood glucose ratio was 0.30 ± 0.06 (range, 0.21–0.38 [normal > 60]). The CSF lactate concentration was low in all patients. The mean CSF lactate concentration was 0.89 ± 0.57 mmol/L (range, 0.80–0.96 mmol/L [normal range, 1.0–2.1 mmol/L]). Glucose levels in CSF and serum, CSF/blood glucose ratios, and CSF lactate concentration are summarized in ►**Table 2**. The results of video-EEG studies showed focal epileptiform activity in three patients, generalized epileptiform activity in two patients, and slow background activity in one patient, respectively. No abnormalities were detected in the electrophysiological studies including motor and sensory nerve conduction velocities, visual, and acoustic-evoked potentials. Only one patient demonstrated abnormal neuroimaging as cortical atrophy and corpus callosum dysgenesis. Abdominal ultrasounds with a special focus on the liver, pancreas, and kidney were normal. All patients showed urinary ketosis when checked twice daily with urine dip sticks. The values of urinary ketosis ranged from +2 to +3. With the onset of ketosis, five patients became seizure-free and later anticonvulsants were discontinued over a period of 1 week. The KD did not achieve complete seizure control despite a decrease in seizure frequency in patient 4. Therefore, the antiepileptic therapy was continued for his seizure control; however, the number of antiepileptics was reduced from four to two drugs. After the complete seizure control was achieved by treatment with the KD in patient 1, the symptoms recurred because of refusal to continue with the KD. In this patient, the classic 4:1 KD was changed to the modified Atkins diet. The modified Atkins diet was well tolerated with +2/ + 3 values of urinary ketosis. While on the KD, epileptiform discharges were completely normalized in all patients except for patient 4. Slowing of background activity was still present in this patient. Other neurological features such as ataxia, spasticity, and dystonia showed a less striking improvement than seizure control. However, PED was completely resolved (►**Table 3**). There was no significant change in the IQ level and microcephaly after treatment with the KD. Nevertheless, the positive effects of KD therapy were detected to a variable degree on the cognitive functions of the patients, so that alertness, concentration, motivation, and activity resulted in a marked improvement in all patients (►**Table 3**). No patient was lost during follow-up. The early-onset adverse effects of the KD; such as nausea, vomiting, fatigue, and constipation were observed in five patients. During follow-up; the late-onset adverse effects of the KD, such as osteopenia, kidney stones, pancreatitis, prolonged QT intervals or cardiomyopathy, iron-deficiency anemia, impaired platelet function, and optic neuropathy, were monitored but not detected in any patients. The effectiveness and adverse effects of the KD are summarized in ►**Table 3**.

Discussion

The glucose and lactate concentrations of CSF are adequate biomarkers for the diagnostic work up of Glut1D.[22] Hypoglycorrhachia accompanied by normal values for blood glucose concentration, low CSF/blood glucose ratios, and low level CSF lactate concentration were observed in all patients in this study. We conducted molecular mutational analysis in only one of the six patients because of technical insufficiencies. This patient (patient 2) showed a heterozygous R153H (p.Arg153His) missense mutation in exon 4 of the *SLC2A1* gene, which was recently identified by Leen et al.[9] Arg153 is one of the known mutation hotspots in Glut1D.[8,9] Leen et al[9] reported the missense mutation p. Arg153His in a 7-year-old boy with the nonclassical phenotype of mild mental retardation with continuous ataxia and

Table 2 Glucose levels in CSF and serum, CSF/blood glucose ratios, and CSF lactate concentration at diagnosis

Patients	CSF glucose (mmol/L)	Blood glucose (mmol/L)	CSF/blood glucose ratio	CSF lactate concentration (mmol/L)
1	1.72	4.75	0.36	0.94
2	1.86	4.88	0.38	0.96
3	1.42	5.06	0.28	0.90
4	1.58	5.22	0.30	0.86
5	1.38	6.49	0.21	0.8
6	1.61	5.03	0.32	0.90

Abbreviation: CSF; cerebrospinal fluid; DS, deficiency syndrome; GLUT-1, glucose transporter protein 1 deficiency syndrome.

Table 3 Effectiveness and adverse effects of KD in the patients with GLUT-1 DS

Patients	1	2	3	4	5	6
Age at onset of KD	11.5 y	13 y	8 y	7 y	2.5 y	4 y
Duration of KD treatment	6 mo	13 mo	14 mo	12 mo	6 mo	24 mo
Compliance and tolerance of KD	↓ ↓	↑	↑↑	↑	↑↑	↑↑
Qualitative test for urine ketone bodies	+3	+2/+3	+3	+3	+3	+2
Seizure frequency before KD	12–15/wk	6–8/wk	4–6/wk	2–3/wk	6–8/wk	26/wk
Seizure frequency after KD	–	–	–	6–8/wk	–	–
Alertness	↑	↑↑	↑	↑	↑	↑
Concentration	↑	↑↑	↑	↑	↑	↑↑
Motivation	↑↑	↑	↑	↑	↑	↑↑
Activity	↑	↑	↑	↑	↑	↑↑
Dysarthria	→	→	→	→	↓	↓
Ataxia	↓	→	→	→	↓	↓ ↓
Spasticity	↓	↓ ↓	→	→	→	↓ ↓
Microcephaly	0	→	→	→	0	0
MR (IQ level) before KD/application time	64 (WISC-IV)	66 (WISC-IV)	60 (WISC-IV)	48 (WISC-IV)	Unspecified IDD[a]	54 (SBISC-IV)
MR (IQ level) after KD	62 (WISC-IV)	68 (WISC-IV)	64 (WISC-IV)	NE	NE	58 (SBISC-IV)
Epileptic discharges on video EEG after KD	–	–	–	↓	–	–
Movement disorder after KD	→	0	0	0	↓	–
Early-onset complications of KD	Nausea, constipation	Nausea, fatigue	–	Nausea, vomiting, fatigue	Nausea	Constipation
Late-onset complications of KD	–	–	–	–	–	–

Abbreviations: –, disappeared; 0, absent; DS, deficiency syndrome; EEG, electroencephalography; GLUT-1, glucose transporter protein 1 deficiency syndrome; IDD, intellectual developmental disorders; IQ, intelligence quotient; KD, ketogenic diet; MR, mental retardation; NE, not examined; SBISC-IV, Stanford-Binet Intelligence Scale –IV;[17] WISC-IV, Wechsler Intelligence Scale for Children–IV;[16]↑, increased; ↑↑, further increased; →, unchangeable; ↓, decreased; ↓ ↓, further decreased.

[a]According to the World Health Organization (WHO)'s International Classification of Diseases Working Group on the Classification of Intellectual Disabilities.[19]

paroxysmal dystonia and choreoathetosis. We describe the same mutation in a 13-year-old female with the classical phenotype of mild mental retardation with myoclonic seizure, ataxia, spasticity, and microcephaly. These different phenotypic findings suggest that the presence of multifactorial pathogenesis has an effect on the clinical course and presentation of Glut1D. More researches are necessary to contribute to the pathogenesis and to determine which factors are effective on the clinical phenotype in Glut1D. The classical phenotype of Glut1D presents in infancy with hypotonia and early-onset seizures which are unresponsive to anticonvulsants and complex movement disorder with individual elements of ataxia, dystonia, and spasticity.[6–9] No specific EEG pattern in Glut1D has yet been identified, and a normal interictal EEG can be seen in the patients.[23] Developmental milestones, in particular language, are delayed. In severe cases, secondary microcephaly becomes prominent.[6,7,17] Our study illustrates the wide phenotypic heterogeneity and the challenges posed in diagnosing the disease. Although all patients had experienced infantile seizures, they are unresponsive to conventional antiepileptic drugs. The mean time of delay in diagnosis was 86.3 $\pm$ 48.5 months (range, 29–148 months). All patients had seizures starting within the first years of life, characterized by myoclonic, complex partial and absence seizures. The other neurologic manifestation of our patients demonstrated a variable combination of ataxia, spasticity, dystonia, PED, microcephaly, and mental retardation. All patients in this study were compatible with the classical phenotype of Glut1D based on their clinical findings.

The KD is the treatment of choice in Glut1D and provides an alternative source of fuel to the brain. KDs include high fat, adequate protein, and low carbohydrate for the production of ketone bodies. Ketone bodies are generated in the liver from fatty acid degradation, and cross the BBB via facilitated diffusion mediated by the monocarboxylate transporter 1.[6,7] A ratio of 4:1 classical KD was found to supply the highest amount of energy in the treatment of Glut1D.[9,12] However, one of the major problematic issues in the treatment with classical KD is that it is restrictive, therefore, it is not always possible for it to be tolerated and accepted by children, and especially by adolescents. In the literature, the main alternative to KDs for the treatment of Glut1D include 3.5:1 fat/other nutrient ratio, 3:1 fat/other nutrient ratio, 2.5:1 fat/other nutrient ratio, 2:1 fat/other nutrient ratio, medium chain triglycerides, and the modified Atkins diet.[6,11,12,24–27] The modified Atkins diet is less restrictive in terms of the total protein and calories consumed, is more palatable, and is easily prepared by caregivers.[25–27]

The Mediterranean diet is characterized by a high proportion of cereals, vegetables, legumes, fruit, and unsaturated fatty acids. In general, the Mediterranean diet is adopted in Turkey, but it does not lead to extra difficulties in terms of maintaining KD therapy. Olive oil is a major component of this diet. Olive oil, a monounsaturated fat, is composed primarily of triglycerides and contains aliphatic and triterpenic alcohols, sterols, hydrocarbons, phenolic compounds, and its microconstituents.[28] We used olive oil as the ketosis fat in all patients who received the KD. Although the classic 4:1 KD was not tolerated in one of six patients in this study, according to our experience, the tolerability of KD therapies is increasing with olive oil as the ketosis fat. In addition, the phenolic compound of olive oil shows high antioxidant activity, and it has preventive potential in cardiovascular and neurodegenerative disorders.[28,29]

The most striking result of KD therapy in patient 6 was that PED completely resolved and there was a marked improvement in ataxic gait, such that she was able to walk and even run long distances for the first time in her life. This result may be associated with the relatively early diagnosis and treatment of the patient; therefore, early diagnosis and treatment of Glut1D may allow normal development in children.[12]

During follow-up, the early-onset adverse effects of the KD such as nausea, vomiting, constipation, and fatigue, were observed in five patients but late-onset complications were not detected in any patients (►**Table 3**).

Another very significant clinical benefit obtained by treatment with the KD was the improvement in the patients' cognitive activity. With the KD therapy, alertness, concentration, motivation, and activity were significantly improved in all the patients. However, in the measurements of the intelligence scale to determine IQ, there was no significant change in our patients. The literature contains several reports of improved cognitive impairment after treatment of with KD, but no or very few positive effects in the general IQ scores were documented.[11,17] Our findings were compatible with these results. We reassessed the cognitive functions of four patients with intelligence tests during follow-up. There was no significant difference between pretreatment and posttreatment results in intelligence tests (►**Table 3**).

These finding may be associated with the lack of reliable cognitive assessment or the limitations of IQ tests, in terms of sensitivity, to measure qualitatively different cognitive changes in children with mental retardation. Prospective follow-up studies with more comprehensive neurocognitive tests are needed.

The KD also has a positive effect on movement disorders such as spasticity, ataxia, dystonia, and PED.[9–12] In our study, the PED was completely resolved in patient 6, but the other neurological features consisting of a combination of spastic, ataxic, and dystonic disorders resulted in only a slight improvement of variable degree in four patients.

Our study showed that the classical ketogenic and modified Atkins diet therapies are an effective treatment choice in children with classical Glut1D for management of intractable seizures and cognitive function. The improvement in other neurological manifestations such as, ataxia, spasticity, and dystonia appeared less striking than the cognition and seizure control. Assessing accurate rates of tolerability and complications of the KD can be possible only through large multicenter studies.

The limitation of our study is its lack of genetic studies in five patients. It is not possible to conduct genetic analysis in many countries because of technical insufficiencies. Moreover, the mutations are not identified in all patients with

Glut1D, which means that clinical and laboratory evaluation is crucial for the diagnosis. In this study, we point out that the diagnosis of this treatable metabolic disease is possible with clinical and laboratory investigations including CSF and blood analysis.

Conclusion

Glut1D is a relatively rare, but treatable disorder. Glut1D should be considered in all children with unknown etiology of epilepsy, developmental delay, and/or movement disorder. The CSF/blood glucose ratio is an important laboratory finding for the diagnosis; therefore, a fasting lumbar puncture should be performed. Early diagnosis and treatment modalities such as KD may offer protection from the potentially deleterious effects of hypoglycorrhachia on neurodevelopment, especially in infants and children.

Authors' Contributions

G.H. conceived the study. P.H., K.M., and K.S. reviewed the literature, K.F., C.M., Ç.A.O., and K.B.A. were involved in patient care, including the process of the procedure, and routine clinical follow-up. G.H and K.B.A performed literature review and wrote the article. K.B.A. also conducted the statistical analysis. H.P., K.M., and S.K. also made helpful suggestions to improve the article.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Informed consent was obtained from all parents or legal guardians of the children included. This study was approval by the Local Ethics Committee of Erciyes University.

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