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Clinical Observations

New Paradigm for the Treatment of Glucose Transporter 1 Deficiency Syndrome: Low Glycemic Index Diet and Modified High Amylopectin Cornstarch

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ABSTRACT

OBJECTIVE: Glucose transporter 1 deficiency syndrome is an autosomal, dominantly inherited neurometabolic disorder caused by mutations in the *SLC2A1* gene. Decreased glucose transport into the brain results in seizures and cognitive dysfunction. The ketogenic diet is the treatment of choice, but complicated with compliance problems. Stabilization of blood glucose levels by low glycemic index diet and modified high amylopectin cornstarch would provide steady-state glucose transport into the brain to prevent seizures and cognitive dysfunction in patients with glucose transporter 1 deficiency syndrome as an alternative treatment. **PATIENT:** We report a new glucose transporter 1 deficiency syndrome patient (c.988C>T; p. Arg330X in the *SLC2A1*) treated with modified high amylopectin cornstarch (Glycosade) and low glycemic index diet because of compliance problems with the ketogenic diet. She was diagnosed at 11.5 years of age and was treated with the ketogenic diet between ages 12 and 18 years. **RESULTS:** She was started on modified high amylopectin cornstarch at bedtime and low glycemic index diet with meals and snacks every 3-4 hours. Within the first 6 months of therapy, she improved in her seizures and cognitive functions, but experienced compliance problems afterwards. Neuropsychological assessment was stable at 12 months of therapy. **CONCLUSION:** This diet was easy to apply compared with the ketogenic diet and resulted in stable neuropsychological functioning of this glucose transporter 1 deficiency syndrome patient. Modified high amylopectin cornstarch and low glycemic index diet might be an alternative treatment in glucose transporter 1 deficiency syndrome patients with compliance problems to the ketogenic diet treatment, but additional patients should be treated to prove usefulness of this new treatment.

Keywords: GLUT-1 deficiency syndrome, ketogenic diet, low glycemic index diet, modified high amylopectin cornstarch (Glycosade), compliance

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Introduction

The primary defect of glucose transport into the brain resulting in persistent hypoglycorrhachia as a cause of seizures and developmental delay was first reported by De Vivo.[1] Glucose transport from the bloodstream across the blood–brain barrier to the central nervous system is

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TABLE.
Neuropsychological Assessment Results at Baseline and 1 Year of Treatment With Glycosade and Low Glycemic Index Diet

Neuropsychological Assessment Results	Baseline Standard Score (Mean =100; SD = 15)	12 Months of Therapy Standard Score (Mean = 100; SD = 15)	Reliable Change Index (Z Score)
WAIS-IV* Full Scale IQ	40	42	0.47
Verbal comprehension index	50	52	0.36
Perceptual reasoning index	50	51	0.19
Working memory index	53	50	−0.50
Processing speed index	50	50	0.00
Academic achievement* (WIAT-III)	Reading = 41	Reading = 45	1.09
	Math = 40	Math = 40	0.0
	Spelling = 40	Spelling = 40	0.0
Language skills (PPVT-4)	Vocabulary = 40	Vocabulary = 20	−3.37†
Beery VMI	<45	<45	0.0

Abbreviations:
PPVT-4 = Peabody Picture Vocabulary Test, fourth edition
VMI = Visual-motor Integration
WAIS-IV = Wechsler Adult Intelligence Scale-IV
WIAT-III = Wechsler Individual Achievement Test, third edition
* Canadian normative data reported.
† Significant change.

facilitated exclusively by glucose transporter 1 (GLUT1) encoded by the *SLC2A1* (MIM# 138140) gene. Mutations in the *SLC2A1* gene cause GLUT1 deficiency syndrome (GLUT1-DS) (MIM# 606777)[2] affecting brain functions. The most common inheritance pattern is autosomal dominant. About 90% of patients have *de novo* mutations in the *SLC2A1* gene.[2]

The phenotype is a continuum from early onset severe global developmental delay, epileptic encephalopathy, acquired microcephaly, ataxia, dystonia, and spasticity[3-7] to paroxysmal nonepileptic clinical features including intermittent ataxia, choreoathetosis, dystonia, and alternating hemiplegia with or without cognitive dysfunction or intellectual disability.[6,8,9] Low cerebrospinal fluid glucose level is the key biomarker in the presence of normal blood glucose level.[2] The classical ketogenic diet has been the most effective treatment of GLUT1-DS.[1,10] However, compliance problems, especially in teenagers, are the major limitation of this treatment.

In GLUT1-DS, low blood glucose levels cause a marked drop in the brain glucose levels, precipitating seizures and further cognitive dysfunction. Low glycemic index diet aims to stabilize blood glucose levels by restriction of carbohydrate types, which produce the largest rise in blood sugar levels.[11] Modified high amylopectin cornstarch (Glycosade) stabilizes blood glucose levels by its longer duration of action and slower rise and fall in blood glucose levels. We hypothesize that stabilization of blood glucose levels by low glycemic index diet and modified high amylopectin cornstarch would provide steady-state glucose transport into the brain to prevent seizures as well as cognitive dysfunction in patients with GLUT1-DS.

We report the clinical and neuropsychological outcome of a patient with GLUT1-DS who was treated with a combined low glycemic index diet with frequent feedings throughout the day and a modified high amylopectin cornstarch at bedtime. This treatment was applied because of compliance problems with the ketogenic diet.

Patient and Results

This 19-year-old girl was born to nonconsanguineous parents after an uneventful pregnancy at term. First concerns were raised at age 15 months when she did not acquire independent sitting. She had her first generalized tonic seizure at age 2 years and was started on clobazam. Her first electroencephalograph (EEG) was normal during wakefulness and sleep. Her awake EEG showed generalized symmetrical paroxysmal epileptiform discharges with spike components and slow background activity at age 5 years. A continuous video-EEG recording revealed high-amplitude generalized spike and polyspike and slow wave discharges at 2.5–3 seconds and captured 40 seizures characterized by eye blinking and eye fluttering at age 8 years. She began taking lamotrigine and topiramate in addition to clobazam.

Investigations for global developmental delay, epilepsy, and ataxia were normal for vitamin E level, transferrin isoelectric focusing, alpha-fetoprotein, plasma pipecolic acid, plasma phytanic acid, very long chain fatty acids, acylcarnitine profile, plasma amino acid analysis, homocysteine, lactate, ammonia, urine organic acid analysis, urine sulfocysteine, urine oligosaccharides, and mucopolysaccharides. Genetic investigations were negative for karyotype, Friedreich ataxia, Fragile X testing, *PANK2* gene sequencing, and CAG repeat testing for *SCA1, SCA2, MJD1, SCA7* and *SCA8* genes for spinocerebellar ataxias. Her brain magnetic resonance imaging and proton magnetic resonance spectroscopy were normal at age 10 years.

Video-EEG monitoring showed continuous high amplitude 2.5- to 3-Hz general spike and wave complex before breakfast, which was normalized within 30 minutes of consuming breakfast and taking antiseizure medications at age 11 years. Similar improvements were recorded after lunch without taking antiseizure medications suggestive of GLUT1-DS. The direct sequencing of the *SLC2A1* gene revealed a pathogenic nonsense mutation (c.988C>T; p. Arg330X) confirming the diagnosis of GLUT1-DS at age 11.5 years.

She began a medium-chain triglyceride ketogenic diet. Her medium-chain triglyceride oil intake was gradually increased to maintain ketosis up to 4 mmol/L. She was maintained on clobazam and lamotrigine for ongoing seizure management. Because of compliance problems and not achieving ketosis, the ketogenic diet was discontinued at age 18 years. Neurological examination was remarkable for an ataxic gait, abnormal cerebellar tests, and dysarthria at the time of her first presentation to our clinic before initiation of treatment with low glycemic index diet and modified high amylopectin cornstarch.

We started modified high amylopectin cornstarch 2 g/kg (120 g) at bedtime and implemented a low glycemic index diet with meals and snacks every 3-4 hours between 7 am until bedtime modified high amylopectin cornstarch intake. Caregivers were provided a food list adapted from the diabetic diet, with additional information sourced from the Glycemic Index Diet.[12] She strictly avoided any refined sugar and white flour–based products. Her average carbohydrate intake was 294 g/day (food + modified high amylopectin cornstarch) (range 240-380 g) and fat intake was 55 g/day (range 39-84 g). Sixty percent of calories