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Research Article

Clinical Characteristics and Diagnosis Value of Functional Movement Disorders in GLUT1-DS

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Abstract

Objective: To explore the clinical characteristics and diagnosis of Glucose Transporter 1 Deficiency Syndrome (GLUT1-DS), and analyze the diagnostic significance of functional movement disorders.

Method: The clinical data of 3 children with GLUT1-DS were collected to analyze their clinical manifestations.

Results: Three cases of male patients with SLC2A1 gene mutation were included in this retrospective study. All three cases showed normal cranial MRI, liver, thyroid, adrenal and renal functions, with no manifestation in metabolic disorders of organic acids, amino acids, and fatty acids in blood and urine metabolism screening. All three cases displayed abnormality in electroencephalogram. Case 1 was further characterized by dystonia, and the other two cases display with gait ataxia.

Conclusion: Epileptic children with functional movement disorders should be considered as GLUT1-DS candidate, which could facilitate early confirmation through genetic test.

Keywords: GLUT1-DS; Functional movement disorders; Epileptic seizures; Dystonia; Gait ataxia; Diagnosis

Abbreviations

GLUT1-DS: Glucose Transporter 1 Deficiency Syndrome; GLUT1: Glucose Transporter Type 1; KDT: Ketogenic Diet Therapy; FMD: Functional Movement Disorder; EDTA: Ethylene Diethylenediamine Tetraacetic Acid; OMIM: Online Mendelian Inheritance in Man; EACD: European Academy of Childhood Disability; MRI: Magnetic Resonance Imaging; EEG: Electroencephalogram

Introduction

Glucose Transporter Type 1 Deficiency Syndrome (GLUT1-DS) is a dominant genetic disorder due to the decreased glucose supply to the brain [1]. GLUT1-DS is caused by impaired glucose transport through the blood brain barrier. The defective glucose supply to the brain tissues results in a series of neurological symptoms including diverse motor disorders, drug-resistant epilepsy, and developmental retardation [2]. GLUT1-DS can be attributed to the genetic mutations of the *SLC2A1* gene (GLUT1 encoding gene) [3]. The *SLC2A1* gene contains 10 exons and 33802 base pairs at 34.2 locus in the p-arm of chromosome 1, and it encodes GLUT1 consisting of 492 amino acids of 54.1 kDA [4]. Glucose Transporter Type 1 (GLUT1) is the key glucose transporter for glucose uptake in different tissues, which is highly expressed in the brain. This protein is located in the vascular endothelial cells of the blood brain barrier and serves as the major carrier for glucose to pass the blood brain barrier [3,4]. Since brain cells are heavily dependent on glucose for energy metabolism, the defective mutation of *SLC2A1* undermines energy resource and function of brain cells [5,6].

GLUT1-DS is a treatable genetic disease, and early diagnosis is crucial for effective intervention. For example, standard Ketogenic Diet Therapy (KDT) is able to provide supplemental ketone bodies as an alternative resource for brain energy metabolism in GLUT1-DS treatment [7]. Early identification and treatment is paramount to maintain normal cognitive development and achieve optimal outcome [8,9]. Apart from genetic screening approach, early clinical manifestations can serve as valuable indicator for GLUT1-DS diagnosis. Epileptic seizures and developmental delays are common symptoms of the nervous system defects in GLUT1-DS patients. However, these clinical features lack specificity for GLUT1-DS diagnosis, and their occurrence already indicate the onset of developmental retardation [1,2]. Therefore, the application of other clinical manifestation as early indicator for GLUT1-DS is of great importance for early diagnosis.

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In this report, we conducted a retrospective research into the clinical data of 3 children with confirmed GLUT1-DS by genetic diagnosis in the Department of Neurology of Kunming Children's Hospital from January 2020 to December 2021. We found that Functional Movement Disorder (FMD) is a common clinical manifestation of three patients, indicating the potential of FMD as a diagnostic feature for GLUT1-DS.

Methods

A retrospective analysis into the clinical data of 3 children with confirmed GLUT1-DS by genetic diagnosis in the Department of Neurology of Kunming Children's Hospital from January 2020 to December 2021. Clinical parameters of the patients, including cranial MRI examination, electroencephalogram, chest X-ray, electrocardiogram, color Doppler ultrasound abdomen, hematuria genetic tandem mass spectrometry analysis, and routine blood biochemical indicators were collected during primary screening. For cerebrospinal fluid examination, the patients were fasted for 4 hours before lumbar puncture, and underwent lumbar puncture after rapid blood glucose measurement. Cerebrospinal fluid glucose was measured and the cerebrospinal fluid glucose/blood glucose ratio was calculated.

Genetic screening

The family members have been informed of the genetic test and signed the informed consent form. 2 mL of venous blood from the patient was collected in an anticoagulant test tube containing Ethylene Diethylenediamine Tetraacetic Acid (EDTA). The genomic DNA sample was extracted and subjected to Sanger sequencing to confirm the mutation in *SLC2A1*. Data analysis was conducted through the human gene mutation database (Online Mendelian Inheritance in Man, OMIM database) to clarify pathogenic mutations in *SLC2A1*.

Functional Movement Disorder (FMD) assessment

Typical movement disorders of GLUT1-DS include abnormal gait, dystonia, and intention tremor. And atypical movement disorders include eye movement disorder, hemiplegia, monoplegia, and quadriplegia [10]. In this study, we assessed the movement coordination ability based on the international clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder, which was formulated by the European Academy of Childhood Disability (EACD) in 2019 [11].

Results

Clinical examination results

Three cases of male patients (with the age from 2 years and 1 month old to 4 years and 1 month old) with comprehensive clinical examination records were included in this study. Clinical parameters including cranial MRI examination, electroencephalogram, chest X-ray, electrocardiogram, color Doppler ultrasound abdomen, hematuria genetic tandem mass spectrometry analysis, and routine blood biochemical indicators were collected during primary screening. The results of cranial MRI, electrocardiogram, Liver and renal functions, and the functional markers of thyroid, adrenal gland and bone were normal. The levels of blood glucose, blood ammonia, lactic acid and other parameters in hematuria genetic tandem mass spectrometry analysis also showed normal range. No metabolic disorders of organic acids, amino acids, and fatty acids were found in blood and urine metabolism screening (Table 1). However, all three patients displayed abnormality in the electroencephalogram examination, indicating the disruption of normal electrical activity in the central nervous system. There was a reduction of cerebrospinal fluid glucose level and cerebrospinal fluid glucose/plasma glucose ratio in all three patients, indicating the defective glucose supply to the central nervous system.

SLC2A1 gene sequencing results

SLC2A1 gene mutations were detected in all 4 cases (Table 2). Case 1 harbored a c.496G>A (p.Val166Ile) mutation in exon 4, case 2 contained a c.1377del (p.Phe460Serfs*48) mutation in exon 10, and case 3 had a c.498C>T (p.Val166=) mutation in exon 10. The mutations in case 1 and case 3 belong to missense mutation and the mutation in case 2 belong to frameshift mutation. All three cases belong to heterozygous mutation at *SLC2A1* gene.

Functional movement assessment

Case 1 displayed normal sensitive light reflex and normal pharyngeal reflex, with dysarthria characterized by vague language, laborious speech, and unnatural interruptions. Case 1 was further characterized by dystonia, with increased muscle tone in both lower limbs and normal muscle tone in the upper limbs (Table 3). Case 2 and 3 were characterized with gait ataxia, as manifested by unstable walking, defective coordination of limbs and scissors gait in a "Z" shape. All three cases showed no tremor and normal ocular mobility. Epileptic seizure was reported in all three cases, and anti-epileptic treatment showed no effect.

Discussion

Epileptic seizure is commonly reported in GLUT1-DS patients before the cause of the epilepsy is ascertained and appropriate KDT are initiated [2]. Initial epilepsy treatment fails to correct the underlying metabolic disturbance during early brain development in GLUT1-DS patients, contributing to the long-term disease burden and impaired development of the brain microvasculature in the postnatal period [5-7]. It is imperative to reach international consensus to facilitate prompt diagnosis and guide best standard of managing GLUT1-DS throughout the life cycle.

GLUT1-DS patients are characterized by intermittent epileptic seizures, functional movement disorder, and developmental delays [1,12]. In addition, a reduction of cerebrospinal fluid glucose level and cerebrospinal fluid glucose/plasma glucose ratio also informs the defective function of GLUT1 [13]. All three cases in this report showed classic GLUT1-DS features, including functional movement disorder (dystonia or gait ataxia), epileptic seizures, and a reduced cerebrospinal fluid glucose/plasma glucose ratio. As suggested by a previous study, typical functional movement disorders in GLUT1-DS often manifest as gait abnormalities (89%), dystonia (86%), and intentional tremor (70%), and atypical motor disorders may include eye movement disorders, hemiplegia, monoplegia, and quadriplegia [14]. Since two cases in our study displayed gait ataxia and the other one showed dystonia, the onset of functional movement disorder is an important indicator of GLUT1-DS.

There is evidence that a portion of children with GLUT1-DS show the widening of the extracerebral space or delayed myelination by cranial MRI examination [12]. However, in our cases no such abnormalities were identified, indicating that the cranial MRI examination results are not common indicator of GLUT1-DS. There is also report that the EEG of GLUT1-DS children could be characterized by a clear-cut contralateral EEG slowing [15], which is in agreement with our observation in the EEG pattern of case 2

Table 1: Clinical examination results of 3 recruited cases in the study.

Medical examination	Test results		
	Case 1 (Male, 2 years and 4 months old)	Case 2 (Male, 2 years and 1 month old)	Case 3 (Male, 4 years and 1 month old)
Cranial MRI	Normal	Normal	Normal
Electroencephalogram	Abnormal (Atypical sharp/wide waves)	Abnormal (Whole brain spike slow complex wave)	Abnormal (Multi-spike with slow wave bursts)
Chest X-ray	Normal	Normal	Normal
Electrocardiogram	Normal	Normal	Normal
Color Doppler ultrasound abdomen	Normal viscera	Normal viscera	Normal viscera
Hematuria genetic tandem mass spectrometry analysis	Lactic acid:1.6 mmol/L; Other items are normal	Lactic acid:1.6 mmol/L; Other items are normal	Lactic acid:1.2 mmol/L; Other items are normal
Blood routine test	Normal	Normal	Normal
Plasma ammonia	11.8 umol/L	11.3 umol/L	19.2 umol/L
Liver/renal indicators	Normal	Normal	Normal
Thyroid indicators	Normal	Normal	Normal
Adrenal indicators	Normal	Normal	Normal
Bone markers	Normal	Normal	Normal
Cerebrospinal fluid glucose	2.21 mmol/L	2.05 mmol/L	1.97 mmol/L
Plasma glucose	5.2 mmol/L	4.8 mmol/L	4.6 mmol/L

Table 2: Genetic testing results of *SLC2A1* gene.

Case	Gene	OMIM Inheritance	Exon	HGVS (Human Genome Variation Society) Variant Nomenclature	Variant Type	Zygosity
1	*SLC2A1*	Autosomal dominant	Exon 4	NM_006516.3:c.496G>A(p.Val166Ile)	Missense variant	het
2	*SLC2A1*	Autosomal dominant	Exon 10	NM_006516.3:c.1377del(p.Phe460Serfs*48)	Frameshift variant	het
3	*SLC2A1*	Autosomal dominant	Exon 10	NM_006516.4:c.498C>T (p.Val166=)	Missense variant	het

Table 3: Functional movement coordination assessment.

Case	Gender	Age	Dystonia	Gait ataxia	Dysarthria	Tremor	Ocular Motility Disorders	Epileptic seizure
1	Male	2 years and 4 months	+	-	+	-	-	+
2	Male	2 years and 1 month	-	+	-	-	-	+
3	Male	4 years and 1 month	-	+	-	-	-	+

and case 3. The abnormal EEG pattern in GLUT1-DS is presumably related to immature brain development or energy depletion.

The clinical diagnosis of GLUT1-DS requires the exclusion of central nervous system infections, and a cerebrospinal fluid glucose concentration less than 2.2 mmol/L [16]. Nowadays, genetic mutation in *SLC2A1* gene has become the gold standard for GLUT1-DS diagnosis [7,11]. In our study, all three cases fulfill the above criteria as confirmed GLUT1-DS cases. GLUT1-DS is a treatable genetic disease, and early diagnosis is crucial. Standard Ketogenic Diet Therapy (KDT) is able to maintain normal cognitive development and achieve optimal outcome with early intervention [8,9]. Although developmental delays are a common symptom in GLUT1-DS patients, these clinical features lack specificity for GLUT1-DS and indicate the onset of developmental defects [1,2].

Conclusion

Our study showed that functional movement disorders including dystonia and gait ataxia can also inform GLUT1-DS, which could provide clue for the early confirmation of GLUT1-DS through genetic test.

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