Case Report

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A Male Toddler With Congenital Dysglycosylation Due To A Single Missense Variant Of The ALG11 Purity Gene And Review Of The Literature

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1. Abstract:

1.1. Objective: For the first time in China, we report the clinical and molecular genetic features of a child with congenital dysglycosylation (CDG) caused by a variant in the asparagine-linked glycosylation 11 (ALG11) gene.

1.2. Method: A male child (2 months old) who was first diagnosed with "postnatal convulsive seizures, excitability, and developmental delay" in the Department of Neurology of Hebei Provincial Children's Hospital on January 11, 2023, was selected for the study, and high-throughput sequencing technology was applied to perform whole-exome sequencing, and Sanger sequencing technology was used to validate the suspected mutation sites and their familial Sanger sequencing was used to validate the suspected mutation sites and their family members. The search terms "ALG11", "congenital glycosylation" and "CDG" were used to search the China Knowledge Network (CNN), Wanfang Database (WFDB) and PubMed Database (PubMed), respectively, from the establishment of the database to March 2023, and to combine with this case's patient, we searched the literature. The clinical and genotypic characteristics of patients with ALG11 variant CDG were summarized and analyzed with the data of this case.

1.3. Results: High-throughput sequencing showed that the child had a pure missense mutation in the ALG11 gene c.800C>T p.Ser267Leu, and validation results showed that the mutation was derived from the parents, which was the first case of a child with a pure heterozygote due to a variant in the ALG11 gene in China. The child presented with generalized seizures, peculiar facial features (high forehead, wide eye spacing, collapsed nose, thick lips, windy ears, microcephaly), hypotonia of the limbs, and the ability to perform simple commands and speak simple words. She was followed up to more than 1 year and 2 months of age and showed epilepsy, hypotonia, and mild developmental delay, and was well treated with antiepileptic drugs. The search criteria were met with 2 articles in Chinese and 9 articles in English, which were combined with a total of 18 patients with ALG11 causing CDG in our child. Of these patients, 94% suffered from epilepsy, 78% exhibited hypotonia, 72% had developmental delay, and the remaining symptoms were present in a few individuals. Two of the four reported cases of the purist case survived, and the clinical phenotype of the purist case reported in the present study was much milder.

1.4. Conclusion: ALG11-CDG can develop during fetal life, and the main clinical features are epilepsy, hypotonia, developmental delay and microcephaly, with the type of mutation correlating with the prognosis of the disease.

2.Keywords:
ALG11 gene mutation congenital glycosylation hypotonia epilepsy

Congenital disorder of glycosylation (CDG, OMIM 608540) is a rare autosomal recessive disorder with clinically visible multisystemic involvement, especially epilepsy, neuromotor retardation, and other neurological symptoms, which is a serious risk to the life and health of children1.The prevalence and clinical manifestations of the disorder are varied The incidence and clinical manifestations of the disease vary. In this study, whole exome sequencing was performed on a child presenting with epilepsy and developmental delay, and Sanger sequencing was performed to verify the deletion fragments identified by sequencing, confirming that the child was diagnosed with ALG11-CDG.

3. Clinical information

Precedent Male, 2 years, 1 month, 5 d, presented to our neurology clinic on December 12, 2022, with "1 seizure". The child presented with an unprovoked waking-period generalized seizure characterized by loss of consciousness, upturning of the eyes, cyanosis of the lips and mouth, clenching of the teeth, clenching of the hands into fists, and shaking of the lower limbs of both hands, which lasted for about 5 minutes and resolved spontaneously, and responded favorably to the relief, and was free of convulsive episodes after the administration of oral levetiracetam

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at 20 mg/kg per day. The preexisting patient was the 1st child, 1st birth, mother was conceived naturally and delivered at full term, birth history was not abnormal, history of asphyxia and resuscitation was denied, and the mother was fit during pregnancy. The parents denied consanguineous marriage and were in good health. Physical examination after admission: clear consciousness, mental reaction, special facial features, high forehead, wide eye spacing, collapsed nose, thick lips, beckoning ears, microcephaly (Figure 1-a), head circumference of 44.5 cm, height of 90 cm, can obey the instructions, can say simple words, the skin of the whole body did not see rashes, pigmentation abnormalities. The muscle strength of the limbs was normal, the muscle tone was reduced, there was no involuntary movement, both biceps and triceps tendon reflexes were normal, both knee tendon reflexes were normal, and the bilateral baroreceptor's sign and Kirschner's sign were negative. Laboratory tests: routine blood tests and blood biochemistry were not abnormal; cranial nuclear magnetic field, cardiac ultrasound and electrocardiogram were normal; developmental assessment showed that adaptive and fine motor limbic status and gross motor were normal, and language and personal socialization were mildly delayed; electroencephalogram showed asynchronous release of spikes and slow and sharp waves in the Rolandic region of the brain in waking and sleeping phases bilaterally, with more in the sleeping phases (Fig. 1-b). Diagnosis and treatment: The main diagnosis of the child was "epilepsy", and he was treated with oral levetiracetam at 20 mg/kg per day, with no convulsive seizures up to the time of writing.

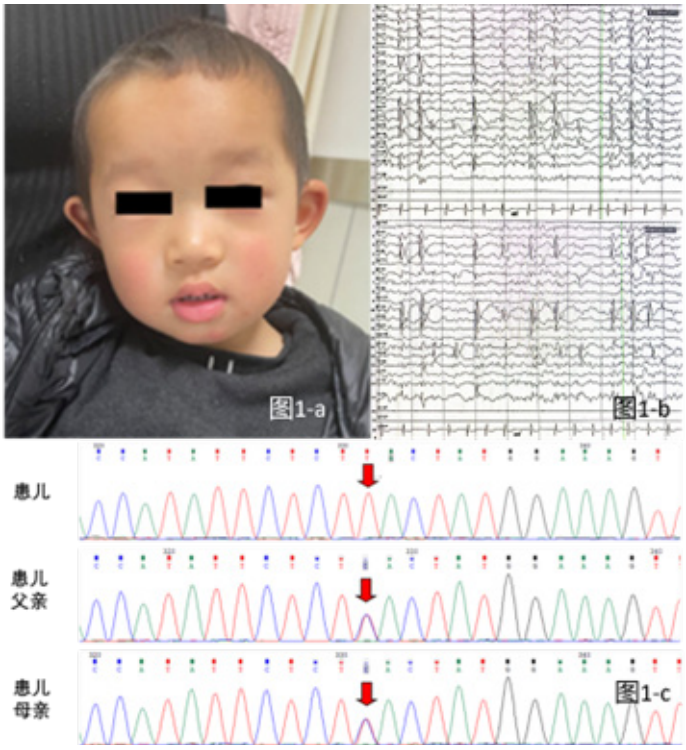

Figure 1-a: Specialized facial features of the child High forehead, wide eye spacing, collapsed nose, thick lips, windswept ears, microcephaly

Figure 1-b: Video EEG results of the child showing asynchronous release of spikes and spikes and slow waves in the bilateral Rolandic area during the wake and sleep phases.

Figure 1-c: Sanger sequencing of the ALG11 gene in children with CDG and their parents: the children had a c.800C>T p.Ser267Leu pure missense variant, carried by both parents, and the variant came from both parents. METHODS: Using second-generation high-throughput sequencing, the subject was found to carry a pure missense variant at the c.800C>T locus of the ALG11 gene, which resulted in the mutation of amino acid 267 of the encoded protein from serine to leucine. The suspected pathogenic mutation site was verified by Sanger sequencing, and the sequencing results were compared with the reference sequence using Mutation Surveyor v4.0 software. The pathogenicity of the mutations was assessed with reference to the 2015 edition of the ACMG guidelines of the American College of Medical Genetics and Genomics.

Whole exome sequencing results: after obtaining informed consent from the parents of the proband, whole exome testing was performed on the proband. One purely synonymous variant (c.800C>T p.Ser267Leu) in the ALG11 gene was detected as a missense variant, which was derived from both parents, and was consistent with an autosomal recessive pattern of inheritance. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, this variant locus was rated as clinically not significant (PM2) (Figure 1-c). Combining the clinical features and genetic test results, the child was finally diagnosed with "CDG and epilepsy due to ALG11 gene variant". Treatment results and follow-up: After the administration of levetiracetam oral solution to the pre-certified person, he was seizure-free and in general condition. He came to our neurology clinic for follow-up every 2 weeks, and was followed up until he was 3 years old and 1 month old, and the child was seizure-free, and his cognition and development were significantly improved compared with the previous period.

4. Literature review materials

The Asparagine-linked glycosylation 11 gene (ALG11, OMIM: 613666) is located at sub-band 3, band 4, region 1, long arm of chromosome 13 and encodes a protein, mannosyltransferase. This enzyme exercises the function of metabolizing GDP-mannose by sequentially adding the 4th and 5th of the 9 mannose sugars to the oligosaccharides on the outer leaflet of the endoplasmic reticulum2, affecting the formation of oligosaccharide chains and thus the function of proteins. ALG11 gene variants can cause The mutation locus carried by a child with ALG11 gene variants causing CDG reported in this article is the first report in China. Combined with previous reports in the literature, the following findings are summarized in terms of the genotypic and clinical phenotypic characteristics of children carrying the ALG11 gene with CDG. The four children in this case, who were also pureblooded, had similar clinical symptoms, including epilepsy, decreased or increased muscle tone, microcephaly, recurrent vomiting, developmental delay, and impaired visual acuity. The EEGs of a 1.4-month-old boy with the mutation site at c.T257C (p.L86S) reported by Rind et al. and of a 14-year-old boy with c.127T °C reported by Haanpää et al. showed more waves of epileptic activity, abnormal serum transferrinase, and are still alive; the other 2 pure cases, a 2-year-old girl with the c.T257C (p.L86S) mutation reported by Rind et al. and a 2-month-old boy with the

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c.935A>C mutation reported by Arai et al. The former has an abnormal serum transferrin and the latter a normal serum transferrin, and the 2-month-old boy has intractable epilepsy, and in these 2 cases, the EEGs were were severe, for burst suppression, and cranial NMR showed cerebral atrophy and poor myelination, both of which eventually died.Compared to the above four children, the present case had mild symptoms, spike release in the Rolandic region of the EEG waveform, and no abnormalities in the cranial NMR.

The severe phenotype mainly consisted of cases 6, 7, 14, 11, 8, and 15. 2 cases of a 3-year-old boy with c.479G > T and c.45-2A > T and a 3-month-old boy with c.479G > T and c.36dupG, respectively, with severe abnormalities of serum transferrinase, and 1 neonate with mutation loci c.44G > C and c.806G > A, reported by Li Li et al. in China. c.806G > A. No transferrinase test was performed, and all three children died after ineffective drug treatment with phenobarbital, sodium valproate, levetiracetam, topiramate, and corticotropin, as well as more severe EEG and cranial NMR results.A 2-year-old, 5-month-old female toddler with mutation loci c.935A > G, c.1223 T > G, and a serum A 5-month-old female infant diagnosed by molecular studies by Pereira et al. had abnormal serum transferrinase and abnormalities in cranial NMR and EEG; and a 5-month-old 23-day-old male infant reported by Fu Lina et al. in China had mutations at c.1403G > A and c.1307G > T. All three of the above children had refractory epilepsy and were still alive. All three of these children had refractory epilepsy and were still alive. The less severe phenotypes were cases 9 and 17, a 4-month-old female infant with the c.1241T > A mutation and mild abnormalities in serum transferrinase reported by Teneiji et al. A 2-year-old, 7-month-old boy with the mutation locus c.476T > C reported by Erdal et al. Cranial NMR demonstrated cerebral atrophy and dysmyelination in both cases, which remained viable. Cases 3, 4, 5, 10, and 12 were phenotypically mild.Cases 3, 4, and 5 reported by Thiel et al. 2 girls and 1 boy with an age distribution of 4.5 to 8.5 years, mutation loci c.623_642del, c.836A>C, and c.1142T>C, c.1192G>A, and c.953A>C, and 1 case reported by Teneiji et al. 4-month-old female infant with mutations at c.1123_1126delAACA, c.986_988delAGA, and 1 male fetus at 36 weeks gestational age with mutations at c.44G>C and c.161C>T reported by Mulkey et al. All five children were heterozygous for the mutation, and the EEG and cranial NMR were unremarkable, and the epilepsy was easily controlled.

Case	Base change	Amino acid change	Pure/ Heterozygous	Type of mutation	Prognosis	reference
1	c.T257C	p.L86S	Pure	missense	survive	Rind et al.(2010)
2	c.T257C	p.L86S	Pure	missense	die	
3	c.623_642del c.836A>C	p.Y279S	Hetero zygous	missense code shift	survive	Thiel et al.(2012)
4	c.1142T>C c.1192G>A	p.L381S p.E398K	Hetero zygous	missense	survive	
5	c.953A>C	p.Q318P	Hetero zygous	missense	survive	
6	c.479G > T c.45-2A > T	p.G160V	Hetero zygous	missense splice	dead	Régal et al.(2014)
7	c.479G > T c.36dupG	p.G160V	Hetero zygous	missense recurrent	dead	
8	none	none	none	molecular research diagnostics	survive	Pereira et al.(2017)
9	c.1241T > A	p.Iso414N	Hetero zygous	missense	survive	Teneiji et al.(2014)
10	c.1123_1126 delAACA c.986_988delAGA	p.N375FfsX6 p.K329del	Hetero zygous	code shift	survive	
11	c.935A > G c.1223T > G	p.E312G p.M408R	Hetero zygous	2 missense	survive	Haanpää et al.(2019)
12	c.44G>C c.161C>T	p.Arg15Thrp. Ser54Leu	Hetero zygous	2 missense	survive	Mulkey et al.(2019)
13	c.127T>C	p.L46P	Pure	missense	survive	Haanpää et al.(2019)
14	c.44G>C c.806G>A	p.Arg15Thrp.Trp269*	Hetero zygous	2 missense	dead	et al.(2020)
15	c 1403G >A c1307G >T	p.R468H p.G436V	Hetero zygous	2 missense	survive	et al.(2021)
16	c.935A>C	p.Glu312Ala	Pure	missense	dead	Arai et al.(2022)
17	c.476T>C	uncharted	Hetero zygous	missense	survive	Erdal et al.(2023)
18	c.800CT	p.Ser267 Leu	Pure	missense	survive	The prior witnesses of this study

Table 1: All children with reported ALG gene variants in China and abroad

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5. Discussion

Congenital disorders of glycosylation (CDG) are a group of single-gene inherited disorders involving the biosynthesis of glycoproteins and glycolipids, which can be caused by mutations in a variety of genes, and are usually characterized by neurological symptoms including microcephaly, epilepsy, hypotonia, cerebellar hypoplasia, and mental retardation3. The ALG11 gene encodes the guanosine diphosphate mannose, Man3GlcNAc2-PP-dolichol/ Man4GlcNAc2-PP-dolichol a-1,2-mannosyltransferase, the enzyme that catalyzes the addition of the 4th and 5th mannose sugars to oligosaccharide precursors, and its mutation in the absence of this enzyme leads to abnormal processing of proteins and lipids, triggering CDG4. The 1st patient due to mutations in the ALG11 gene was reported in 2010, and she had epilepsy, hypotonia, developmental She had epilepsy, hypotonia, developmental delay, and microcephaly5.With the widespread use of genetic testing technology, a variety of new symptoms such as deafness, vision loss, feeding difficulties, and abnormalities of the liver and coagulation have appeared in the reported cases, with varying clinical signs2,6-11.

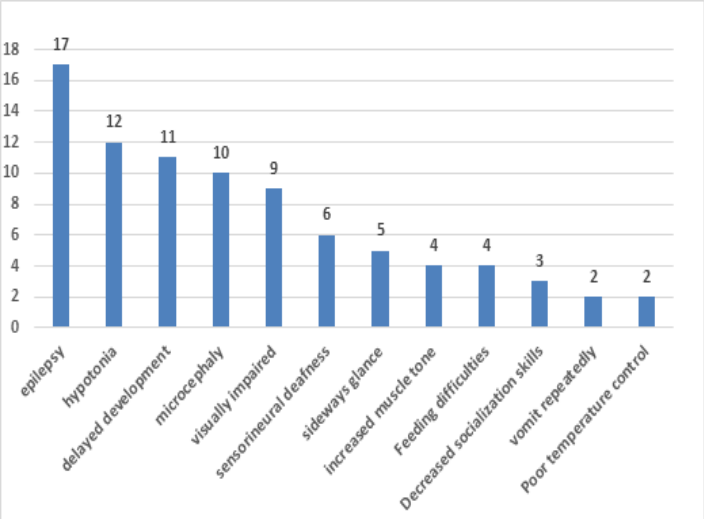

Figure 2: Distribution of clinical symptoms in 18 children with ALG

Among the types of ALG gene variants that have been reported, cases 4,11,12,14,15 are caused by 2 missense variants and may present with sensorineural deafness and strabismus, in addition to the usual common symptoms such as epilepsy and hypotonia. The patients' epilepsy was usually refractory10,12,13 and in severe cases fatal12, and in one case the epilepsy was controlled with the addition of a ketogenic diet. Cases consist of 1 missense mutation and 1 splice, shift, or repeat mutation Children with epilepsy are generally resistant to medication, and in severe cases can die from seizure-induced respiratory insufficiency6,14. Seizures are attenuated with topiramate in case 66. Only 1 patient was sickened by 2 code-shift mutations, and this patient did not have specific changes8. The genotypes were pure single missense variant in 4 cases1,9,11 and heterozygous single missense variant in 3 cases1,8,14, the type of single gene variant in this child was pure missense variant. Three deaths and two survivors have been reported with a single missense variant in a purebred2,11. The surviving patients had similar symptoms and well-controlled epilepsy9, and two of the familial deaths were considered to be related to close parental consanguinity and identical genetic variants2. It is suggested that the clinical phenotype of this type of gene variant may be milder and epilepsy better controlled than other types of clinical phenotypes. In conclusion, it is considered that patients who may be affected by only 1 missense variant locus have more surviving individuals and better antiepileptic treatment than patients with 2 missense variants and a combination of 1 missense variant locus and other variants, and that the latter 2 have more individuals with refractory epilepsy and more individuals who die.

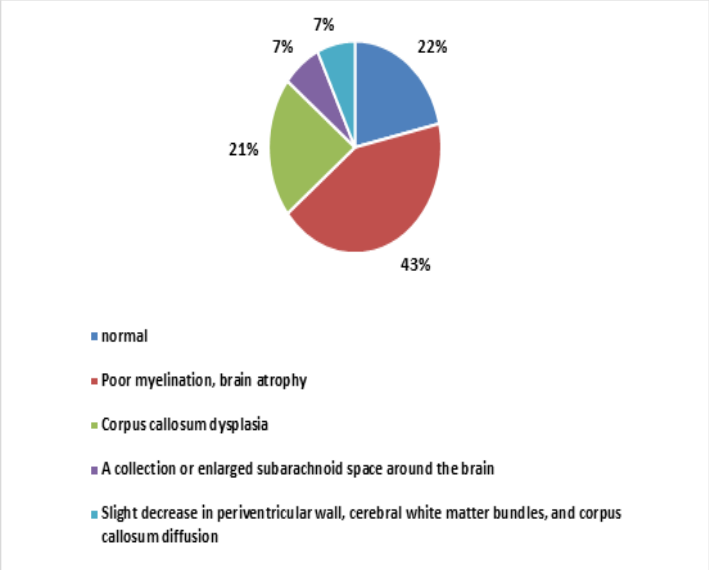

Figure 3: Distribution of cranial nuclear magnetic findings in 14 ALG patients

Cases of ALG11 gene variants have been reported, and serum transferrin glycosylation profiles may show normal, mild or even severe abnormalities. Patients who are purely heterozygous for a single missense variant, heterozygous for 2 missense variants, and heterozygous for 2 code-shifting mutations are severely symptomatic and die in severe cases, but have normal serum transferrin glycosylation profiles8-11. The one patient with mild abnormalities was a heterozygous single missense variant and remained alive8. Serum transferrin glycosylation profiles were heavily abnormal in pure single missense variants, heterozygous single missense variants and combinations of missense variant loci and other variants, and in fatal cases6,9. It is suggested that a normal presentation of serum transferrin glycosylation profile cannot exclude this disease, and more future studies are still needed regarding the correlation between serum transferrin glycosylation profile analysis and clinical phenotype. Cranial NMR findings in patients with ALG11-CDG include normal, poorly myelinated, cerebral atrophy, and hypoplasia of the corpus callosum6,7-10,12. Most of the video-EEG findings show inhibitory bursts and highly dysrhythmic rhythms1,6,9,11-13. One recently reported patient did not have a high degree of dysrhythmia, a slow background

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activity that was more specific7. In this case, the EEG of the child showed asynchronous release of spikes and spikes and slow waves in the bilateral Rolandic area during the waking and sleeping phases, and the cranial nuclear magnetic examination was normal, but we cannot rule out the emergence of new symptoms after ageing, and we need to further follow up and improve the EEG and cranial nuclear magnetic examination. In summary, there are differences in the clinical phenotypes of ALG11-CDG patients, and the results of serum transferrin glycosylation profiling cannot be used as a basis for diagnosis of the disease, and whole-exome genetic testing plays an important role in the early diagnosis of the disease. Moderate antiepileptic treatment is effective in individuals with a single missense variant, and refractory epilepsy is usually present in the clinical phenotype of the remaining genotypes.

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