Molecular Syndromology

Novel Insights from Clinical Practice

Mol Syndromol
DOI: 10.1159/000530118

Received: January 18, 2023
Accepted: March 7, 2023
Published online: April 21, 2023

Autism Spectrum Disorder in Two Unrelated Patients with Homozygous Variants in Either ALG8 or ALG11

Gozde Uzunyayla-Inci[a] Ertugrul Kiykim[a] Tanyel Zubarioglu[a] Gozde Yesil[b] Cigdem Aktuglu Zeybek[a]

[a]Division of Nutrition and Metabolism, Department of Pediatrics, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey; [b]Department of Medical Genetics, İstanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Established Facts

- The prevalence of autism spectrum disorder (ASD) has been increasing rapidly in recent years.
- The pathophysiology of ASDs remains unclear; however, genetic defects and multifactorial causes have been reported to play an important role in genetic disorders.

Novel Insights

- With this report, isolated autism spectrum disorder should be described in the clinical spectrum of congenital disorders of glycosylation (CDG) in the literature
- Autism should be listed among the neurological findings of CDG.

Keywords
Congenital disorders of glycosylation · Autism spectrum disorder · ALG8-CDG · Autism · Intellectual disability

Abstract
Background: Autism spectrum disorder (ASD) is used to describe individuals with a specific combination of disorders in social communication and repetitive behaviors, highly restricted interests, and/or sensory behavior that begin early in life. The prevalence of ASD has been increasing rapidly in recent years. Pathophysiology of ASDs remains still unclear; however, genetic defects and multifactorial causes have been reported to play an important role in genetic disorders. The prevalence of inborn errors of metabolism (IEM) reported among patients with ASD is 2–5%. The clinical presentation of congenital disorders of glycosylation (CDG) may be in the form of psychiatric disorder only. ***Case Study:*** Case 1: a 5-year-old female patient was admitted for investigation of ASD. She had a dysmorphic facial appearance, inverted nipples, abnormal fat distribution, ataxic gait, and autistic features. Her transferrin isoelectric focusing test was compatible with a type 1 CDG pattern. A homozygous variant in ALG8 gene revealed the diagnosis of ALG8-CDG

karger@karger.com
www.karger.com/msy

Correspondence to:
Gozde Uzunyayla-Inci, drgozdeuzunyayla@yahoo.com

Karger

(CDG Type 1H). Case 2: a 2-year-old male patient was admitted with complaints of ASD for investigation of an underlying IEM due to speech delay. Physical examination revealed hypertelorism, small hands, and autistic behavior. Transferrin isoelectric focusing test was also found normal. As a result of the WES, a homozygous variant was detected in ALG11 confirming the diagnosis of CDG type 1p. ***Conclusion:*** CDG should also be considered in the differential diagnosis of autistic patients with dysmorphic findings. The aim of our study was to emphasize that autism should be listed among the neurological findings of CDG.

Introduction

Autism spectrum disorder (ASD) is used to describe individuals with a specific combination of disorders in social communication and repetitive behaviors, highly restricted interests, and/or sensory behavior that begin early in life [Lord et al., 2020]. The prevalence of ASD has been increasing rapidly in recent years as reported in the last report of the Centers for Disease Control and Prevention. According to this report, the prevalence of autism has increased from 1.7% to 3.9% worldwide [Maenner et al., 2021]. The Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend that all children be screened specifically for ASD during regular well-child visits at 18 months and 24 months. Isolated loss of early words and social responsiveness are mentioned as the emerging clinical findings which support the diagnosis of ASD [Centers for Disease Control and Prevention, 2022].

Etiology of ASD is multifactorial, and genetic disorders play an important role. Phenylketonuria, homocystinuria, cobalamin deficiency, argininemia, mucopolysaccharidosis, and some types of congenital disorders of glycosylation (CDG) can be listed as inborn errors of metabolism (IEM), in which autism should be the presenting sign at the course of the disease.

CDG include a rapidly growing spectrum of IEM caused by defective glycosylation of proteins and lipids [Höck et al., 2015]. Multiple prenatal abnormalities, gastrointestinal symptoms, seizures, ataxia, psychomotor retardation, dysmorphic findings, coagulopathy, and increased transaminase levels are main findings of CDG. Neurological involvement is a frequent finding of the disease; however, it can involve all systems or be seen as a single organ involvement [Marquardt and Denecke, 2003]. Psychomotor retardation, hypotonia, impaired liver functions, coagulopathy, feeding difficulties, convulsions, and visual disturbances are main clinical manifestations in the early childhood period [Cylwik et al., 2013]. ASDs may also be a phenotypic feature of CDG.

ALG8-CDG (OMIM #608104) is one of the CDG syndromes that is caused by variants in the ALG8 gene which encodes glucosyltransferase 2 (dolylyl-phosphateglucose 1-mannose 9-N acetylglucosamine glucosyltransferase). Clinical presentation includes dysmorphic facial features, hypotonia, ataxia, psychomotor retardation, renal failure, hepatomegaly, coagulopathy, edema, and ascites, including hydrops fetalis, cardiorespiratory problems, and protein-losing enteropathy [Chantret et al., 2003]. ALG11-CDG (CDG type 1p) is a type of CDG caused by a deficiency of mannosyl transferase 11 enzyme (OMIM #613661). It is particularly characterized by nervous system and hearing involvement. In the carbohydrate-deficient transferrin analysis, increased di- and asialo-transferrin and decreased tetrasialo-transferrin can be detected. In some ALG11-CDG cases, carbohydrate-deficient transferrin analysis can be detected as normal [Jaeken and Pe'anne, 2017].

Here, a 5-year-old female patient and a 2-year-old male patient who presented with ASD without the cardinal findings and diagnosed with CDG were reported. With this report, ASD should be described in the clinical spectrum of CDG in the literature.

Case Study

Case 1

A 5-year-old female patient was admitted to our outpatients' clinic for investigation of underlying IEMs of ASD. She was first diagnosed with ASD by a child psychiatry clinic at 3 years of age with complaints of social impairment and speech delay. She was the first child of consanguineous parents. Her prenatal, natal, and postnatal history was uneventful. Her weight, length, and occipitofrontal circumference were in normal ranges. She achieved her neurodevelopmental milestones with a moderate delay. There was a marked retardation in her expressive language development as at the age of 3 years, she could only use 10–15 words, and she had no sentences.

In physical examination, she had a normal growth. She had a dysmorphic facial appearance including epicanthus, hypertelorism, mild micrognathia, inverted nipples, and abnormal fat distribution, especially pronounced around the abdomen. She could only walk with support and had an ataxic gait. Based on her dysmorphic features and abnormal neurologic examination, CDG was included in the differential diagnosis.

Hematological, biochemical, and primary metabolic analysis investigations were normal. Brain magnetic resonance imaging was normal, and her electroencephalography showed diffuse, irregular background activity and isolated sharp wave activity in both temporo-occipital and parieto-occipital hemispheres.

Table 1. Clinical and demographic characteristics of patient 1 and patient 2

	Sex	Consanguinity	Age of ASD findings	Age of diagnosis	Dysmorphic features	GIS findings	Hepatic involvement	Neurological findings	Transferrin isoelectric focusing	Gene	Protein change	Nucleotide change
Patient 1	F	(+)	36 months	5 years	Epicanthus, hypertelorism, micrognathia, inverted nipples, abnormal fat distribution	Ø	Ø	Ataxic gait, abnormal EEG	Increased mono-oligo/di-oligo and a-oligo/di-oligo ratio	ALG8	p.Leu195Pro	c.584T>C
Patient 2	M	(+)	18 months	2 years	Hypertelorism, micrognathia	Ø	Ø	Ø	Normal	ALG11	p. (Ala85Val)	c.254C>T

ASD, autism spectrum disorder; GIS, gastrointestinal system; F, female; M, male, EEG, electroencephalogram.

Transferrin isoelectric focusing test which was performed for a preliminary diagnosis of CDG, mono-oligo/di-oligo ratio and a-oligo/di-oligo ratio were found to be high which was compatible with CDG1. As a result of the whole exome sequence analysis, homozygous c.584T>C change was detected in the ALG8 gene (NM_024079.4 c.584T>C [p.Leu195Pro]).

Her parents were also found to be heterozygous for this change. She is now 12 years old, and in the 7-year follow-up period, no worsening even in clinical and/or biochemical findings was observed.

Case 2

A 2-year-old male patient was admitted to our outpatients' clinic for investigation of underlying IEMs of ASD. He was first diagnosed with ASD by a child psychiatry clinic at 18 months of age, with speech delay and slower neurological development than his sister. He was the second child of consanguineous parents. His prenatal, natal, and postnatal history was uneventful. His weight, length, and occipitofrontal circumference were in normal ranges. He reached neurodevelopmental milestones in retard when compared to the other sibling of the family.

In physical examination, he had a normal growth. He had a dysmorphic facial appearance including hypertelorism, mild micrognathia. Neurological examination of the patient, who showed irritability and autistic behaviors, was normal.

Hematological, biochemical, and primary metabolic analysis investigations were normal. Brain magnetic resonance imaging and EEG revealed no pathologic finding.

Transferrin isoelectric focusing test which was performed for a preliminary diagnosis of CDG was normal. Whole exome sequence analysis revealed c.254C>T p (Ala85Val) variant in ALG11 gene in a homozygous state, confirming the diagnosis of CDG type 1p. He is now 10 years old, and in the 8-year follow-up period after the diagnosis, gastrointestinal system findings, hearing, and vision problems began to be seen. He also developed unprovoked seizures, which were considered to be associated with ALG11-CDG after 6 years of age. His seizures could be successfully managed with a monotherapy of levetiracetam.

Two different platforms were used for sequencing of the genes for the ALG8 gene; whole exome sequencing was performed using Illumina Nextera Rapid Capture Enrichment on the Illumina NextSeq 50 platform. However, molecular analysis of ALG11 was performed in a private laboratory.

Written informed consent was obtained from parents of the patients. Clinical and demographic characteristics of both patients are given in Table 1.

Discussion

The pathophysiology of ASDs remains unclear; however, genetic defects and multifactorial causes have been reported to play an important role in genetic disorders. There is no standard algorithm for investigation of an IEM among ASD patients; however, different interventional approaches have been described in the medical literature to date. It is recommended to investigate for an IEM starting with the first tier metabolic tests

of plasma (amino acids, total homocysteine, acyl carnitine profile, copper, and ceruloplasmin) and urine (organic acid analysis, purines and pyrimidines, creatine metabolites, oligosaccharides, and glycosaminoglycans) [DM van Karnebeek and Stockler-Ipsiroglu, 2014; Zigman et al., 2021].

The prevalence of IEMs reported among patients with ASD is 2–5% [Kiykim et al., 2016]. As a result, investigation of an underlying IEM should be performed for the differential diagnosis of ASD. CDGs are one of the rarest disorders that have been reported to coexist with ASD among IEM [Albokhari et al., 2022].

Autism is a previously reported clinical finding in many types of CDGs. ALG8-CDG, ALG6-CDG, GALNT2-CDG, DOLK-CDG are CDGs associated with autism [Helander et al., 2013; Morava et al., 2016; Zilmer et al., 2020]. ALG8-CDG is a very rare type of CDG; only about 26 patients have been reported in the literature. Albokhari et al. [2022] described 7 new patients with ALG8-CDG in 2022. Autism was defined as a presenting sign in 5 of these 7 patients. Multiple prenatal abnormalities, prematurity, gastrointestinal symptoms, seizures, ataxia, psychomotor retardation, dysmorphic findings (low-set ears, macroglossia, hypertelorism, pes equinovarus deformity), coagulopathy, increased transaminase levels, and thrombocytopenia were mentioned as main clinical findings [Höck et al., 2015].

ALG11-CDG (CDG type 1p) is a very rare type of CDG; only about 7 patients have been reported in the literature to date. Hypotonia, seizures, developmental retardation, and death by 2 years of age was reported in a patient who showed a similar disease course with hypotonia, generalized epilepsy, and opisthotonus [Rind et al., 2010]. In 3 other patients, severely delayed psychomotor development, mental retardation, and seizures within the first year of life dominated the clinical phenotype. Their communication skills were absent, and social interactions were very limited [Thiel et al., 2012]. A 29-month-old female presented with global developmental delay, hypotonia, and a history of poor weight gain, and a 14-year-old Hispanic male patient with a history of myoclonic epilepsy, global developmental delay, hypertonia, and microcephaly [Haanpaa et al., 2019]. Multidrug resistance, generalized tonic-clonic epilepsy, dystonia, global developmental delay, and microcephaly were the clinical findings of 2 patients [Silver et al., 2021]. In the carbohydrate-deficient transferrin analysis, increased di- and asialo-transferrin and decreased tetrasialotransferrin can be detected. However, in some of the cases, it could be normal [Jaeken and Pe'anne, 2017]. ALG11-CDG has no specific treatment. Nevertheless, studies are being developed in order to find therapeutics. It is obvious that this diagnosis has many unknown aspects, and further research is needed.

On the contrary of the literature, our patient had no seizures, hypotonia, peripheral hypertonia, gastrointestinal system findings, and hearing and vision problems at the time of diagnosis. In the following years, seizures and gastrointestinal symptoms began to appear. In addition, our case is one of the rarest cases of ALG11-CDG reports which highlight autism in the clinical spectrum. Both the ALG8 and ALG11 variants of our patients have been described previously in the literature. But none of them were described in the homozygous state.

We present this case series of two children with CDG to raise awareness among pediatricians and child psychiatrists. CDGs, which are ultra-rare IEMs, should be considered in the differential diagnosis of patients presenting with dysmorphic features and ASD. In addition, autism should be listed among the neurological manifestations of CDG.

Statement of Ethics

Ethical approval was not required for this case report in accordance with local/national guidelines. Written informed consent was obtained from the parent/legal guardian of their patients for publication of the details of their medical case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding for research relevant to this report.

Author Contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. Gozde Uzunyayla-Inci serves as the guarantor for the article. She accepts full responsibility for the work, had access to the data, and controlled the decision to publish. She has been involved in conception, design, analysis, and interpretation of the data, and also drafting of the article. Tanyel Zubarioglu and Cigdem Aktuglu Zeybek have been involved in conception, design, analysis, and

interpretation of the data. Gozde Yesil has been involved in analysis and interpretation of the data. Ertugrul Kiykim has been involved in conception, design, interpretation of the data, and revising the article critically for important intellectual content.

Data Availability Statement

All data generated or analyzed during this study are included in this. Further inquiries can be directed to the corresponding author.

References

Albokhari D, Ng BG, Guberinic A, Daniel EJP, Engelhardt NM, Barone R, et al. ALG8-CDG: molecular and phenotypic expansion suggests clinical management guidelines. J Inherit Metab Dis. 2022;45(5):969–80.

Chantret I, Dancourt J, Dupre T, Delenda C, Bucher S, Vuillaumier-Barrot S, et al. A deficiency in dolichyl-P-glucose:Glc1Man9GlcNAc2-PP-dolichyl alpha3-glucosyltransferase defines a new subtype of congenital disorders of glycosylation. J Biol Chem. 2003;278(11):9962–71.

Cylwik B, Naklicki M, Chrostek L, Gruszewska E. Congenital disorders of glycosylation. Part I. Defects of protein N-glycosylation. Acta Biochim Pol. 2013;60(2):151–61.

Centers for Disease Control and Prevention. Autism spectrum disorder homepage. 2022. Available from: https://www.cdc.gov/ncbddd/autism/screening.html.

Haanpää MK, Ng BG, Gallant NM, Singh KE, Brown C, Kimonis V, et al. ALG11-CDG syndrome: expanding the phenotype. Am J Med Genet A. 2019;179(3):498–502.

Helander A, Stödberg T, Jaeken J, Matthijs G, Eriksson M, Eggertsen G. Dolichol Kinase deficiency (DOLK-CDG) with a purely neurological presentation caused by a novel mutation. Mol Genet Metab. 2013;110(3):342–4.

Höck M, Wegleiter K, Ralser E, Kiechl-Kohlendorfer U, Scholl-Bürgi S, Fauth C, et al. ALG8-CDG: novel patients and review of the literature. Orphanet J Rare Dis. 2015;10:73.

Jaeken J, Pe'anne R. What is new in CDG? J Inherit Metab Dis. 2017;40(4):569–86.

Kiykim E, Zeybek CA, Zubarioglu T, Cansever S, Yalcinkaya C, Soyucen E, et al. Inherited metabolic disorders in Turkish patients with autism spectrum disorders. Autism Res. 2016;9(2):217–23.

Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum disorder. Nat Rev Dis Primers. 2020;6(1):5.

Maenner MJ, Shaw KA, Bakian AV. Prevalence and characteristics of autism spectrum disorder among children aged 8 years. Commonity Report Autism (Internet). 2021. Available from: https://www.cdc.gov/ncbddd/autism/addm-community-report/documents/ADDM-Community-Autism-Report-12-2-021_Final-H.pdf.

Marquardt T, Denecke J. Congenital disorders of glycosylation: review of their molecular bases, clinical presentations and specific therapies. Eur J Pediatr. 2003;162(6):359–79.

Morava E, Tiemes V, Thiel C, Seta N, De Lonlay P, De Klerk H, et al. ALG6-CDG: a recognizable phenotype with epilepsy, proximal muscle weakness, ataxia and behavioral and limb anomalies. J Inherit Metab Dis. 2016;39(5):713–23.

Rind N, Schmeiser V, Thiel C, Absmanner B, Lubbehusen J, Hocks J, et al. A severe human metabolic disease caused by deficiency of the endoplasmatic mannosyltransferase hALG11 leads to congenital disorder of glycosylation-Ip. Hum Mol Genet. 2010;19(8):1413–24.

Silver G, Bahl S, Cordeiro D, Thakral A, Athey T, Mercimek-Andrews S. Prevalence of congenital disorders of glycosylation in childhood epilepsy and effects of anti-epileptic drugs on the transferrin isoelectric focusing test. Genes. 2021;12(8):1227.

Thiel C, Rind N, Popovici D, Hoffmann GF, Hanson K, Conway RL, et al. Improved diagnostics lead to identification of three new patients with congenital disorder of glycosylation-Ip. Hum Mutat. 2012;33(3):485–7.

van Karnebeek CD, Stockler-Ipsiroglu S. Early identification of treatable inborn errors of metabolism in children with intellectual disability: the Treatable Intellectual Disability Endeavor protocol in British Columbia. Paediatr Child Health. 2014;19(9):469–71.

Žigman T, Petković Ramadža D, Šimić G, Barić I. Inborn errors of metabolism associated with autism spectrum disorders: approaches to intervention. Front Neurosci. 2021;15:673600.

Zilmer M, Edmondson AC, Khetarpal SA, Alesi V, Zaki MS, Rostasy K, et al. Novel congenital disorder of O-linked glycosylation caused by GALNT2 loss of function. Brain. 2020;143(4):1114–26.