İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2023;23(3):31-40
DOI: 10.26650/jchild.2023.1345981

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Patients Diagnosed with Congenital Glycosylation Defects: A Rainbow of Inherited Metabolic Disorders

Metabolik Bozuklukların Gökkuşağı: Konjenital Glikozilasyon Defekti Tanılı 11 Vakanın Değerlendirilmesi

Sebile Kılavuz[1,2], Derya Bulut[2], Deniz Kor[2], Berna Şeker Yılmaz[2], Atil Bişgin[3], Fadli Demir[4], Bahriye Atmış[5], Derya Alabaz[6], Neslihan Mungan[2], Mustafa Yılmaz[7]

[1]Marmara University Departmen of Pediatric Metabolism and Nutrition, İstanbul, Türkiye
[2]Çukurova University Departmen of Pediatric Metabolism and Nutrition, Adana, Türkiye
[3]Çukurova University Departmen of Medical Genetics, Adana, Türkiye
[4]Çukurova University Departmen of Pediatric Cardiology, Adana, Türkiye
[5]Çukurova University Departmen of Pediatric Nephrology, Adana, Türkiye
[6]Çukurova University Departmen of Pediatric Infectious Disorders, Adana, Turkiye
[7]Çukurova University Departmen of Pediatric Allergy and Immunology, Adana, Türkiye

ORCID ID: S.K. 0000-0002-7527-2620; D.B. 0000-0002-7527-2620; D.K. 0000-0002-7527-2620; B.Ş.Y. 0000-0003-0425-0341; A.B. 0000-0002-7527-2620; F.D. 0000-0002-7728-1811; B.A. 0000-0002-1133-4845; D.A. 0000-0003-4809-2883; N.M. 0000-0001-7862-3038; M.Y. 0000-0002-6213-8289

Citation/Atıf: Kılavuz S, Bulut D, Kor D, Seker Yilmaz B, Bisgin A, Demir F, et al. Evaluation of patients diagnosed with congenital glycosylation defects: a rainbow of inherited metabolic disorders. Çocuk Dergisi - Journal of Child 2023;23(3):31-40. https://doi.org/10.26650/jchild.2023.1345981

ABSTRACT

Introduction: Congenital glycosylation defects (CDGs) manifest with multisystemic symptoms involving the immune, central nervous, endocrine, and musculoskeletal systems. A total of 137 distinct CDG types have been identified to date.
Materials and Methods: Patients diagnosed with CDG in the Division of Pediatric Metabolism and Nutrition, at Çukurova University, between 2013 and 2019 were included in the study. The patients' files were retrospectively reviewed, and demographic, clinical, laboratory and radiological findings and molecular analyses were recorded and evaluated.
Results: The mean age at diagnosis for a total of 11 (6 Female; 5 Male) patients (Four with PMM2-CDG, one with MPI-CDG, one with DOLK-CDG, one with B4GALT1-CDG, three with TMEM165-CDG, and one with PIGN-CDG) was 6.94 years (ranging from 11 months to 22 years). Amongst the patients, 45% (5 individuals) were male. Sixty-three percent of patients exhibited low weight and height (below the 5th percentile). Elevated liver enzymes were observed in 82% of cases, while 82% showed neurodevelopmental delay, 72% had cerebellar atrophy, and 72% experienced growth retardation. Additionally, 73% of patients displayed hepatomegaly and thrombocytopenia, and 63% had renal involvement. An homozygous p.V129M (c.385G>A) mutation in the PMM2 gene confirmed PMM2-CDG diagnosis in four patients. Furthermore, distinct homozygous mutations were detected: p. I399T (c.1193T>C) in the MPI gene, p. Y441S (c.1322A>C) in the DOLK gene, p. Arg126Cys (c.376C>T) in the TMEM165 gene, a novel p. Tyr239* (c.717T>G) mutation in the B4GALT1 gene, and a novel p. Thr266Ala (c.2356A>G) mutation in the PIGN gene.
Conclusion: CDGs exhibit a diverse clinical spectrum, earning them the moniker "the rainbow" of hereditary metabolic disorders. While PMM2-CDG is the most prevalent subtype, only a few instances of other subtypes have been documented. Inverted nipples and abnormal fat pads are primary features of CDGs. The intricate nature of our cases and the rarity of DOLK-CDG, PIGN-CDG, and TMEM-165-CDG diagnoses stand out as notable aspects of this report.

Keywords: glycosylation, congenital glycosylation defects, PMM2, MPI, DOLK, TMEM-165, PIGN, CDG

ÖZ

Giriş: Konjenital glikozilasyon kusurları (CDG), immün, merkezi sinir, endokrin ve kas-iskelet sistemlerini içeren multi sistemik belirtilerle ortaya çıkar. Bugüne kadar toplamda 137 farklı CDG türü tespit edilmiştir.
Materyal ve Metod: Çukurova Üniversitesi Çocuk Metabolizma ve Beslenme Bilim Dalı'nda 2013 ve 2019 yılları arasında takip edilen ve CDG tanısı alan hastalar çalışmaya dahil edildi. Hastaların kayıtları geriye dönük olarak incelendi ve demografik klinik, laboratıvar ve radyolojik bulguları kayıt edilerek değerlendirildi.
Bulgular: Toplam 11 hastanın (Dört PMM2-CDG, bir MPI-CDG, bir DOLK-CDG, bir B4GALT1-CDG, üç TMEM165-CDG ve bir PIGN-CDG) tanı anındaki ortalama yaşları 6.94 yıl (11 ay ile 22 yıl arası) idi. Hastaların %45'i (5 kişi) erkekti. Hastaların %63'ünde ağırlık ve boy, 5. persentilin altında bulunmaktaydı. %82'sinde yüksek karaciğer enzimleri, %82'sinde nörogelişimsel gecikme, %72'sinde serebellar atrofi ve %72'sinde büyüme geriliği gözlendi. Ek olarak, hastaların %73'ünde hepatomegali ve trombositopeni, %63'ünde ise böbrek tutulumu tespit edildi. PMM2 genindeki homozigot p.V129M (c.385G>A) mutasyonu, 4 hastada PMM2-CDG tanısını doğruladı. Ayrıca, MPI geninde p. I399T (c.1193T>C) homozigot mutasyonu, DOLK geninde p. Y441S (c.1322A>C) homozigot mutasyonu, TMEM165 geninde p. Arg126Cys (c.376C>T) homozigot mutasyonu, B4GALT1 geninde novel bir p.Tyr239* (c.717T>G) mutasyonu ve PIGN geninde novel bir p. Thr266Ala (c.2356A>G) mutasyonu tespit edildi.
Sonuç: Konjenital glikozilasyon defektleri çeşitli klinik spektruma sahip olup, onları "genetik metabolik bozuklukların gökkuşağı" olarak adlandırmamıza sebep olmaktadır. Çalışmamızda PMM2-CDG en yaygın görülen tip iken, diğer tiplerden sadece birkaç örnek bulunmaktadır. Konjenital glikozilasyon defektlerinin ana özellikleri arasında ters meme uçları ve anormal yağ yastıkçıkları yer almaktadır. Vakaların karmaşıklığı ve DOLK-CDG, PIGN-CDG ve TMEM-165-CDG tanılarının nadirliği, bu araştırmanın dikkat çeken yönlerini oluşturmaktadır.

Anahtar Kelimeler: glikozilasyon, konjenital glikozilasyon kusurları, PMM2, MPI, DOLK, TMEM-165, PIGN, CDG

Corresponding Author/Sorumlu Yazar: Sebile Kılavuz **E-mail:** dr.skilavuz@gmail.com

Submitted/Başvuru: 18.08.2023 • **Revision Requested/Revizyon Talebi:** 18.07.2023 • **Last Revision Received/Son Revizyon:** 01.09.2023 • **Accepted/Kabul:** 01.09.2023 • **Published Online/Online Yayın:** 24.12.2023

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INTRODUCTION

Congenital Glycosylation Defects (CDG), first described by Belgian paediatrician Jaak Jaeken in 1980, exhibit multisystem involvement and are named after the abnormalities observed in the separation of transferrin isoforms (1). Almost all inherited disorders in glycan biosynthesis have been identified in the last 20 years, and approximately 137 types of CDG's have been classified to date. CDGs are a group of rare disorders presenting with clinically and biochemically heterogeneous features affecting numerous organ systems (2). They arise from defects in synthesising glycans of glycoproteins and glycolipids and the attachment of proteins and lipids. Whilst some disorders affect only one glycosylation pathway, others can impact multiple pathways simultaneously. Disorders can arise from defects in sugar activation, presentation, and transport; abnormalities in glycosidase and glycosyltransferase enzymes; disruptions in golgi homeostasis; and regulations of protein glycosylation. CDGs are categorised into groups based on their effects on N-glycosylation (31 types), O-glycosylation (34 types), lipid and GPI glycosylation defects (25 types), and multiple glycosylation pathways (47 types). Additionally, deglycosylation defects like NGLY1-CDG have also been identified. According to the new classification, CDGs are named with mutated genes (e.g., MPI-CDG) (1).

In undefined clinical conditions, when neurological and multiorgan involvement are accompanied by developmental delay, CDG should be considered. Transferrin isoelectric focusing (TIF) can be used as a diagnostic method. However, it should be noted that TIF can diagnose only a limited number of CDG types, especially those associated with sialic acid deficiencies (3). Partial deficiencies in sialic acid result in two types of cathodal shifts: Type 1 and Type 2 patterns. If a Type 1 pattern is detected, based on clinical findings, PMM2-CDG or MPI-CDG should be considered initially. If these diseases are not identified, dolichol-associated glycan analysis, direct mutation analysis targeting known CDG genes, or whole exome sequencing/whole genome sequencing (WES/WGS) analysis should be performed. In cases of Type 2 patterns, a defect in the glycan pathway at an advanced stage may be encountered. Protein-associated glycan analysis, CDG gene panel, or WES/WGS analysis should be considered. Additionally, the level of apolipoprotein C-III is an important laboratory parameter that specifically detects O-glycosylation disorders (4).

N-glycosylation disorders affect multiorgan systems, particularly eyes, hepatic and immune systems, and central and peripheral nervous systems. The general and diverse nature of clinical features complicates the ability of clinicians to diagnose CDG. Developmental delay, hypotonia, coagulation disorders, impaired brain development, and endocrine abnormalities can also accompany the condition (5).

N-glycosylation defects are classified into two types; CDG type 1 (CDG-1) may develop due to disruptions in lipid-linked oligosaccharide or protein transfer or processing in one or both N-glycans. CDG Type 2 (CDG-2) arises from the abnormal processing of incompletely attached glycan to proteins (1). A Total of 133 genes are implicated in CDG, with 177 different clinical phenotypes (5).

MATERIALS AND METHODS

Patients diagnosed with CDG and followed-up in the Division of Pediatric Metabolism and Nutrition, at Çukurova University, between 2013 and 2019 were included in the study. The study was approved by the Ethics in Research Committee of Çukurova University Faculty of Medicine, Adana, Türkiye (approval number: 2019/04-10). Written informed consent was taken from all patients' legal representatives. The patients' files were retrospectively reviewed, and demographic, clinical, laboratory and radiological findings and molecular analyses were recorded and evaluated.

Results: The mean age of diagnosis for the total of 11 patients (four with PMM2-CDG, one with MPI-CDG, one with DOLK-CDG, one with B4-GALT1-CDG, three with TMEM165-CDG, and one with PIGN-CDG) was 6.94 years (11 months to 22 years) (Table 1, Table 2). Forty-five percent of the patients were male, and 91% had consanguineous parents. Sixty-three per cent (63%) of patients exhibited low weight and height (below the 5th percentile). Liver enzyme elevation was observed in 82% of patients, neurodevelopmental delay in 82%, cerebellar atrophy in 72%, and growth retardation in 72%. Additionally, 73% of patients had hepatomegaly, 63% had thrombocytopenia, and 63% had renal involvement. Two siblings and one cousin of our eleven patients had similar complaints and sadly died before a confirmed diagnosis (Figure 2, Table 1). Among the 11 patients, PIGN-CDG and TMEM165-CDG (18%) patients had died: one due to cardiac and respiratory failure and the other due to sepsis and kidney failure, respectively. Individuals with each CDG were described in the case presentation section.

Case presentations:

PMM2-CDG cases (Phosphomannomutase-2 Deficiency)

Case 1: A 7.5-year-old girl was delivered at full term with a birth weight of 2010 g via normal spontaneous vaginal delivery (NSVD). At three months of age, she was referred to a paediatrician due to her inability to control her head and developmental delay. During investigations, a grade 1/6 systolic murmur was detected upon auscultation, and an echocardiogram (ECHO) unveiled pericardial effusion. When she reached six months of age, approximately 80 cc of serohemorrhagic fluid was percutaneously drained from the subxiphoid region—seizures begun at one year old, leading to the initiation of levetiracetam treatment. By age three, hemophagocytic lymphohistiocytosis (HLH) was considered bicytopenia, and bone marrow aspirate results emerged. Treatment with intravenous immunoglobulin and dexamethasone was initiated. At four years old, ureteropelvic dilatation was evident in a urinary ultrasonography (USG). Frequent lower respiratory tract infections necessitated hospitalisation twice a month. The patient's parents were consanguineous, and her cousin displayed similar clinical features.

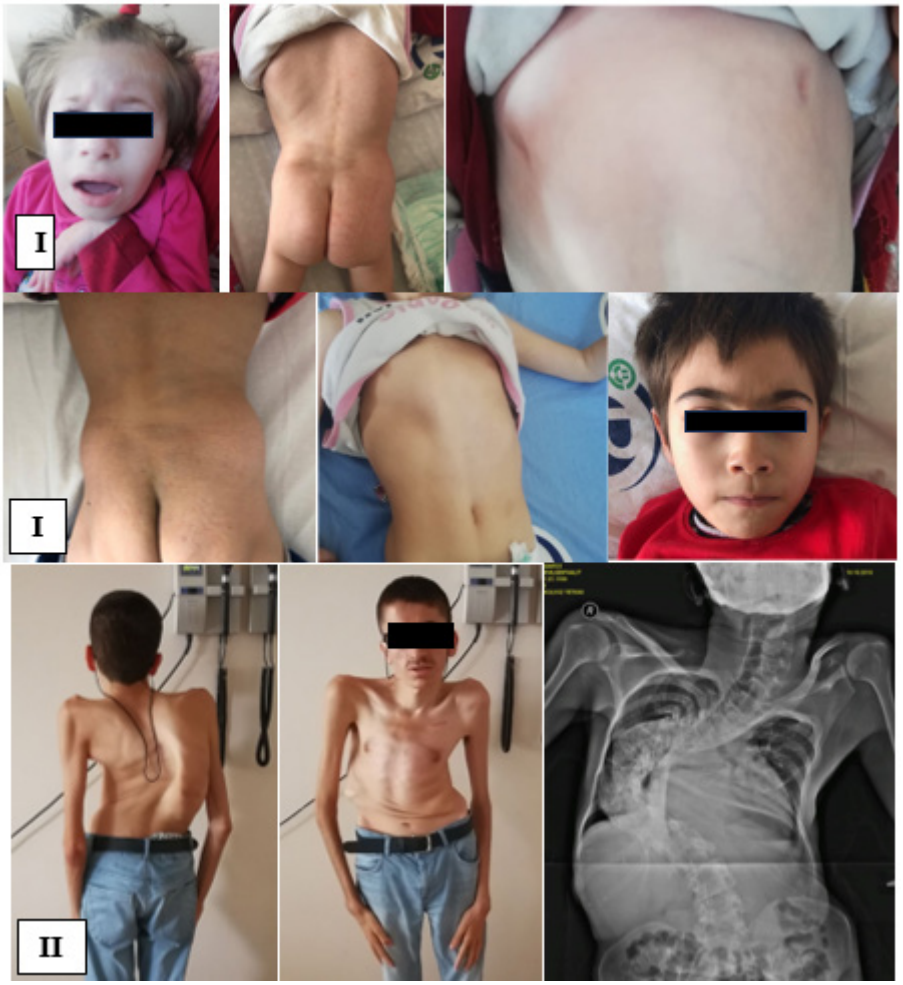


Figure 1: Clinical features of selected CDG cases. I-II. Dysmorphic facial features, abnormal fat pads, inverted nipples of patients with PMM2-CDG [case 1 and 2] III. Dysmorphic facial appearance of Case 8 with PIGN-CDG and his kyphoscoliosis on X-ray.

Upon physical examination, her weight measured 9800 g (<5th percentile), and her height was 82 cm (<5th percentile). She was able to smile and recognise her mother. However, she was confined to a wheelchair, and deep tendon reflexes (DTR) in all four extremities were diminished. Her fingers were slender and elongated, displaying inverted nipples, abnormal fat pads, and pectus carinatum (Figure 1-I). Axial hypotonia and strabismus were notable findings. A fundus examination unveiled retinal atrophy, macular fibrosis, and optic disc pallor in her right eye. Laboratory assessments indicated thrombocytopenia, neutropenia, and low protein S levels, while aspartate transaminase (AST), alanine transaminase (ALT), and prolactin levels were elevated. The coagulation profile appeared normal. Based on the prevailing clinical and laboratory findings, TIF analysis demonstrated a decrease in penta- and tetrasialotransferrin fractions, coupled with an increase in disialo- and asialotransferrin fractions, consistent with the pattern of type 1 CDG. Echocardiography (ECHO) uncovered both pericardial effusion and a significant patent foramen ovale. Further auditory tests exhibited bilateral sensorineural hearing loss.

Case 2: A 5-year-old girl, the cousin of case 1, was admitted to the hospital due to neurodevelopmental delay and recurring lower respiratory tract infections. She was born at full term with a weight of 2900 g via NSVD. Her parents were consanguineous. During the physical examination, her weight was 5200 g (<5th percentile), and her height was 98 cm (<5th percentile). Strabismus, inverted nipples, abnormal fat pads, pectus carinatum, and mongolian spots were evident (Figure 1-II). She was hypotonic but could control her head and sit with support. Abdominal examination indicated hepatomegaly. Laboratory assessments revealed thrombocytopenia, neutropenia, elevated liver enzymes and prolactin levels. Her coagulation profile was normal, but serum protein S levels were notably low. An ECHO displayed left ventricular dilatation alongside mild mitral and aortic valve regurgitation. Abdominal USG supported the hepatomegaly and showed increased parenchymal echogenicity in both kidneys and the liver. Electromyography (EMG) revealed signs of neurogenic involvement, while cranial magnetic resonance imaging (MRI) demonstrated cerebellar atrophy.

Case 3: A 3-year-old male was delivered at term via cesarean section (C/S) with a birth weight of 4000 grams to

consanguineous parents. A Dandy-Walker malformation had been identified during the neonatal period. Family history revealed a previously deceased 13-year-old sister with similar findings. At three months, he was referred to our clinic for neuromotor regression. His height was 10.2 kilograms (<5th percentile), while his height measured 83 centimetres (<5th percentile), with prominent microcephaly. His physical exam findings were inverted nipples and abnormal fat pads. Strabismus was noted, along with axial hypotonia and diminished DTRs. Biochemical tests yielded normal results. Cranial MRI showed severe cerebellar atrophy, an enlarged fourth ventricle, a cystic appearance within the posterior fossa, and a confirmed Dandy-Walker malformation.

Case 4: A 1.5-year-old male was born at full term via C/S, weighing 2800 g at birth. At postnatal ten days, he was admitted to the emergency room (ER) due to feeding difficulties and somnolence, and thrombocytopenia and hypoglycemia were detected in lab tests. Pericardial effusion was detected at age four months after a respiratory infection. On admission, he had growth retardation, developmental delay, microcephaly, hypotonia with diminished DTRs, hepatomegaly, inguinal hernia, inverted nipples, and a large Mongolian spot on physical examination. Laboratory tests showed thrombocytopenia, hypertriglyceridemia, hypercholesterolemia, and a prolonged coagulation profile. Abdominal USG indicated hepatomegaly (103 mm), splenomegaly (82 mm), and grade 2 hyperechogenicity within liver parenchyma and both kidneys. Cranial MRI showed cerebellar hypoplasia, and ECHO demonstrated the presence of pericardial effusion. TIF analyses were abnormal with a Type 1 pattern, suggesting PMM2-CDG. Molecular analysis showed a pathogenic homozygous p.Val129Met (c.385G>A) variant in PMM2, confirming the diagnosis.

Case 5: A 6.5-year-old female was born at term via NSVY with a birth weight of 3500 g. Multicystic dysplastic kidneys were detected at age eight months. She was hospitalised at 9 months of age for fatigue, poor feeding, vomiting, and short myoclonic seizures associated with hypoglycemia, and carbamazepine treatment was initiated for seizures. Hypoglycemia-related tests during the seizure showed high blood ketones and lactate, low cortisol, and abnormal liver function tests. Parents were consanguineous, and a cousin was reported to have similar findings. Physical examination showed a weight of 18 kg (5-10th percentile) and a height of 109 cm (<5th percentile). Her neurological and other system examinations were normal. She could walk independently. Laboratory tests revealed high liver enzymes, low blood sugar levels, a normal coagulation profile, and a normal hemogram. Spot urine protein-to-creatinine ratio was normal. Abdominal USG showed increased liver dimension (117 mm), granular appearance of the liver parenchyma, and multicystic dysplastic kidneys. Voiding cystourethrography revealed vesicoureteral reflux. The left kidney was compensatively hypertrophic in addition to the bladder dysfunction. DMSA scan indicated a non-functioning right kidney. EEG showed generalised slow vawe activities. The molecular analysis detected a pathogenic homozygous p.

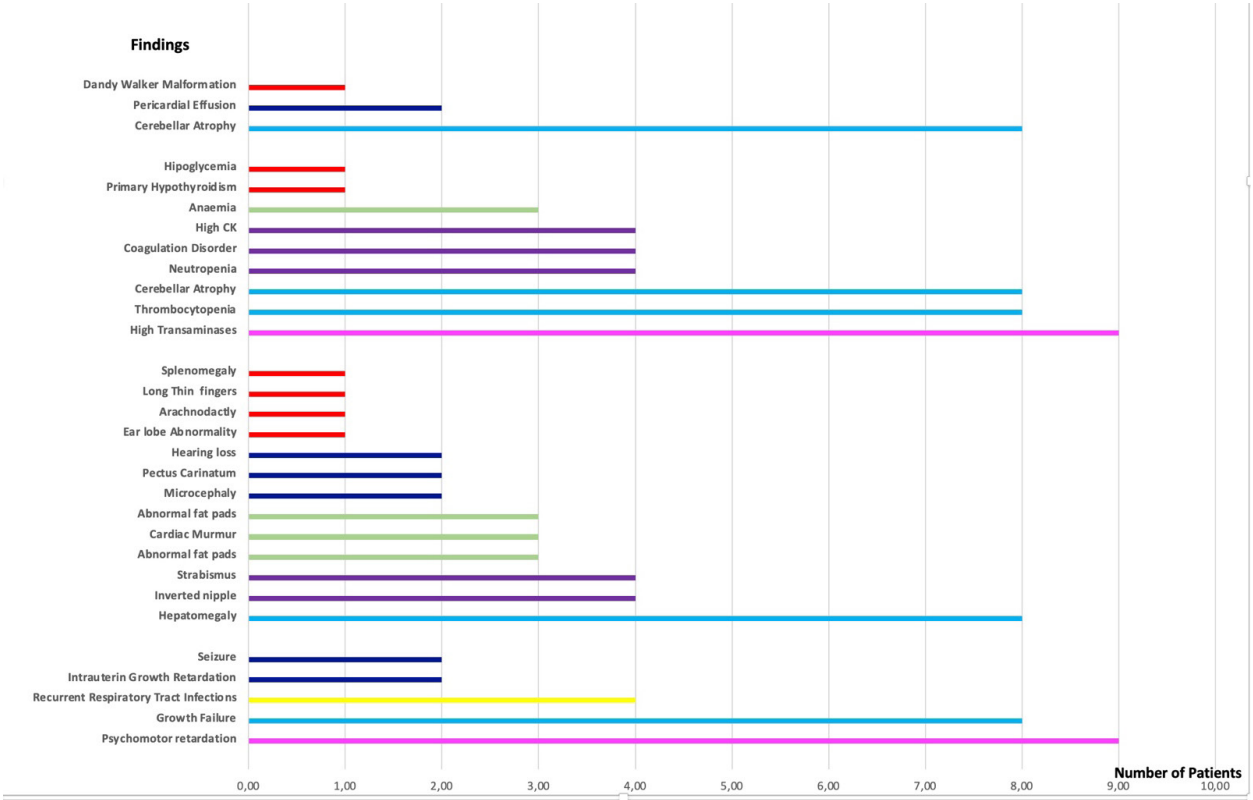


Figure 2: Distribution of Clinical, Physical Examination, Laboratory, and Radiological Findings in 11 Patients Diagnosed with Congenital Glycosylation Defects

Table 1: CDG: Congenital Glycosylation Defect, VUS: Variant of Uncertain Significance p: Percentile.

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Diagnosis	PMM2-CDG	PMM2-CDG	PMM2-CDG	PMM2-CDG	MPI-CDG	DOLK-CDG	B4-GALT1-CDG	PIGN-CDG	TMEM165-CDG	TMEM165-CDG	TMEM165-CDG
Age at diagnosis (Years)	7.5	5	3	1.5	6.5	0.91	17	23	3	8	0.91
Intrauterin Growth Retardation	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO
Recurrent Lower Respiratory Tract Infections	YES	YES	NO	NO	NO	NO	YES	NO	YES	NO	NO
Seizure	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
Neuromotor Regression	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES
Growth Failure	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	NO
Weight <5p	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	NO
Height <5p	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	NO
Microcephaly	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO
Strabismus	YES	YES	YES	NO	NO	NO	YES	NO	NO	NO	NO
Pectus Carinatum	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Arachnodactyly	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Inverted nipples	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO
Abnormal fatty pads	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO
Hepatomegaly	YES	YES	NO	YES	YES	NO	NO	YES	YES	YES	YES
Splenomegaly	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO
Cardiovascular System Abnormality	NO	YES	NO	NO	NO	YES	NO	YES	NO	NO	NO
Hearing Loss	Sensorineural	NO	NO	NO	NO	Sensorineural	NO	NA	NO	NO	NO
Anemia	YES	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Neutropenia	YES	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO
Thrombocytopenia	YES	YES	NO	YES	NO	YES	YES	NO	YES	YES	YES
Coagulation Disorders	NO	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Creatin Kinase Elevation	NO	NO	NO	NO	NO	NO	NO	YES	YES	YES	YES
Elevated Liver Enzymes	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES
Hypothyroidism	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Hypoglycemia	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
Anemia	YES	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO
Neutropenia	YES	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO
Hipothyroidism	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Renal Involvement	NO	YES	NO	YES	YES	NO	NO	YES	YES	YES	YES
Pericardial Effusion	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Cerebellar Atrophy	YES	YES	YES	YES	NO	NO	YES	NO	YES	YES	YES
Dandy Walker Malformation	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO
Gene	*PMM2*	*PMM2*	*PMM2*	*PMM2*	*MPI*	*DOLK*	*B4-GALT1*	*PIGN*	*TMEM165*	*TMEM165*	*TMEM165*
Genotype											
Zygosity	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Mutation Class	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	VUS	VUS	Pathogenic	Pathogenic	Pathogenic
Known/Novel	Known	Known	Known	Known	Known	Known	Novel	Novel	Known	Known	Known

Evaluation of clinical findings, physical examination, laboratory, radiological findings, and genetic analyses of patients diagnosed with CDG.

Ile399Thr (c.1193T>C) variant in *MPI*, leading to the diagnosis of MPI-CDG.

Case 6: A 6-month-old patient was delivered to non-consanguineous parents at 37 gestational weeks via C/S, weighing 1900 grams at birth. Due to her low birth weight, she was hospitalised. Poor sucking and hypotonia were observed at follow-up. Parents reported watery mucoid stools 8-9 times per day, coupled with failure to thrive since birth. At age one month, she was hospitalised for three months in the intensive care unit (ICU) for intractable fever, septicemia, and dehydration. Following a BCG (Bacille Calmette-Guerin) vaccination, she developed a fever and hypotonia. At five months of age, she was hospitalised again due to diarrhoea, vomiting, and poor weight gain. Her weight measured 3640 grams (<5th percentile), height was 58 cm (<5th percentile), and head

Table 2. CDG (Congenital Glycosylation Defect) Subtypes Observed in Our Patients and their Transferrin Isoelectric Focusing (TIF) Pattern.

Name	Type of Disorder	Clinically Affected Organ and Tissue	Defective Protein	TIF
MPI-CDG	Protein N-Glycosylation Disorder	Intestine, Liver	Mannose 6-phosphate isomerase	**Type 1**
PMM2-CDG	Protein N-Glycosylation Disorder	Nervous system, Adipose tissue, and almost all organs	Phosphomannomutase 2	**Type 1**
DOLK-CDG	Disorders in Multiple and other Glycosylation Pathways (Disorders in Dolichol Synthesis)	Brain, Heart, Skin	Dolikol Kinaz	**Type 1**
B4GALT1-CDG	Disorders in Glycosyltransferase Enzymes	Face (dysmorphic), eyes (myopia)	B-1,4-galactosyltransferaz	**Type 2**
TMEM165-CDG	Others	Brain, Skeleton (especially cartilage), Joints, Heart, Liver, Kidneys	Transmembrane protein 165	**Type 2**
PIGN-CDG	Disorder in Glycosylphosphatidylinositol Synthesis	Brain, Skeleton (palate, fingers), Cardiovascular system, Kidneys	Glycosylphosphatidylinositol ethanolamine phosphate transferaz 1	-

circumference was 38 cm (<5th percentile). A large anterior fontanelle was noticeable, although no facial dysmorphia was identified. Abdominal examination unveiled hepatomegaly. She exhibited axial hypotonia and lacked head control. A grade 2/6 murmur was found during her cardiovascular examination. Her feeding difficulties led her to be brought to the pediatric emergency department (ED). There, elevated transaminases (AST: 1100 U/L, ALT: 800 U/L) and an abnormal coagulation profile (INR: 2.69) were identified, prompting her subsequent hospitalisation.

Over time, her liver enzymes normalised, but neutropenia emerged. Given this neutropenia (25000/mm3), bone marrow aspiration was performed, revealing a lack of mature neutrophils. Considering these findings, Kostmann syndrome was suspected, but no mutation was detected in the HAX1 gene.

At thirteen months, she was readmitted to the hospital due to fever, diarrhoea, vomiting, and lethargy. Laboratory analyses showed a white blood cell count of 4500/mm3 and an absolute neutrophil count of 100/mm3. Her coagulation profile indicated prolonged PT, APTT, INR, and low fibrinogen levels. Echocardiography unveiled an atrial septal defect. Electromyography (EMG) yielded normal results, and cranial MRI displayed bilateral periventricular white matter hyperintensities consistent with hypoxic-ischemic encephalopathy. Hearing tests indicated sensorineural hearing loss. A subsequent bone marrow aspiration depicted a bone marrow rich in medullary cells with a normal megakaryocytic series within age-appropriate limits. The majority of granulocytic cells were in the myelocytic phase, displaying insufficient lobulation in mature forms. The bone marrow aspiration disclosed arrested granulopoiesis.

Metabolic tests returned normal results. However, during her stay in the ICU, the patient's clinical condition continued to deteriorate due to multi-organ failure following septicemia. INR and liver enzyme levels increased, and severe metabolic acidosis ensued. Unfortunately, the patient ultimately passed away due to multi-organ failure.

Postmortem whole exome sequencing (WES) later unveiled a previously known homozygous p. Tyr441Ser (p.Y441S) (c.1322A>C) mutation in the DOLK gene, ultimately confirming the diagnosis of DOLK-CDG after the patient passed away.

Case 7: A nineteen-year-old female was born to consanguineous parents at 37 GW, weighing 2700 gr. At one month of age, she was admitted to the hospital due to failure to thrive and pneumonia. During hospitalisation, elevated liver enzyme levels were detected, sparking suspicion of hepatitis. Additionally, levothyroxine treatment was initiated for primary hypothyroidism. She experienced multiple hospitalisations throughout her childhood due to recurring lower respiratory tract infections. By age five, she was diagnosed with neutropenia during a hospital stay. An eye examination revealed high myopia, restricted outward movement of the left eye, and amblyopia and proptosis. Furthermore, recurrent aphthous lesions were observed in both oral and anal regions.

Laboratory analyses indicated intermittent low absolute neutrophil counts, thrombocytopenia, anaemia, and fluctuating transaminase levels. Brain and orbital MRI results demonstrated mild left cerebellar and vermian hypoplasia, a retro sellar arachnoid cyst, and bilateral frontal subcortical lesions. Whole exome sequencing (WES) analysis brought to light a novel homozygous p.Tyr239* (c.717T>G) mutation

within the B4GALT1 gene. This discovery conclusively led to the diagnosis of B4GALT1-CDG.

Case 8: A twenty-three-year-old male was investigated for fatigue and muscle weakness in his legs at age ten. He was eventually referred to our care at seventeen due to kyphoscoliosis and elevated liver enzymes. The onset of scoliosis was noted at seven years old. He had recurrent episodes of elevated creatine kinase levels, during which he reported passing dark brownish-coloured urine. His parents were consanguineous. Physical examination revealed a weight of 39.7 kg (<5th percentile), and a height of 151.5 cm (<5th percentile). He exhibited facial dysmorphia, a high palate, and severe kyphoscoliosis (Figure 1-III). Intellectual disability was also evident. During cardiovascular assessment, a grade 2/6 murmur was detected. He displayed intermittent elevations in AST, ALT (peaking at 1600-1800 U/L), and CK levels (reaching a maximum of 1000 U/L). Cranial MRI yielded normal results, while cervical, thoracic, and lumbar MRIs displayed severe kyphoscoliosis, intact vertebral bodies, and spinal cord. Abdominal USG indicated hepatomegaly (18 cm), liver and renal parenchymal disease, and mild pelvicaliectasia in the right kidney. A muscle biopsy further revealed vacuolar myopathy. His eyes exhibited macular degeneration, and electromyography (EMG) displayed myogenic involvement. An echocardiography uncovered a left ventricular wall abnormality, global posterior lateral wall hypokinesia, left ventricular hypertrophy, mild aortic and tricuspid valve regurgitation, moderate mitral regurgitation, left ventricular systolic dysfunction, and noncompaction cardiomyopathy. His ejection fraction was measured at 36%. Cardiac MRI findings indicated global and segmental impairments in left ventricular function, high basal left ventricular myocardial mass, dilation, and moderate mitral regurgitation. Consequently, a cardiac pacemaker was implanted. Whole exome sequencing (WES) unveiled a homozygous, previously unknown p.Thr266Ala (c.2356A>G) mutation in the PIGN gene, resulting in the diagnosis of PIGN-CDG. Unfortunately, functional studies were not conducted, as the patient's condition deteriorated and she ultimately died.

Case 9: A three-year-old female patient was born at term, weighing 3200 grams. At one year of age, she was hospitalised two times due to hypotonia, polyuria, polydipsia, electrolyte imbalance, and pneumonia. She was admitted to the intensive care unit due to respiratory failure and stayed on mechanical ventilation for one week. She developed Candida pneumonia. Her motor and mental development was consistently delayed. She gained head control at the age of two. Currently, she is able to sit with support and is unable to speak.

Case 10: An eight-year-old male patient was born at term, weighing 2750 grams, via NSVY. He was hospitalised for three days in the NICU due to meconium aspiration syndrome. Frequent hospital admissions occurred due to growth retardation and neurodevelopmental delay. He underwent surgery for pes equinovarus. She could walk with support and was unable to speak.

Case 11: An eleven-month-old male patient was born at term, weighing 2900 grams, via NSVY. At two months old, he was hospitalised due to vomiting and electrolyte imbalance. Sodium, potassium, and magnesium supplementation were needed for the electrolyte imbalance. Chronic renal failure developed after a pyelonephritis attack (Candida spp.). He passed away at two years of age due to sepsis and kidney failure.

Cases 9, 10, and 11 were siblings and presented facial dysmorphia, a long philtrum, a high palate, and long eyelashes. Hypotonia and hepatomegaly were prominent findings. Their visual, auditory, and cardiological examinations were normal. Unlike the others, case 10 had contractures in both elbows, restricted movement, and short 3rd, 4th, and 5th toes.

Laboratory analyses showed elevated AST, ALT, and CK levels, electrolyte imbalance (hypokalemia, hyponatremia, hypophosphatemia), coagulation disorders, and metabolic alkalosis in the blood gases. Urine protein/creatinine ratios were high. Case 11 also had elevated plasma creatinine levels. Epiphyseal, metaphyseal, and diaphyseal dysplasia were observed in all X-rays. Abdominal USG revealed hepatomegaly, nephrolithiasis, and minimal hydronephrosis.

Case 10 had grade 2 renal parenchymal disease on renal ultrasonography and bilateral diffuse reduced parenchymal activity on the DMSA scan. Cranial MRIs showed cerebellar hypoplasia and a widening of the subarachnoid space. Patients required high doses of sodium, potassium, and magnesium. Muscle biopsy results showed variable muscle size under hematoxylin and eosin (HE) staining. Increased lipid droplets were noted in type 1 muscle fibres with HE staining. TIF results indicated a Type 2 pattern.

WES analysis identified a homozygous pathogenic p.Arg126Cys (c.376C>T) mutation in the TMEM165 gene in Case 9. Both parents were heterozygous carriers for the same mutation. The same mutation was found homozygous in the other two siblings.

DISCUSSION

Congenital disorders of glycosylation generally present with multisystemic involvement (6). Similar to other inherited metabolic disorders, the age of symptom onset and clinical phenotypes vary from mild to severe (6, 7). Most CDG patients may exhibit findings associated with early-onset neurovisceral phenotypes since birth. Detailed clinical evaluation can reveal craniofacial dysmorphisms, growth retardation and a history of non-immune hydrops fetalis during pregnancy, which can guide advanced biochemical and molecular analyses (8). Patients in our study consisted of different CDG types (Table 2), and ages of diagnosis ranged from 11 months to 23 years. In our study, early diagnosis of PMM2-CDG patients were made possible on account of using TIF and single gene analysis due to pericardial effusion, inverted nipples, and abnormal fat pads. The diagnosis age of PMM2-CDG patients ranged from 1.5 to 7.5 years. PMM2-CDG is the most common type of CDG. The severity of

enzyme deficiency and other unidentified factors contribute to a broad clinical spectrum of the disease. While some cases might not exhibit developmental delay, others might exhibit severe developmental delay. Axial hypotonia, hyporeflexia, abnormal eye movements, strabismus, retinitis pigmentosa, stroke-like symptoms, epilepsy, microcephaly, macrocephaly, olivopontocerebellar hypoplasia, peripheral neuropathy, and myopathy might also be observed. Cerebellar involvement is the most consistent finding (9). Cerebellar atrophy was detected in all of our patients. Many patients may exhibit abnormal fat pads, inverted nipples, and arachnodactyly. Abnormal fat distribution may disappear with age. The abnormal fat pads in cases 1 and 2 were very pronounced (Figure 1-I, Figure 1-II). Mild cases may not exhibit dysmorphic features. Endocrine disorders and thrombotic complications might also occur. Many patients can survive into the adulthood period (9).

In our study, PMM2-CDG-diagnosed patients (25%) had epilepsy. While Yılmaz and colleagues observed epilepsy in 36% of their cases (10), this rate was 50% in the French cohort (11). Our patients had psychomotor developmental delay and cerebellar atrophy in cranial MRI. Hepatomegaly was presented in 3/4 of patients, and elevated liver enzymes were presented in 2/4 of PMM2-CDG patients. The frequency of sensorineural hearing loss in PMM2-CDG- patients has been reported to range from 3% to 33% (10, 12, 13). Kasapkara and colleagues reported sensorineural hearing loss in a patient with a similar mutation to our PMM2-CDG-diagnosed patients (14). We also detected sensorineural hearing loss in one of our patients. The most common mutation reported in the literature was c.422G>A (R141H), while the homozygous p.V129M (c.385G>A) mutation was detected in 4 of our patients, possibly due to a regional effect.

In our study, one patient was diagnosed with MPI-CDG (Phosphomannose isomerase deficiency) (CDG-Ib). So far, at least 35 patients have been diagnosed with MPI-CDG. Similar to the literature, our patient did not exhibit any central nervous system involvement, had no dysmorphisms, and was diagnosed while being investigated for intermittent elevated liver enzymes and hypoglycemia. Vomiting, bleeding diathesis, protein-losing enteropathy, recurrent thrombosis, hypoglycemia, liver fibrosis, and symptoms of hypoglycemia (hyperinsulinemic and normoinsulinemic) can lead to expansion of the biliary tract. Treatment can include mannose, liver transplantation, and heparin (15). Our patient's clinical condition remained stable with mannose treatment without hypoglycemic attacks. Cases similar to ours have been described in the literature, and these patients were also diagnosed with polycystic kidney and microcystic changes in the kidney (16, 17).

Regarding DOLK-CDG (CDG-Im), dolichol kinase deficiency catalyses the final step of dolichol phosphate synthesis due to dolichol kinase deficiency (18). Dolichol kinase deficiency is associated with a severe clinical phenotype. Approximately 18 patients have been described to date (19). Patients can exhibit varying cardiac findings, such as dilated cardiomyopathy, neurological findings, especially epilepsy, ichthyosis, hair and eyebrow loss, and dysmorphia. Our patient had died due to severe pulmonary infection at six months of age, similar to other infantile cases in the literature (20). Another research article detailed the cases of two patients of Turkish origin who shared the same homozygous p. Tyr441Ser mutation as in our case. Tragically, these patients succumbed to infections at seven and four months, respectively. Notably, our patient did not exhibit dilated cardiomyopathy, a typical feature often reported in the literature.

Furthermore, an atrial septal defect was identified in our patient's ECHO (21). Cases have been documented in the literature wherein individuals presented with symptoms of heart failure, neutropenia, recurrent infections, and microcytic anaemia. The disease pathogenesis was characterised by a disruption in leukocyte production and differentiation (22). In Case 8, bone marrow aspiration revealed a defect in lymphocyte differentiation, initially prompting consideration of Kostmann syndrome; however, no genetic mutation could be identified. Regrettably, our patient passed away due to liver failure following recurrent infections, ultimately leading to multi-organ failure.

B4GALT1-CDG (also known as CDG-IId), which stands for β-1, 4-galactosyltransferase deficiency 1, is a subtype of CDG known for its pronounced cerebellar atrophy (23). Case 7 exhibited mild cerebellar vermian hypoplasia. Alongside fluctuating neutropenia and liver enzyme levels, a significant clinical feature was short stature. The mutation identified in Case 7 (p.Tyr239* or c.717T>G) was not previously documented in the ClinVar database. B4GALT1-CDG can manifest with developmental delay, hypotonia, thrombosis, stroke, coagulation disorders, elevated creatine kinase levels, and prolonged APTT. Notably, macrocephaly and the coincidental presence of Dandy-Walker Malformation are also possible occurrences. (24, 25).

PIGN-CDG, recognised as Multiple Congenital Anomaly-Hypotonia-Seizure Syndrome 1, is characterised by various manifestations. These include dysmorphism, cardiac anomalies like PDA, PFO, and ASD, respiratory system findings such as lung hypoplasia and diaphragmatic hernia, as well as anal stenosis, imperforate anus, hydronephrosis, hydrocele, dysplastic kidneys, vesicoureteral reflux, bladder trabeculation, gastroesophageal reflux, seizures, hypotonia, intellectual disability, psychomotor retardation, spasticity, tremors, cerebral atrophy, cerebellar atrophy, hyporeflexia, hyperreflexia, and choreoathetosis. Although epilepsy commonly presents in PIGN-CDG patients, its absence in our case was notable. Case 7 displayed intermittent elevation of liver enzymes, episodes of rhabdomyolysis, cardiac involvement, psychomotor retardation, and severe kyphoscoliosis. (26, 27). The literature also reports another patient diagnosed with PIGN-CDG with moderate kyphoscoliosis (28).

TMEM165-CDG (also known as CDG IIk) originates from a genetic disorder involving transmembrane protein 165. Its clinical presentation may encompass short stature, growth retardation, failure to thrive, microcephaly, dysmorphic

features, midfacial hypoplasia, ocular abnormalities, dysplastic ribs, hepatomegaly, feeding difficulties during infancy, psychomotor retardation, seizures, abnormalities in white matter, thrombocytopenia, as well as elevation of AST, ALT, and CK level (29). Patients 9, 10, and 11 were three siblings who prominently exhibited facial dysmorphia, renal parenchymal disease, electrolyte abnormalities, psychomotor retardation, and bone dysplasias. Consistent with the established literature, all three individuals exhibited elevated AST, ALT, and CK levels, which culminated in the diagnosis of TMEM165-CDG. This diagnosis was further substantiated by identifying a confirmed pathogenic mutation as previously documented (30).

CONCLUSION

Timely diagnosis is paramount for several forms of CDG where treatment options are available. The lack of awareness and limitations in diagnostic methods contribute to confusion in roughly half of CDG cases. While the pathophysiology of many types remains partially understood, illuminating the concealed aspects within the intricate problem will advance treatment strategies. Nevertheless, relying solely on molecular methods for CDG diagnosis remains intricate, as exemplified by our patient with an uncertain clinical significance of the PIGN mutation, who regrettably passed away. Collaborative efforts among diagnostic techniques, research endeavours, and referring physicians will bolster the efficacy of molecular testing. The integration of genomic and glycomics approaches will expedite and reinforce diagnostic procedures.

Our study encompassed various CDG types originating from distinct pathogenic mechanisms. Despite variances in clinical presentations from documented cases in the literature, neurodevelopmental delay, heightened vulnerability to infections, elevated liver enzyme levels, thrombocytopenia, and cerebellar atrophy emerged as the most prevalent indicators in our patients, warranting suspicion of CDG diagnosis. Furthermore, Whole Exome Sequencing (WES) proved instrumental in identifying CDG in instances involving immune deficiency or neutropenia. Additionally, it is essential to contemplate the possibility of CDG in cases featuring multicystic kidney disease, acute renal failure, bone involvement, coagulation disorders, and a propensity for thrombosis.

Ethics Committee Approval: This study was approved by the ethics committee of the Ethics in Research Committee of Çukurova University Faculty of Medicine, Adana, Türkiye (approval number: 2019/04-10).

Informed Consent: Legal custodian's assent of the children participated in the research was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.K., D.B., D.K., A.B., B.A., N.M., M.Y.; Data Acquisition- S.K., D.B., D.K., B.S.Y., F.D., D.A., M.Y., N.M.; Data Analysis/Interpretation- S.K., M.Y, N.M.; Drafting Manuscript- S.K., N.M.; Critical Revision of Manuscript- S.K., N.M.; Final Approval and Accountability- S.K., D.B., D.K., B.S.Y., A.B., F.D., B.A., D.A., N.M., M.Y.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Etik Komite Onayı: Bu çalışma Çukurova Üniversitesi Tıp Fakültesi Araştırma Etiği Kurulu etik kurulu tarafından onaylandı, Adana, Türkiye (onay numarası: 2019/04-10).

Bilgilendirilmiş Onam: Araştırmaya katılan çocukların yasal vasisinin onayı alınmıştır

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- S.K., D.B., D.K., A.B., B.A., N.M., M.Y.; Veri Toplama- S.K., D.B., D.K., B.S.Y., F.D., D.A., M.Y., N.M.; Veri Analizi/Yorumlama- S.K., M.Y, N.M.; Yazı Taslağı- S.K., N.M.; İçeriğin Eleştirel İncelemesi- S.K., N.M.; Son Onay ve Sorumluluk- S.K., D.B., D.K., B.S.Y., A.B., F.D., B.A., D.A., N.M., M.Y.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

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