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EDITED BY

Francois Foulquier,
UMR8576 Unité de Glycobiologie
Structurale et Fonctionnelle (UGSF),
France

REVIEWED BY

Peter Witters,
University Hospitals Leuven, Belgium
Katrin Ūunap,
University of Tartu, Estonia

*CORRESPONDENCE

Dariusz Rokicki,
✉ d.rokicki@ipczd.pl

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Perinatal manifestations of congenital disorders of glycosylation—A clue to early diagnosis

Milena Greczan¹, Dariusz Rokicki^{1*}, Dorota Wesót-Kucharska¹,
Magdalena Kaczor¹, Agata Rawiak¹ and
Aleksandra Jezela-Stanek²

¹Department of Pediatrics, Nutrition and Metabolic Diseases, Children's Memorial Health Institute, Warsaw, Poland, ²Department of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Disease, Warsaw, Poland

N-glycosylation defects—isolated or mixed with other glycosylation defects—are the most frequent congenital disorders of glycosylation and present mostly in childhood, with a specific combination of non-specific phenotypic features. The diagnosis, however, is often delayed. The aim of this study is to describe the perinatal phenotype of congenital disorders of N-glycosylation. We present an analysis of perinatal symptoms in a group of 24 one-center Polish patients with N-glycosylation defects—isolated or mixed. The paper expands the perinatal phenotype of CDGs and shows that some distinctive combinations of symptoms present in the perinatal period should raise a suspicion of CDGs in a differential diagnosis.

KEYWORDS

CDG (congenital disorders of glycosylation), glycosylation, effusion, dysmorphism, thrombocytopenia, hydrops fetalis

1 Introduction

Congenital disorders of glycosylation (CDGs) are a group of inborn monogenic errors of glycoprotein and glycolipid formation and/or assembly (Chang et al., 2018; Altassan et al., 2019). The group is numerous, heterogeneous, and is divided into four subgroups, based on the pathomechanism: congenital disorders of N-glycosylation, disorders of O-glycosylation, disorders of glycolipids and glycosphosphatidylinositol anchor synthesis (GPI-CDG), and mixed disorders of glycosylation (Chang et al., 2018).

Disorders of N-glycosylation form the most prevalent CDG subgroup, and their pediatric phenotype is well described. The symptoms usually involve multiple organs, and the course of the disease may be severe, milder with relapsing episodes of exacerbations and/or slowly improving (Péanne et al., 2018; Altassan et al., 2019). The most common features of N-glycosylation are dysmorphism, like inverted nipples, upslanted palpebral fissures, and abnormal fat pads over the buttocks; cerebellar hypoplasia; hepatopathy; nephromegaly; proteinuria; hypertension; hypoalbuminemia; coagulation defects (both

TABLE 1 Clinical symptoms found in different CDG types.

Symptom	PMM2-CDG <i>n</i> = 15	MPI-CDG <i>n</i> = 1	SRD5A3-CDG <i>n</i> = 4	ATP6AP1-CDG <i>n</i> = 1	ALG1-CDG <i>n</i> = 2	DPAGT1-CDG <i>n</i> = 1	Total <i>n</i> = 24
Prenatal symptoms	in 6/14 pts; 1 pt no data	in 0 pts	in 1 pt; 3 pts no data	in 1 pt	in 1 pt	in 1 pt	in 10/20
Poor fetal movements	3	-	-	-	-	-	3
Hydrops fetalis	1	-	-	1	-	-	2
Pericardial effusion	2	-	-	-	-	-	2
Hydrocele testis	1	-	-	-	-	-	1
Impending asphyxia	1	-	-	-	-	-	1
Multi-VSD	-	-	1	-	-	-	1
Ventricular cysts	-	-	1	-	-	-	1
Shortening of the long bones	-	-	1	-	-	-	1
Polyhydramnios	-	-	-	-	1	-	1
Hypotrophy	-	-	-	-	-	1	1
Oligohydramnios	-	-	-	-	-	1	1
Suspicion of situs inversus	-	-	-	-	-	1	1
Dysmorphia	in 9/12 pts; 3 pts no data	in 0 pts	in 3 pts	in 1 pt	in 2 pts	in 1 pt	in 16/21
Inverted nipples	8	-	-	-	-	-	8
Wide-set nipples	3	-	-	-	1	-	4
Upslanted palpebral fissures	2	-	-	-	-	-	2
Gothic palate	1	-	-	-	1	-	2
Low-set ears	1	-	1	-	1	-	3
Large ears	1	-	-	-	-	-	1
Orange peel skin	1	-	-	-	-	-	1
Abnormal fat pads	3	-	-	-	-	-	3
Joint contractures	4	-	-	-	-	1	5
Cryptorchidism	3	-	-	-	-	1	4
Generalized edema	6	-	-	-	-	-	6
Thin nasal bridge	1	-	-	-	-	-	1
Hypotelorism	1	-	-	-	-	-	1
Barrel-shaped chest	1	-	-	-	-	-	1
Long fingers	1	-	-	-	-	-	1
Hypotrophy	-	-	1	-	-	1	2
Hypertelorism	-	-	1	-	1	-	2
Downslanted palpebral fissures	-	-	1	-	-	-	1
Micrognathia	-	-	1	-	1	-	2
Retrognathia	-	-	1	-	1	-	2
Not specified facial dysmorphia	2	-	3	1	-	-	6

(Continued on following page)

TABLE 1 (Continued) Clinical symptoms found in different CDG types.

Symptom	PMM2-CDG <i>n</i> = 15	MPI-CDG <i>n</i> = 1	SRD5A3-CDG <i>n</i> = 4	ATP6AP1-CDG <i>n</i> = 1	ALG1-CDG <i>n</i> = 2	DPAGT1-CDG <i>n</i> = 1	Total <i>n</i> = 24
Bird-like nose	-	-	-	-	1	-	1
Microcephaly	-	-	-	-	1	-	1
Cutis laxa	-	-	-	1	-	-	1
Adaptive disturbances	in 10 pts	in 0 pts	in 1 pt	in 0 pts	in 1 pt	in 1 pt	in 14/24
Hypoglycemia	5	-	1	-	-	-	6
Transient respiratory problems	9	-	-	-	1	1	11
RDS (X-ray)	2	-	-	-	1	-	3
Neurologic symptoms	in 12/12 pts; 3 pts no data	in 0 pts	in 4 pts	no data	in 2 pts	in 1 pt	in 19/20
Hypotonia	8	-	3	-	1	-	12
Hypertonia	3	-	1	-	1	1	6
Central hypertonia with peripheral hypotonia	1	-	-	-	-	-	1
Poor sucking	4	-	-	-	1	-	5
Poorly expressed neonatal reflexes	3	-	-	-	1	-	4
Dystonia	-	-	1	-	-	-	1
Absent tendon reflexes	1	-	-	-	-	-	1
Overexpressed tendon reflexes	-	-	-	-	-	1	1
Ocular symptoms	in 13/13 pts; 2 pts no data	in 0 pts	in 4 pts	in 0 pts	in 1 pt	in 1 pt	in 19/22
Nystagmus	4	-	3	-	1	-	8
Roving eye movements	6	-	-	-	-	-	6
Strabismus	3	-	-	-	-	-	3
Pale retina	7	-	-	-	-	-	7
Hypoplastic macula	1	-	-	-	-	-	1
Hypoplastic optic nerve	1	-	-	-	-	-	1
Retinal pigment clumping	-	-	1	-	-	-	1
Cataract	-	-	-	-	-	1	1
Hematological symptoms	in 10/10 pts; 5 pts no data	in 0 pts	in 1/1 pt; 3 pts no data	in 1 pt	in 1/1 pt; 1 pt no data	in 1 pt	in 14/15
Thrombocytopenia	6	-	-	-	-	-	7
Anemia	5	-	1	1	-	1	8
Neutropenia	1	-	-	-	1	-	1
Thrombocythemia	1 + 1*	-	-	-	-	-	1 + 1*
Hyperleukocytosis	4 + 2*	-	-	-	-	-	5 + 2*
Elevated INR	2	-	-	-	1	-	2
Elevated APTT	2	-	-	-	-	-	2

(Continued on following page)

TABLE 1 (Continued) Clinical symptoms found in different CDG types.

Symptom	PMM2-CDG <i>n</i> = 15	MPI-CDG <i>n</i> = 1	SRD5A3-CDG <i>n</i> = 4	ATP6AP1-CDG <i>n</i> = 1	ALG1-CDG <i>n</i> = 2	DPAGT1-CDG <i>n</i> = 1	Total <i>n</i> = 24
Protein S deficiency	4/4	n/a	-	n/a	-	n/a	4
Protein C deficiency	3/4	n/a	n/a	n/a	n/a	n/a	5
AT III deficiency	4/5	n/a	n/a	n/a	1	n/a	5
Bruises, petechiae	5	-	n/a	-	1	-	6
Bleeding from mucosas	2	-	-	-	1	-	2
Gastrointestinal	in 6/15 pts	in 0 pts	in 0 pts	in 0 pts	in 2/2 pts	in 1/1 pt	9/24 pts
Regurgitations	3	-	-	-	1	1	5
Food retention	2	-	-	-	-	1	3
No swallowing reflex	0	-	-	-	1	-	1
Nasogastric tube	4	-	-	-	1	1	6
Parenteral nutrition	3	-	-	-	1	1	5
Cardiac	in 12/15 pts	no data	in 1/2 pts; 2 pts n/a	no data	in 1/2 pts	no data	14/19 pts
Pericardial effusion	9		-		-		9
HCM	3		-		-		3
IVS thickening	6		-		-		6
PFO	6		1		1		8
PDA	2		-		-		2
PST	1		-		-		1
Multi-VSD	-		1		-		1
Repolarisation abnormalities	1		-		-		1
Sinus tachycardia	1		-		-		1
CNS pathology	in 10/10 pts	no data	no data	no data	in 0/2 pts	in 1/1 pt	11/13 pts
Cerebellar hypoplasia	5				-	-	5
Ventriculomegaly	2				-	-	2
IVH	6				-	1	7
Pineal cyst	1				-	-	1
Arachnoid cyst	1				-	-	1
Biochemical	10 pts	no data	in 1 pt; 3 pts no data	in 1 pt	in 2/2 pts	No data	14/14
Hypoalbuminemia	7		1	n/a	2		10
Hypertransaminasemia	3		-	1	-		4
Hypocholesterolemia	5		n/a	1	1		7
Proteinuria	7		-	n/a	1		8
Endocrine hypothyreosis	3	0	0	0	0	0	3

Pts, patients; multi-VSD, multi-ventricular septal defect; RDS, respiratory distress syndrome; INR, international normalized ratio; APTT, activated partial thromboplastin time; AT III, antithrombin III; HCM, hypertrophic cardiomyopathy; IVS, intraventricular septum; PFO, patent foramen ovale; PDA, patent ductus arteriosus; CNS, central nervous system; IVH, intraventricular hemorrhage.

pro- and anticoagulating factor deficiencies); cytopenias; and third-space effusions (Malhotra et al., 2009). All these symptoms, as well as generalized edema, cardiomyopathy, or cutis laxa, may be present also in the neonate (van de Kamp et al., 2007; Marklová and Albahri, 2008; Malhotra et al., 2009; Funke et al., 2013). Prenatally CDGs may manifest as non-immune hydros fetalis, cerebellar hypoplasia, skeletal deformities, polyhydramnios or Ballantyne syndrome (Morava et al., 2012; Altassan et al., 2019; Čechová et al., 2020). Current knowledge on the perinatal manifestation is, however, still scarce. The literature claims that diagnosing CDG on the basis of clinical data during the neonatal period is not easy and requires a high index of suspicion (Edwards et al., 2006; Thong et al., 2009). Indeed, as supported by our experience, the diagnosis is usually delayed and is rarely made in the neonatal period (Funke et al., 2013; Schulte Althoff, 2016).

The aim of this study is to broaden the knowledge about the perinatal symptoms of CDGs by analyzing a group of Polish CDG patients.

2 Materials and methods

We identified 35 CDG patients hospitalized in our Institute in years 1995–2022; out of this group, 33 patients had N-glycosylation or mixed glycosylation defects. The group of 24 CDG patients, for whom perinatal data were available, was further analyzed.

3 Results

The analyzed group consisted of 24 patients: 19 with isolated N-glycosylation defects, i.e., 15 patients with PMM2-CDG, 2 with ALG1-CDG, 1 patient with DPAGT1-CDG, and 1 patient with MPI-CDG; 4 patients with the dolichol synthesis defect SRD5A3-CDG; and 1 patient with the disorder of Golgi homeostasis ATP6AP1-CDG. The detailed clinical information about the patients is summarized in [Supplementary Table S1](#) and [Table 1](#).

Majority of patients were delivered on term (87,5%, i.e., 21/24–21 patients of 24 for whom these data are available), with normal birth body weight (79,1%; i.e., 19/24); the median body weight was 3,000 g (15–50 percentile for the term neonate, according to WHO growth charts; range 1,360–4,180 g), median head circumference 33 cm (15–50 percentile; range 31–35 cm), and median birth body length 54 cm (>97 percentile; range 49–56 cm). The Apgar score was abnormal in 71% of patients (15/21), with abnormal results ranging from four to eight points in the first minute to five to nine points in the 10th minute and the lowest score in DPAGT1- and one ALG1-CDG patient (4–5). The delivery by cesarean section prevailed (69%, 9/13) and was caused by lack

of labor progress (4), abnormal fetus position (2), premature labor (1), twin pregnancy in the systemic lupus erythematosus mother (1), and impending asphyxia in one case. The pregnancies were complicated in 8/24 cases (mother's: thrombocytopenia in the ninth month (1), severe anemia (2), massive lower limb edemas (1), hypothyroidism (1), gestational diabetes mellitus type 2 (1), and pregnancy-induced hypertension (1)).

Perinatal symptoms were present in 79% of patients (19/24).

Prenatal symptoms were described in 50% of patients (10/20) and encompassed: poor fetal movements (3), mild pericardial effusion (2), non-immune hydros fetalis (2), polyhydramnios (1), oligohydramnios, hypotrophy and suspicion of situs inverses (one, in a DPAGT1-CDG patient), impending asphyxia (1) and a combination of multi-ventricular septal defect (mVSD), ventricular cysts, and shortening of the long bones in one SRD5A3-CDG patient.

In all patients, some symptoms of illness were seen in the first days of life. Dysmorphic features were found in 76% (16/21) and included: inverted nipples (8), wide-set nipples (4), generalized edema (6), big joint contractures (5), abnormal fat distribution (3), low-set ears (3), upslanted palpebral fissures (2), hypotrophy (2), hypertelorism (2), gothic palate (2), micrognathia (2), retrognathia (2), and single cases of downslanted palpebral fissures, bilateral cataracts, high forehead, small forehead, barrel-shaped chest, bird-like nose, and hypotelorism. In boys, urogenital malformations were found, i.e., cryptorchidism (4/16 boys), hydrocele testis (2/16 boys), micropenis (1/16 boys), and hypoplastic scrotum (1/16 boys).

Almost half of the group suffered from transient adaptive respiratory problems starting in the first minutes to hours of life (45%, 11/24), with six patients requiring nCPAP or mechanical ventilation for 1–43 days and five requiring oxygen supplementation at least for a few hours. The chest X-ray revealed features of RDS (Respiratory Distress Syndrome) in three patients, including two prematurely born (29 and 32 weeks of gestation) and pneumonia in one. Six patients also had hypoglycemia in the first 1–2 days of life and received intravenous glucose infusions. Four patients developed jaundice, requiring phototherapy.

The neurological evaluation revealed muscle tone disturbances in 90% of patients (18/20), specifically 12 patients had hypotonia, while seven had hypertonia, which was combined with dystonia in one patient. In all patients, for whom those data were available (4/4), tendon reflexes were present in the neonatal period; however, in one, they were overexpressed. Neonatal reflexes were poorly expressed in seven patients, including poor sucking in four.

Another distinctive group of abnormalities found in the study group was ocular symptoms: nystagmus (64% of patients, 14/22), most often described as roving eye movements (6) or vertical-upward-eye movements (5). Horizontal nystagmus was found only in two patients. Three patients also had strabismus. In

some patients, those symptoms were paroxysmal. Another prevalent ocular finding was pale retina (78%, 7/9), in four cases described even as “albinotic”. There were also single cases of retinal pigment clumping around the optic nerve, hypoplastic macula, oval optic disc, and bilateral cataracts.

Signs of coagulopathy such as bruises, petechiae, bleeding from injection sites, or bleeding from the mucosas were found in 29% of patients (7/24).

Gastrointestinal disturbances were present in 37% of patients (9/24): regurgitations, vomiting, poor sucking, and lack of swallowing reflex. Six patients required feeding by the nasogastric tube and/or parenteral nutrition (4).

In cardiological evaluation, the most common symptom was mild pericardial effusion, found in nine patients, and patent foramen ovale, (PFO) in eight. Mild cardiomyopathy was found in five patients, and isolated thickening of the intraventricular septum (IVS), in another five. Two patients suffered from cardiac arrhythmias from the first days of life, and it was paroxysmal supraventricular tachycardia (PST) in one and significant sinus tachycardia in the other. None of the patients required pericardial drainage in the neonatal period.

Brain imaging revealed intraventricular hemorrhage (IVH) I° or II° in 72% (6/8) of patients and ventriculomegaly (2/8) in ultrasound, while MRI scan revealed cerebellar hypoplasia in 72% (6/8) of examined patients.

In laboratory tests, hematological disturbances were prevalent, which concerned 78% of patients (14/18). The most frequent were cytopenia, i.e., severe thrombocytopenia (7) (transient in one case), thrombocytosis (1) (and one in the fourth week of life), anemia (7), hyperleukocytosis (5) (and one in the fourth week of life), and leukopenia (1). Coagulation assessment revealed profound antithrombin III deficiency in 83% (5/6) of patients, protein C in 83% (5/6), and protein S in 100% (4/4) examined patients; partial antithrombin time was elongated in two of three cases, and the international normalized ratio was slightly elevated in three of four patients (range 1,1–1,78). Biochemical tests revealed normal transaminases in 67% (8/12), while in the other four patients they were only mildly elevated; hypoalbuminemia was present in 100% of diagnosed patients (10/10), proteinuria in 10, and erythrocyturia in 4 patients. Also, thyroid gland evaluation was normal in 72% (8/11) of patients, with hypothyroidism found in the remaining three.

The course of the disease in the perinatal period was mild in 11 patients; thus, they were discharged in the first week of life. Patients more severely ill (14) required hospitalization for multiple weeks. No patient demised in the neonatal period. In all patients with severe course, some distinctive symptoms were more frequent, like generalized edema, hematological disturbances (thrombocytopenia or thrombocytosis, anemia, and hyperleukocytosis), and signs of coagulopathy, respiratory failure, pericardial effusion, and intolerance of enteral feeding.

None of our patients received a proper diagnosis in their neonatal period, and the median time to recognize the disease by transferrin isofocusing was six months of age (range 1–108 months). The most frequently noted initial diagnoses were congenital CMV infection, sepsis, RDS, myocarditis, pericarditis, pylorostenosis, cerebral palsy, and Smith–Lemli–Opitz syndrome.

4 Discussion

The group of congenital disorders of N-glycosylation consists of at least 31 diseases, with different enzyme or transporter deficiencies, which lead to a similar pathophysiological effect: defect of synthesis and/or processing of glycoproteins and glycolipids (Abu Bakar et al., 2018). Some types of CDGs have their distinctive features, but there is still a pool of symptoms that are common for a majority of N-glycosylation CDGs and some of the mixed glycosylation disorders involving the N-glycosylation pathway, like psychomotor retardation, hypotonia, peripheral neuropathy, stroke-like episodes, nephrotic syndrome, failure to thrive, nystagmus, strabismus, retinitis pigmentosa, third space effusions, cardiomyopathy, liver disease, or microcystic kidneys presenting as hyperechogenic in ultrasonography (USG) (Hertz-Pannier et al., 2006; Goreta et al., 2012; Öncül et al., 2022). Dysmorphic features usually described in those patients are inverted, wide-set nipples, abnormal fat pads, orange peel skin, high forehead, large ears, or thin upper lip (Verheijen et al., 2020). CDG patients with defective N-glycosylation also share common laboratory deviations such as hypertransaminasemia (most prominent in MPI-CDG, but also in others), hypoalbuminemia, low plasma cholesterol, laboratory indices of hypothyroidism (the actual cause of which is often a deficiency of the thyroxin-binding globulin), cytopenias, proteinuria, and serum clotting factor deficiencies (such as protein S, protein C, AT III, and factors IX, XI, II, V, VII, VIII, and X) (Truin et al., 2008; Verheijen et al., 2020).

N-glycosylation deficiency symptoms, such as non-immune hydrops fetalis, polyhydramnios, cardiomyopathy, pericardial effusions, skeletal abnormalities, or mirror syndrome (Ballantyne syndrome), may also occur prenatally (van de Kamp et al., 2007; Malhotra et al., 2009; Lei et al., 2021).

The results of our study confirm that many of aforementioned symptoms are present also in the perinatal period. In the analyzed group, we found pre- and neonatal non-immune generalized edemas, cardiomyopathy, pericardial effusions, and dysmorphic features like inverted, wide-set nipples, cryptorchidism, and abnormal fat pads, although according to the

literature, the latter are rarely present in neonates (Goreta et al., 2012). In the first days of life, our patients also presented other typical symptoms, such as hypotonia, strabismus, failure to thrive, regurgitations, cerebellar hypoplasia, bleeding, coagulopathy, cytopenia (mainly thrombocytopenia or anemia), proteinuria, hypoalbuminemia, or serum clotting factor deficiencies.

Furthermore, our study also revealed some symptoms that are rarely described in the literature but were frequent in our study group and are discussed in the following paragraphs.

The interesting frequent finding (found in 45% of patients) is transient respiratory deterioration in the first minutes or hours of life, sometimes correlated with RDS features in RTG (mainly in prematurely born, but not only), requiring at least oxygen therapy or artificial ventilation for some time (range 1–43 days in the described group), and mostly not correlated with elevated inflammatory parameters. Such symptoms have been described in single cases previously, but its pathomechanism remains unknown (Schulte Althoff et al., 2016; van de Kamp et al., 2007). Hypothetically, pulmonary edema—as a part of generalized edema—might be the cause; another possibility is surfactant dysfunction due to hypoglycosylation of surfactant protein B and surfactant protein A (Taponen et al., 2013; Yang et al., 2014), but these considerations are beyond the subject of this paper.

Another finding rarely described previously is muscle hypertonia, which was present in seven patients, and a presence of tendon reflexes in all examined patients. According to the literature and personal experience, hyporeflexia is found in a majority of infants and older children with CDGs (Marklová and Albahri, 2007). Poor neonatal reflexes, including poor sucking and swallowing, were also frequent findings in the study group. This, together with enteral nutrition intolerance, manifested by typical regurgitations, vomiting, and undigested food retention, led to parenteral nutrition combined with nasogastric tube feeding in the neonatal period in a big fraction of our patients.

Not a common finding in the literature concerning CDGs, was also big joint contractures, found in 23% of patients in our study group.

An unusual type of nystagmus was prevalent in our cohort; it was described as roving eye movements or upward eye deviations and was often confused with epileptic seizures, particularly because it was paroxysmal in some patients. Another prevalent ocular finding was pale, albinotic retina, while in the literature, retinitis pigmentosa is described as the most frequent symptom (Lettice et al., 2010).

In addition to typical CDG hematological deviations, a part of our group presented transient significant hyperleukocytosis ($30,144\text{--}80 \times 10^9/\text{L}$) that started in the neonatal period and normalized during the next few weeks of life and was not correlated with other signs or indices of infection. In two

cases, it was also accompanied by significant thrombocytosis. According to our knowledge, such a phenomenon has never been described previously.

Interestingly, some of the well-known CDG symptoms have not been noted in a majority of the study group in their perinatal age, which are hyporeflexia, hypertransaminasemia, and hypothyroidism. Abdominal ultrasound was also normal in the majority of patients in their first days of life, without typical hepatomegaly or renal ultrasound findings, such as kidney enlargement, hyperechogenicity, and altered corticomedullary differentiation (Tiwary et al., 2022). Renal ultrasound abnormalities appeared gradually in the first few weeks or months of life in the described group.

More than half of our patients presented with a severe phenotype, which was more specific and easier to recognize. Still, almost the same number of patients showed a mild neonatal phenotype, and they were discharged from the hospital in the first weeks of life, without even posing a suspicion of CDGs. One of those patients with a “mild” neonatal phenotype (No. 5) presented to our hospital at the age of three months, in order to perform diagnostics of poor body weight gain. His/her dysmorphic features were highly suggestive of CDG, so during examination, the echocardiogram was performed, revealing impending cardiac tamponade. Another patient (No. 3), presented as a neonate with intensive vomiting and food retention and was suspected of having pylorostenosis. He/she underwent pyloroplasty in the third week of life, which was complicated by dehiscence of the stomach wall and general deterioration, partially due to *Pseudomonas aeruginosa* and *Candida albicans* sepsis. In addition, this surgery did not fix the enteral feeding problem, the patient required parenteral nutrition, so venesection was performed, which was complicated by the upper limb vein thrombosis.

This paper presents and extends the perinatal phenotype of congenital N-glycosylation disorders. It is important to emphasize that although the individual CDG symptoms seem to be non-specific, the occurrence of a combination of several of them, with the involvement of different systems, should direct the differential diagnosis specifically toward congenital disorders of N-glycosylation. Despite the specific treatment being available only to a few of them, early diagnosis may influence patient's further medical care and genetic counseling for the family, concerning family planning. It may reduce a number of procedures, which are at higher risk in this group of patients, such as surgery, and monitor patients for the occurrence of potential life-threatening complications of the disease.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author.

Author contributions

MG: conceptualization, methodology, investigation, resources, data curation, and writing—original draft. DR: resources and data curation. DW-K, MK, and AR: data curation. AJ-S: conceptualization. All authors agreed to be accountable for the content of the work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fgene.2022.1019283/full#supplementary-material>

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