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STATE OF THE ART ISTH 2022

# Hemostatic defects in congenital disorders of glycosylation

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## Abstract

A "state of the Art" lecture titled "Hemostatic Defects in Congenital Disorders of Glycosylation" was presented at the ISTH 2022 congress. Congenital disorders of glycosylation (CDGs) are rare, inherited, metabolic diseases. The diagnosis of CDG is often challenging due to the broad variety of disorders, the variable level of severity, and phenotypic heterogeneity. Most CDGs are multisystem disorders, and neurologic involvement is frequent. Patients with CDG often present coagulation abnormalities characterized by low levels of procoagulant or anticoagulant factors. Antithrombin deficiency is frequently associated with factor XI deficiency and less frequently with a protein C, protein S, or factor IX deficiency. This coagulation profile differs from those observed in liver failure, disseminated intravascular coagulation, and vitamin K deficiency, and so, should prompt the physician to consider a diagnosis of CDG. Coagulopathy can lead to thrombotic and/or hemorrhagic complications. In patients with phosphomannomutase 2 deficiency (the most common CDG), thrombotic events are more frequent than hemorrhagic events. In other types of CDGs, both hemorrhagic and thrombotic events have been described. Overall, the hemostatic balance in these patients is precarious and necessitates close monitoring in a setting of acute illness with greater metabolic needs. Here, we review the most relevant hemostatic defects observed in CDG and their clinical implications. Finally, we summarize relevant new data on this topic presented at the ISTH 2022 congress.

**KEYWORDS**
antithrombin, coagulation, congenital disorders of glycosylation, FIX, FXI, glycosylation, protein C, protein S

## Essentials

- Congenital disorders of glycosylation are often associated with abnormalities of hemostasis.
- Antithrombin and factor XI deficiencies are frequently associated in these disorders.
- Protein C, protein S, or factor IX deficiency are also, but less frequently, reported.
- Patients are prone to thrombotic and bleeding events with overall hemostatic instability.

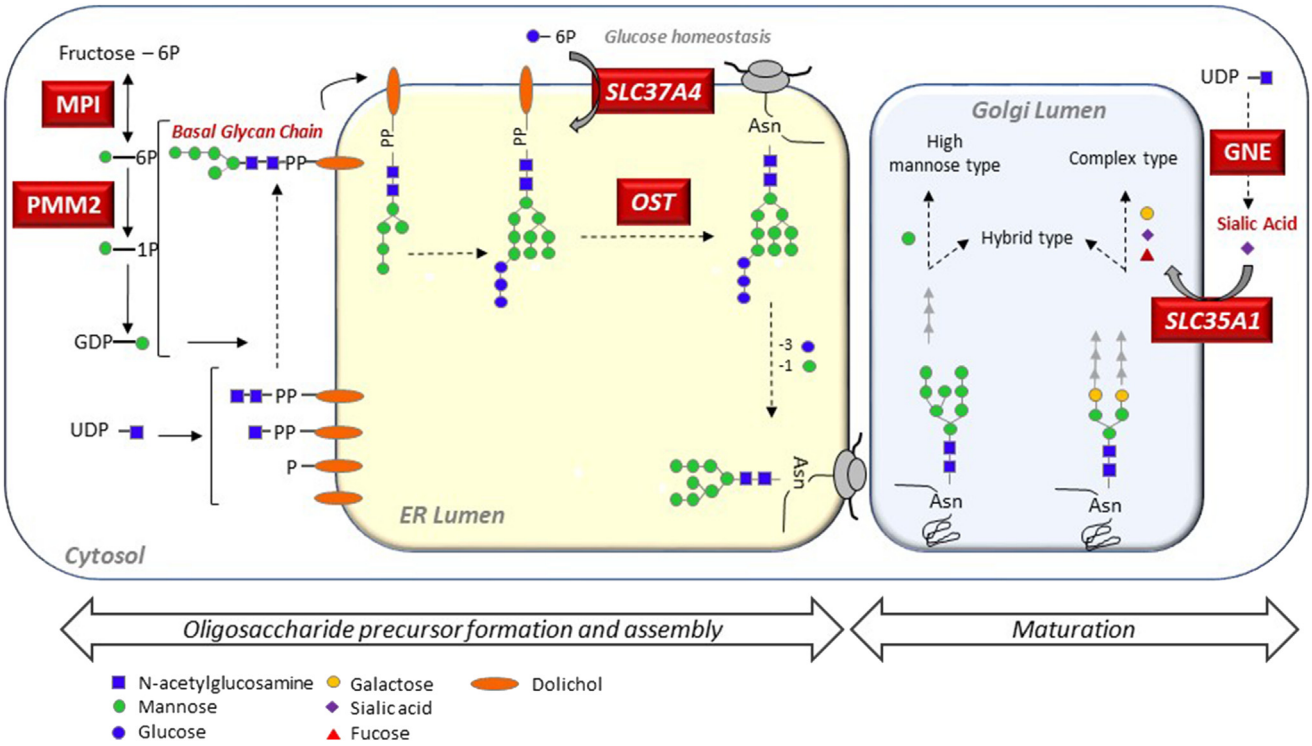


**FIGURE 1** The N-glycosylation process and major CDG associated with hemostasis abnormalities or thrombocytopenia. A simplified scheme of the glycosylation process and the different subcellular compartments is shown. The enzymes and transporters cited in the text are presented in red boxes. N-glycosylation starts in the cytosol where monosaccharides are first activated to sugar nucleotides (UDP-ose and GDP-ose) before being transferred to the membrane intermediate dolichol phosphate (dol-P). Phosphomannomutase 2 (PMM2) and mannose-6-phosphate isomerase (MPI) are involved in these early steps and, when defective or absent, are responsible for CDG-I: PMM2-CDG (the most prevalent type of CDG) and MPI-CDG which are both associated with a quantitative defect in N-glycans. The transfer of the glycan chain from the dolichol phosphate to the peptide chain is catalyzed by the oligosaccharyltransferase (OST) complex. Defects in the glucose-6-phosphate transporter (SLC37A4), glucosamine-2-epimerase/N-acetylmannosamine kinase (GNE) or CMP-sialic acid transporter (SLC35A1) are responsible for CDG-II, characterized by a remodeling defect in N-glycans and associated with combined coagulation factor deficiencies (SLC37A4-CDG) or thrombocytopenia (SLC35A1-CDG and GNE-CDG). Asn, asparagine; GDP, guanosine diphosphate; GNE, glucosamine-2-epimerase/N-acetylmannosamine kinase; MPI, mannose phosphate isomerase; OST, oligosaccharyltransferase; PMM2, phosphomannomutase 2; SLC35A1, solute carrier family 35 member A1; SLC37A4, solute carrier family 37 member 4; UDP, uridine diphosphate.

## 1 | INTRODUCTION

Given the ubiquitous nature of glycosylation, congenital disorders of this process can result in multisystem disorders and (in many cases) coagulopathies. In patients with few or no signs or symptoms, the discovery of coagulation abnormalities following a thrombotic event or in routine laboratory tests before a surgical operation can prompt further investigation and can lead to diagnosis of a congenital disorder of glycosylation (CDG). However, the coagulation profiles associated with CDG are often unusual and poorly understood, which can lead to misdiagnosis.

Here, we review the main steps in the glycosylation process, definition of CDG, CDG's impact on coagulation, typical presentation of type I CDG (also referred to as CDG-I), and some examples of type II CDG (CDG-II).

## 2 | THE GLYCOSYLATION PROCESS

Glycosylation is the most frequent ubiquitous posttranslational protein modification [1], and more than 50% of all proteins are glycosylated [2]. In fact, glycosylation corresponds to a series of enzymatic reactions that activate and add monosaccharides or glycan moieties to proteins and lipids; hence, this process is essential for protein maturation and function. There are two main categories of glycosylation: N-glycosylation and O-glycosylation. N-glycosylation comprises the attachment of N-glycans to the amide group of asparagine of proteins and proceeds in three steps: (i) formation of a lipid-linked oligosaccharide precursor, (ii) assembly, and (iii) maturation of the N-glycan (Figure 1). The first two steps take place in the cytosol and the endoplasmic reticulum, while the third occurs in the Golgi apparatus [3]. Monosaccharides are first activated as sugar nucleotides (uridine

diphosphate [UDP]-ose and guanosine diphosphate [GDP]-ose) in the cytosol and are then transferred to the membrane intermediate dolichol phosphate (Dol-P). The assembly step in N-glycosylation starts with the transfer of N-acetylglucosamine (GlcNAc) phosphate from UDP-GlcNAc to Dol-P, forming GlcNAc-pyrophosphatedolichol (GlcNAc-PP-Dol). A GlcNAc and 5 mannoses (Man) are then added sequentially to this dolichol-linked monosaccharide, forming the Man5GlcNAc2-PP-dolichol intermediate. The mannose comes from a metabolic pathway involving two cytosolic enzymes: mannose-6-phosphate isomerase (MPI) and phosphomannomutase 2 (PMM2). MPI is involved in the first step in the biosynthesis of GDP-mannose because it converts fructose 6-phosphate to mannose 6-phosphate. In the second step, PMM2 catalyzes the transformation of mannose 6-phosphate into mannose 1-phosphate (Figure 1). The Man5GlcNAc2-PP-dolichol intermediate is translocated into the lumen of the endoplasmic reticulum and then elongated by the addition of mannose and glucose (Glc) residues. The glucose-6-phosphate transporter encoded by the *SLC37A4* gene is not directly involved in N-glycosylation but maintains glucose homeostasis. The completed Glc3Man9GlcNAc2 oligosaccharide is then transferred by an oligosaccharyltransferase (OST) complex to the asparagine of an Asn-X-Ser/Thr consensus sequence within a polypeptide being synthesized. Finally, maturation in the Golgi apparatus involves demannosylation and then the addition of N-acetylglucosamine, galactose, sialic acid, or fucose residues. This generates a wide variety of N-glycans and leads to two major classes of oligosaccharides: polymannosylated oligosaccharides and complex oligosaccharides. Hybrid forms were also found (Figure 1). The terminal sugar of these chains is generally a sialic acid linked to a galactose. The biosynthesis of sialic acid involves the UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase (GNE).

O-glycosylation consists of the attachment of O-glycans to the hydroxyl group of a serine or threonine in a protein. O-glycan synthesis consists of assembly only and does not involve maturation. In contrary to N-glycosylation, O-glycan synthesis mainly occurs in the Golgi apparatus. O-glycans are more diverse than N-glycans. Mucin-type glycans and glycosaminoglycans are examples of biologically important O-glycans.

Hereafter, we will focus on N-glycosylation because it is affected more frequently than O-glycosylation by CDG.

## 3 | WHAT IS A CONGENITAL DISORDER OF GLYCOSYLATION?

CDGs are diagnosed in clinical biochemistry laboratories via serum transferrin isoform analyses, mutation analyses with dedicated gene panels, and/or clinical exome sequencing. Types I and II CGD (also referred to as CDG-I and CDG-II, respectively) are defined by the glycosylation pattern of serum transferrin, which is only N-glycosylated. In human plasma, the most abundant glycan isoform of transferrin is tetrasialotransferrin. A defect in N-glycosylation leads to a decrease in terminal sialic acids and results in a change in transferrin's sialylation profile. Thus, one can distinguish between a type I pattern (an abnormally low tetrasialotransferrin level and elevated disialo- and asialotransferrin levels) with a quantitative defect in N-glycan synthesis (CDG-I) and a type II pattern (additionally with elevated trisialo- and monosialotransferrin level) suggestive of a remodeling defect (CDG-II).

To date, 170 different CDGs have been described [4] (https://www.cdghub.com/cdgs/). In a study of the molecular diagnoses of 1350 patients, Peanne et al. found that 94% of the individuals had a CDG-I and 6% had a CDG-II. [5] In Europe, the estimated prevalence of CDG is between 0.1 and 0.5 per 100,000 live births, although the known allelic frequency of PMM2-CDG (a CDG-I and the most frequent CDG overall [5]) suggests that this is an underestimate [6,7].

Glycan chains are typically involved in many of a glycoprotein's functions (ie, folding, secretion, binding, and/or clearance). Thus, an impairment in glycosylation can have widespread multisystem consequences that damage organs such as the brain, liver, and heart.

PMM2-CDG is generally diagnosed during childhood. The initial clinical presentation usually combines neurologic involvement (psychomotor and intellectual disability, hypotonia, ataxia, and cerebellar hypoplasia) with other developmental manifestations (dysmorphic features, internal strabismus, retinitis pigmentosa, scoliosis, etc.) [8,9]. Some signs in infants (inverted nipples and fat pads) are pathognomonic for PMM2-CDG. Multiorgan damage is frequent, and liver and heart involvement is particularly common. Along with developmental abnormalities, the childhood of the most severely affected patients may be marked by acute neurologic complications called stroke-like episodes, which mainly occur during episodes of fever [10,11]. Although the signs and symptoms of stroke-like episodes are similar to those of acute vascular events, no ischemic lesions are observed [12]. The episodes' pathophysiology might be related to a channelopathy [12]. Finally, thrombotic manifestations are also frequently reported in people with PMM2-CDG [13].

MPI-CDG (also a CDG-I) is less common than PMM2-CDG and has a very different clinical presentation, with visceral manifestations (particular hepatic fibrosis and cirrhosis, diarrhea, protein-losing enteropathy, and vomiting) but no neurologic or dysmorphic features [14,15]. Hemorrhage (mainly related to esophageal varices) and thrombotic events are also reported in cases of MPI-CDG.

However, the disease severity varies greatly from one CDG to another and can range from death in early childhood to the (quasi) absence of symptoms in adulthood. Although a clear genotype-phenotype correlation has not been found for PMM2-CDG, several studies have showed that some pathogenic genotypic variants are correlated with the disease severity [16–18].

## 4 | TYPE-I CONGENITAL DISORDERS OF GLYCOSYLATION AND HEMOSTASIS

### 4.1 | An unusual coagulation profile

Coagulation is frequently affected in CDG-I. Combined deficiencies in antithrombin (AT), factor XI (FXI), protein C (PC), factor IX (FIX), and

**TABLE** Coagulation profiles in different clinical settings.

| Coagulation profiles in different clinical settings | No. of glycosylation sites | Normal range | Healthy | DIC/HCI | Vit K def | CDG-I | SLC37A4-CDG |
|---|---|---|---|---|---|---|---|
| **Procoagulant factors** | | | | | | | |
| FII | N-gly: 3 | >70% | N | ↓ | ↓ | N | ↓ |
| FV | N-gly: 37 | >60% | N | ↓ | N | N | ↓ |
| FVII | N-gly: 2; O-gly: 2 | >70% | N | ↓ | ↓ | N | N |
| FX | N-gly: 2; O-gly: 2 | >70% | N | ↓ | ↓ | N | N |
| FVIII | N-gly: 24 | >60% | N | N or ↓ | N | N | N |
| FIX | N-gly: 2; O-gly: 6 | >50% | N | ↓ | ↓ | N or ↓ | N |
| FXI | N-gly: 5 | >60% | N | ↓ | N | ↓ | ↓ |
| Fibrinogen | N-gly: 5; O-gly: 2 | 1.8-4 g/L | N | ↓ | N | N | N |
| **Coagulation inhibitors** | | | | | | | |
| Antithrombin | N-gly: 4 | >75% | N | ↓ | N | ↓ | ↓ |
| Protein C | N-gly: 4 | >50% | N | ↓ | ↓ | ↓ | N |
| Protein S | N-gly: 3 | >60% | N | ↓ | ↓ | N or ↓ | ↓ |
| **Primary hemostasis** | | | | | | | |
| Platelets | Multiple N- and O-gly (GPIbα, αIIbβ3, α2β1) | 175-500 g/L | N | ↓ | N | N | N |

N indicates that the factor levels are within the normal range, while the down arrow indicates that the levels are below the normal range.
DIC, disseminated intravascular coagulation; HCI, hepatocellular insufficiency; N-gly, N-glycosylation; O-gly, O-glycosylation; Vit K def, vitamin K deficiency.

protein S (PS) were initially described in a variety of case reports and in small case series [19–23]. Even though the prevalence of coagulation abnormalities remains difficult to establish (because they are not systematically investigated), we reported the presence of AT and FXI deficiencies in 71% and 57%, respectively, of a small series of patients with CDG-I; PC and PS deficiencies were less common (in 29% and 26% of the patients, respectively), and only 11% of the patients had an FIX deficiency [24].

This combination of AT, FXI, and PC deficiencies and (in some cases) low PS and/or FIX levels is characteristic of CDG, and differs markedly from the well-known coagulation profiles observed in cases of liver failure, disseminated intravascular coagulation, and vitamin K deficiency (Table). As mentioned above, some people with CDG have few symptoms, no neurologic involvement or dysmorphic features, and only mild developmental abnormalities (such as strabismus, cleft lip, cleft palate, and minor heart malformations). These abnormalities may require surgical treatment; indeed, a CDG is sometimes suspected fortuitously through the discovery of multiple coagulation factor deficiencies prior to surgery and in the absence of another obvious etiology. Another potential entry point for diagnosis is a thromboembolic event; the combination of AT deficiency (detected during a screen for thrombophilia) with FXI deficiency (detected during the investigation of a prolonged activated partial thromboplastin time) should also prompt the physician to consider a CDG—especially when PC and PS deficiencies are also noted [23,25]. It is worth noting that hereditary-combined AT and FXI deficiency is much less common (estimated prevalence: 1 per 5,000,000,000 live births) than a CDG.

In humans, all coagulation factors/inhibitors are glycosylated. Except for FVIII and von Willebrand factor (VWF), all of them are synthesized in hepatocytes. FV and FVIII are the most highly glycosylated factors and have 37 and 24 potential N-glycosylation sites, respectively (https://www.uniprot.org/uniprotkb/P12259 and https://www.uniprot.org/uniprotkb/P00451). VWF is also highly glycosylated, because carbohydrates account for 20% of its molecular mass. However, low FVIII activity has been reported in 3 patients with a deficiency in transmembrane protein 165 (TMEM165-CDG) [26] and in 1 patient with STT3A-CDG (STT3 is a catalytic subunit of OST), in which the levels of both FVIII and VWF are low (Figure 1) [27]. Levels and activities of other coagulation factors (such as FII, FV, FVII, and FX) and fibrinogen are normal in PMM2-CDG. However, two-dimensional electrophoresis of serum proteins revealed the presence of abnormal fibrinogen isoforms in patients with PMM2-CDG [28].

The particular susceptibility of AT, FXI, PC, PS, and FIX to glycosylation defects is therefore difficult to explain. A relationship between hypoglycosylation and the impairments observed in patients with CDG has not been unambiguously evidenced, and the putative underlying mechanisms have not been fully elucidated. However, extensive studies of antithrombin in CDG have provided some clues. First, the abnormally low circulating levels of antigenic antithrombin in patients with CDG are suggestive of poor secretion and/or

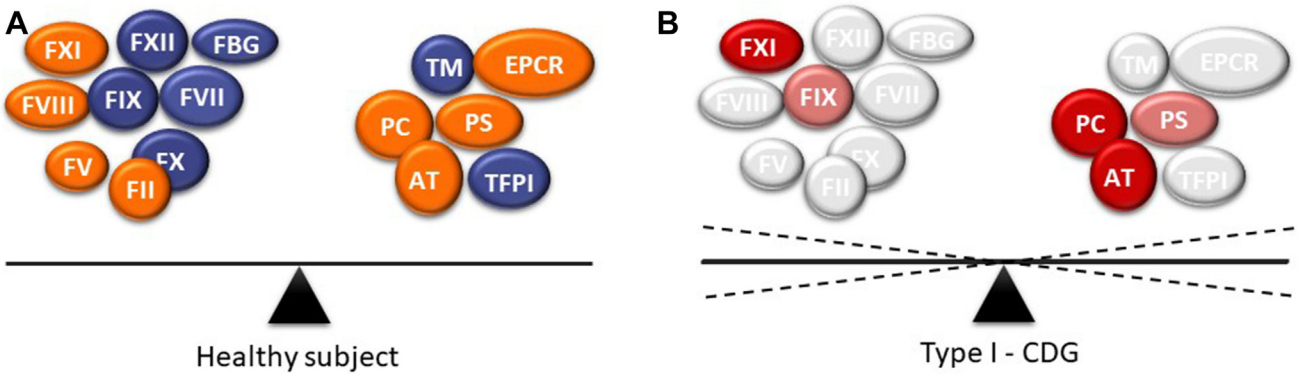


**FIGURE 2** The coagulation balance in CDG-I. (A) The coagulation balance in a healthy subject. Coagulation factors or receptors shown in orange are only N-glycosylated, while those shown in blue have both N-glycan and O-glycan chains. (B) The coagulation balance in PMM2-CDG and MPI-CDG: the most frequently deficient coagulation factors are shown in red, and those that are not affected are shown in grey. EPCR, endothelial protein C receptor; FBG, fibrinogen; TFPI, tissue factor pathway inhibitor.

elevated clearance. Analyses of plasma glycoforms have evidenced elevated levels of hypoglycosylated antithrombin, as also observed with FXI and FXII. Low N-glycosylation of antithrombin might well lead to aberrant folding and thus a relative decrease in secretion. Impaired glycosylation might also affect the clearance of antithrombin. Indeed, the absence of N-glycan at antithrombin's Asn 135 is associated with a higher affinity for heparin but also more rapid clearance [29–31].

Platelet adhesion proteins are also glycosylated. The GPIb-V-IX complex (a receptor for VWF) is highly glycosylated. In particular, the GPIbα subunit has more than 40 O-glycosylation sites, and integrin αIIbβ3 (responsible for binding to fibrinogen and VWF) has 11 N-glycosylation sites [24,32,33].

## 4.2 | The coagulation balance in congenital disorders of glycosylation

Given that both procoagulant and anticoagulant factors are affected in CDG, it is difficult to predict the impact of a given observed defect on the coagulation balance (Figure 2). Moreover, conventional hemostasis assays do not provide information on the overall coagulation balance. To overcome this problem, we applied a thrombin generation assay (TGA) to plasma samples from 35 patients with CDG [24]. Because the PC system cannot be activated in the absence of thrombomodulin, we also ran the TGA on samples spiked with a soluble preparation of this protein. First, TGA revealed a baseline elevation of thrombin generation in patients with CDG. Second, after spiking the samples with thrombomodulin, we observed an impairment of the PC system: 54% of the patients displayed a hypercoagulant phenotype *in vitro*. This prothrombotic phenotype might be further worsened by endothelial dysfunction (as observed in a cell-based model) and thus might lead to the impairment of the PC system. Indeed, the inactivation of PMM2 in the endothelial cell line hCMEC/D3 led to a defect in PC activation due to the lower surface expression of thrombomodulin and endothelial PC receptor [34]. However, these results were obtained with an endothelial cell line, and so, they must now be confirmed with endothelial cells derived from patients with CDG.

The prothrombotic phenotype is in line with the observed prevalence of thromboembolic disease in patients with CDG. A literature review of 344 patients with PMM2-CDG revealed that 43 (12.5%) had experienced a thrombotic event, including deep venous thrombosis, arterial thrombosis, and even cerebral thrombosis [35]. A number of risk factors for thrombosis have been identified: surgery, prolonged immobilization, presence of a catheter, and occurrence of a stroke-like event. Given the unstable hemostatic system in these patients, some thrombotic events are complicated by disseminated intravascular coagulation [13]. Thrombosis can occur at an early age, but is primarily a common complication in adults with PMM2-CDG.

The frequency of bleeding complications varies widely from one literature report to another. In a study of 100 patients with PMM2-CDG, Linssen et al. reported 14 (14%) bleeding complications [13]. In contrast, we observed only 2 cerebral hemorrhages (2%) in our study of a cohort of 96 patients with PMM2-CDG [8].

Any disturbance in the balance between procoagulant and anticoagulant factors can lead to hemorrhagic or thrombotic events. With the exception of antithrombin deficiencies, coagulation abnormalities tend to correct themselves during the course of the disease [36]. Furthermore, some clinical situations (such as fever) have a detrimental effect on glycosylation and reduce the residual activity of glycosylation-related enzymes. Risk of thrombosis or hemorrhage in a patient can thus vary as a function of changes in coagulation status and intercurrent events. It is therefore advisable to monitor the coagulation profile closely during the patient's follow-up in general and during an episode of fever in particular.

### 4.3 | Coagulation monitoring and management of the thrombotic/bleeding risk in type-I congenital disorders of glycosylation

Coagulation testing and monitoring are necessary in several situations [15,35]. Upon diagnosis, a patient with a CDG must be comprehensively screened for baseline coagulation disorders. This screen should include the prothrombin time, activated partial prothrombin time, fibrinogen level, levels of procoagulant factors (FII, FV, FVII, FVIII, FIX, FX, and FXI), and levels of coagulation inhibitors (AT, PC, and PS). The patient's coagulation status can then be monitored during annual follow-up consultations or more frequently in the event of acute illness or other indications. Usually, in both these cases, only the deficient factors are assayed. Coagulation testing can also be useful for evaluating the effectiveness of dietary D-mannose supplementation in MPI-CDG because the coagulation parameters usually normalize after a few weeks of treatment with mannose [14]. Finally, in clinical situations with a risk of decompensation, the prothrombin time, fibrinogen level, and D-dimer level should also be assayed (ie, in addition to the deficient factors) because of the risk of disseminated intravascular coagulation.

There are no specific guidelines on the prevention or treatment of thrombotic events in patients with CDG, and so, the latest general guidelines for adults and children should be followed [37–39]. In particular, fresh frozen plasma is used during periods of acute illness to minimize the bleeding risk and facilitate the management of hemorrhagic events in patients with combined deficiencies [15,35]. Prothrombin complex concentrates can also be used, with a preference for products containing PC and PS if the patient lacks one or the other of these anticoagulant proteins. However, neither FXI concentrates nor recombinant activated FVII can be administered because of their highly prothrombotic potential [40,41].

## 5 | TYPE-II CONGENITAL DISORDERS OF GLYCOSYLATION AND HEMOSTASIS

CDG-II (ie, disorders affecting the composition of the glycan chains) are far less common than CDG-I and account for only 6% of all CDGs [5]. Various enzymes and transporters are affected, with very different impacts on hemostasis. For example, a deficiency in the glucose-6-phosphate transporter encoded by the *SLC37A4* gene (involved in glucose homeostasis; Figure 1) was reported in a series of 7 patients with similar patterns of coagulation factor deficiency. Along with the AT, FXI, and PS deficiencies frequently observed in CDG-I, 6 of the 7 patients also had FII and FV deficiencies; this is not usually reported in CDG-I [42]. The signs and symptoms of this CDG-II were mild and ranged from the absence of symptoms to slight developmental abnormalities. None of the patients experienced a thrombotic event.

The glycosylation abnormalities observed in patients with CDG-II can also affect primary hemostasis. Macrothrombocytopenia was observed in siblings with a deficiency in SLC35A1, a transporter involved in the sialylation process (Figure 1) [43–45]. These patients were initially misdiagnosed as having idiopathic thrombocytopenic purpura. In SLC35A1-CDG, the terminal sialic acid transfer to the glycan chains of platelet glycoproteins is lacking. The underlying galactose is therefore exposed, which leads to accelerated platelet clearance. Indeed, it is now well established that platelet sialylation has a major role in clearance [46]. Young platelets with highly sialylated surface glycoproteins progressively lose these terminal sialic acids as they age, leading to their capture via the Ashwell-Morell receptor. In line with these data, platelets from patients with SLC35A1-CDG were cleared very quickly (relative to control platelets) after injection into mice [45]. Similarly, another CDG related to a deficiency in GNE is reportedly associated with macrothrombocytopenia, [47–51] Data on this novel pathogenic variant were presented at the ISTH 2022 congress. Similar to SLC35A1-CDG, GNE-CDG might be associated with platelet hyposialylation and thus accelerated hepatic clearance—as evidenced by Noordermeer et al. [52] Interestingly, even though platelets are highly glycosylated, there is little evidence of an impact of CDG on platelets—other than the cases of macrothrombocytopenia related to CDG-II affecting sialylation. Van Geet et al. reported low levels of GPIb-mediated platelet reactivity with collagen under flow conditions in a patient with monoacylglycerol acyltransferase 2-CDG (a CDG-II) [19]. Because CDG-I is more common, we have more data on platelet glycoproteins in this context. In a study of patients with PMM2-CDG, de la Morena-Barrio et al. found a low sialic acid content on the platelet surface; in contrast, an analysis of the main platelet glycoproteins did not evidence major quantitative or qualitative abnormalities [53]. Other studies (eg, those using light transmission aggregometry) demonstrated an increase in platelet reactivity in the presence of ADP, arachidonic acid, and collagen [19,54].

## 6 | CONCLUSION

The present review shows that CDGs are frequently associated with coagulation abnormalities and (less frequently) thrombocytopenia. Our clinical experience and the literature data show that a CDG can be revealed by hemostatic abnormalities. Thus, when abnormal hemostasis and thrombocytopenia are discovered incidentally and lack an obvious underlying cause, the physician should consider a diagnosis of CDG, screen for glycosylation abnormalities, and prescribe targeted molecular tests. Although CDGs are rare, their prevalence has probably been underestimated. Furthermore, the diagnosis of CDG is challenging because of the broad spectrum of clinical phenotypes and a great lack of awareness of these disorders among nonspecialist physicians. Moreover, some CDG probably are yet to be discovered. At the ISTH 2022 congress, Marin-Qilez et al. [55] presented the clinical and platelet phenotypes of 3 patients for whom new UDP-galactose-4-epimerase variants were discovered by whole-exome sequencing. These variants were likely to reduce the enzyme's activity and thus lead to a CDG. An impact on the hemostatic system was

combined with an impairment in proplatelet formation and GPIbα externalization, and the end result was lifelong macrothrombocytopenia with bleeding diathesis. Importantly, this discovery emphasized (i) the role of glycosylation in both primary hemostasis and coagulation and (ii) the value of broad molecular screens in increasing the diagnostic yield. CDGs also encompass inherited defects in platelet sialylation, which result in accelerated platelet clearance. At the ISTH 2022 congress, Zieger et al. [56] reported on a patient bearing a novel pathogenic variant in the gene coding for GNE; the mutation led to a CDG with severe thrombocytopenia and life-threatening intracranial bleeding.

The development of treatments is a priority in the field of CDG; indeed, treatment options are lacking for most subtypes of CDG. This development is notably complicated by the presence of a broad mutational spectrum and the lack of animal models of human CDG. As more and more pathogenic variants and disease-causing genes are discovered and as there is an increase in the number of patients with CDG, it should be easier to conduct clinical trials and form a robust scientific basis for clinical applications. If patients present with abnormalities in the hemostatic system at baseline, monitoring hemostasis might be a useful biomarker of a good treatment response.

## AUTHOR CONTRIBUTIONS

T.P., C.A., and D.B. drafted the manuscript. All authors have read and approved the final paper.

## RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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