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Congenital disorders of glycosylation—a challenging group of IEMs

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Summary Congenital disorders of glycosylation (CDG) are a rapidly growing group of inherited errors of metabolism (IEMs) due to an impairment of one or several glycosylation pathways. During recent years over 30 CDG subtypes have been identified at a molecular and biochemical level. The clinical manifestations in CDG are heterogeneous and may be highly variable within the same subtype and even among affected siblings. Novel insights into the extremely complex glycosylation pathways have necessitated several reclassifications of the group of CDG. Today CDG comprise not only the formerly known multisystem glycosylation defects but also some tissue-specific glycosylation defects, implicating a different diagnostic work-up depending on the underlying glycosylation defect. In 2007 the expanding group of CDG is an enormous challenge to all specialists working in the field of IEMs. This review gives a brief overview about the expanded group of CDG and summarizes the main implications for clinicians.

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Abbreviations

CDG	congenital disorders of glycosylation
IEM	inherited error of metabolism

Introduction to the impact of glycosylation

Glycosylation—the transfer of glycans to proteins or lipids—is an extremely diverse and ubiquitous mechanism which changes intrinsic properties of proteins and other glycoconjugates. Considering that the glycome (defined as all glycans synthesized by an organism) is estimated to be 10–10^4 times larger than the proteome, glycosylation is the most complex mechanism of molecule modification in living organisms. Eleven biochemical pathways are known to synthesize glycans in eukaryotes. In at least 6 out of the 11 pathways, inborn errors of glycosylation—or congenital disorders of glycosylation (CDG)—have been reported (Freeze 2006; Lowe and Marth 2003). Most defects have been identified in the N-glycosylation pathway (Jaeken and Matthijs 2007).

CDG in 2007—expanding the group of CDG

Since the first CDG patients were reported in 1984 (Jaeken et al 1984) the group of CDG has expanded enormously, as over 30 CDG subtypes have been identified at a biochemical and molecular level (Jaeken and Matthijs 2007). These novel insights in CDG necessitated several reclassifications and redefinitions (Aebi et al 1999; Jaeken 2003, 2004). The expanding field of CDG challenges all specialists

working on IEM and has considerable implications for the CDG patients, especially for their clinical management and their laboratory work-up. For example, the group of CDG has recently expanded by the discovery of tissue-specific glycosylation defects. In tissue-specific glycosylation defects, hypoglycosylation is mostly detectable not by blood analysis but by investigation of the affected tissue (e.g. skeletal muscle) (Freeze 2006; Jaeken and Matthijs 2007).

CDG are defined as IEMs due to hypo- or hyperglycosylation of glycoconjugates. In most CDG the common downstream effect is hypoglycosylation of glycoconjugates. The defect can be either in the specific glycosylation machinery or in a protein with a broader function than glycosylation, e.g. intracellular protein trafficking (Freeze 2006; Jaeken and Matthijs 2007). Perturbation of intracellular protein trafficking usually leads to an impairment of more than one glycosylation pathway. For example, congenital defects in the conserved oligomeric Golgi (COG) complex were recently shown to cause CDG by mislocalization of the N- as well as O-glycosylation machinery. The COG complex is essential for the appropriate structure and function of the Golgi apparatus through regulation of membrane trafficking (Kranz et al 2007; Wu et al 2004; Zeevaert et al 2008).

Although at the time or writing a final classification system of all putative CDG seems out of reach (Aebi et al 1999; Jaeken 2004; Jaeken and Matthijs 2007), the CDG disease family may be classified into protein- and lipid-glycosylation disorders. Protein-glycosylation disorders encompass defects of (1) N-glycosylation (formerly CDG Ia–Il), (2) combined N- and O-glycosylation (formerly CDG IIa–d), (3) some types of O-glycosylation (*O*-xylose, *O*-mannose, *O,N*-acetylgalactosaminyl, *O*-fucosylglycans), (4) dolichol pathway (dolichol kinase deficiency), and (5) conserved oligomeric Golgi complex (COG deficiency, formerly CDG IIe–f). The recently discovered lipid-glycosylation disorders encompass defects of (1) ganglioside synthesis (GM^3 synthase deficiency) and (2) the GPI anchor system (PIGM deficiency). In addition, there is a rapidly growing group of individuals with yet unidentified glycosylation defects, which are termed as CDG x (Jaeken and Matthijs 2007).

Diagnostic testing for CDG

If CDG is suspected the first-line diagnostic test is the detection of abnormal glycosylation of glycoconjugates. In Europe the most commonly used method for the detection of abnormal N-glycosylation is the isoelectric focusing of the N-glycosylated serum transferrin (Marklova and Albahri 2007). Isoelectric focusing of the purely O-glycosylated serum apolipoprotein CIII is used for detection of some *O*-mucin-type glycosylation disorders (Wopereis et al 2003; 2007). Limitations of these methods should be considered, including false-negative results in very young individuals (fetal and neonatal period) and some proven CDG individuals, false-positive results in secondary glycosylation defects (galactosaemia, fructosaemia, alcohol abuse, haemolytic-uraemic syndrome, very young age), or transferrin protein polymorphisms (Marklova and Albahri 2007). In tissue-specific CDG, tissue-specific tests have to be applied in order to detect abnormal glycosylation.

Detection of the genetic defect is essential for genetic counselling and particularly for prenatal testing, as laboratory test results for abnormal glycosylation of fetal serum protein might be false-negatives. The currently available methods for the identification of the basic defect are time consuming, and mostly only offered by few specialized laboratories. Methods used for further CDG subtyping include lipid-linked oligosaccharide or protein-linked glycan analysis using metabolic labelling and various mass-spectrometric combined techniques. Confirmation of diagnosis is by enzymatic analysis in fibroblasts or leukocytes and/or mutation analysis. In some CDG a transporter or another functional protein is affected (Freeze 2006; Lowe and Marth 2003; Marklova and Albahri 2007).

All diagnostic tools for CDG—including screening tests, expert analysis, and tissue banking—are readily available through EUROGLYCANET. EUROGLYCANET is a European network providing expertise for the advancement of research, diagnosis and treatment in the field of CDG (Matthijs 2005). Clinicians can contact either the network or the national referral centre via http://www.euroglycanet.org/.

The challenge of clinical manifestation—CDG can present with involvement of any organ system at any age to any degree of severity

Broadening of the testing for CDG both in individuals with classical features of CDG and in individuals with unknown diagnosis has identified an expanded group of CDG cases. In recent years more than 900 proven CDG patients have been reported, most of them with CDG Ia (>600 cases) and CDG Ic (>30 cases). In addition, there is a growing group of patients with yet unidentified glycosylation defects (Grunewald 2007; Jaeken and Matthjis 2007).

CDG is an enormous challenge for clinicians, as CDG is often associated with significant morbidity and mortality, especially in early infancy. CDG may present with involvement of any organ system at any age to any degree of severity. Accordingly, CDG should be considered in every patient with an unexplained syndrome. On the other hand, CDG may mimic other metabolic diseases like mitochondriopathies. Most CDG are multisystemic diseases and comprise an extremely heterogeneous spectrum of clinical presentations, including abnormalities of the central nervous system, abnormal fat distribution, eye movement abnormalities, coagulation abnormalities, gastrointestinal symptoms, retinitis pigmentosa, hormonal dysregulation, or dysmorphic features (Grunewald 2007; Jaeken and Matthijs 2007). In addition, there are CDG that affect only one or a few organ systems (Jaeken and Matthijs 2007), for example congenital muscle dystrophies in association with migration disorders of the brain (Godfrey et al 2007; Schachter et al 2004). Variability of clinical manifestation in CDG is another challenge and should be considered when counselling families for CDG. Variability of clinical manifestation has been reported within one CDG subtype and even among affected siblings, but factors which contribute to variability of the clinical phenotype are mainly unknown (Freeze and Aebi 2005).

Diagnosis of the CDG subtype is a main challenge for the clinician who takes care of a CDG family. Timely diagnosis is especially warranted in subtype CDG Ib because there exists an efficient treatment: oral mannose supplementation can bypass the defect in converting mannose to mannose 6-phosphate (Harms et al 2002). Only a few CDG show a specific clinical picture: CDG Ia with fat pads and inverted nipples; CDG Ib with treatable protein-losing enteropathy in the absence of mental retardation; CDG If with ichthyosis and growth retardation; and CDG IIf with macrothrombocytopenia (Grunewald 2007).

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