Complex Phenotypes in Inborn Errors of Metabolism

Overlapping Presentations in Congenital Disorders of Glycosylation and Mitochondrial Disorders

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KEYWORDS

• Glycosylation • Mitochondrial disease • Lactic acid
• Transferrin isoelectric focusing (TIEF) • Stroke-like episodes • Hypoglycemia
• Cutis laxa • Cholestasis

KEY POINTS

- Congenital disorders of glycosylation (CDG) and mitochondrial disorders are multisystem disorders. Both affect the central nervous system and many of their features overlap.
- Coagulation abnormalities, when involving both coagulation and anticoagulation factors, are highly suggestive of CDG and should suggest serum transferrin isoform analysis.
- Abnormal fat distribution and congenital malformations (conotruncal malformation and eye malformations; eg, coloboma) have been described in CDG, but are unique in mitochondrial disease.
- Diabetes and sensorineural deafness are rare in CDG, but common in individuals with mitochondrial diseases.
- Certain disorders affect both the mitochondria and glycosylation, such as NGLY1 deficiency (deglycosylation deficiency) and SLC38A9 defect, leading to Leigh syndrome and type 2 CDG.

INTRODUCTION

Inborn errors of metabolism are frequently divided into disorder groups of (1) intoxication, (2) energy metabolism, and (3) complex molecules. Most intoxication-type disorders affect multiple organ systems. The early, acute, or fluctuating symptoms; and, primarily, central nervous system involvement make identification relatively easy.

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Disorders of the energy metabolism also involve multiple organs and, almost always, the central nervous system but usually in a nonacute pattern. Affected individuals show early symptoms of hypotonia, muscle weakness, and developmental delay; and develop learning disabilities and progressive neurologic symptoms. Because the most energy-demanding organs are the brain, skeletal muscle, heart muscle, and liver, these are most severely affected by mitochondrial disease. Some mitochondrial conditions, such as disorders of mitochondrial maintenance, might present with an acute energy failure, similar to the intoxication-type of inborn errors of metabolism. These individuals show early-onset profound metabolic acidosis, frequently with fatal evolvement.[1]

Congenital disorders of glycosylation (CDG) are disorders of complex molecule synthesis. Due to the essential role of glycosylation in posttranslational protein-modification, CDG can involve any organ or organ system, and mimic any given disease.[2] For the practicing clinician, these inborn errors of metabolism could be significantly overlapping clinically, causing a diagnostic challenge, especially in the early stage of the disease. This article compares the different aspects of mitochondrial disease and CDG, with a focus on overlapping phenotypes and on giving a practical guide for the differential diagnosis.

GLYCOSYLATION

Glycosylation is an essential process for the posttranslational modification of many functional proteins. Examples include hormones and endocrine regulators, such as TSH, TBG, FSH, LH, ACTH, or IGFBP3; or important transport proteins, such as transferrin, ceruloplasmin, or proteins involved cholesterol metabolism. Other factors in coagulation, such as factor IX and XI or antithrombin III, are also glycosylated.[3] Not only secretory proteins but also many cell membrane proteins are heavily glycosylated, playing a role in cell–cell interaction, cellular immunity, and even in cell migration during fetal development. Obviously, due to its ubiquitous presence in the human body and because of the various functions in which glycosylated proteins are involved, abnormal glycosylation has major implications for human health.

Glycosylation involves three cellular compartments. On activating monosaccharides and phosphorylating dolichol as an acceptor for nucleotide sugars, the glycan chain is built in a stepwise enzymatic process in the cytoplasm and then flips into the endoplasmatic reticulum. The dolichol-linked oligosaccharides are transferred to the acceptor protein and transported to the Golgi for final processing. This includes cutting back of mannose residues; importing monosaccharides, such as fucose, galactose, or sialic acid, to the Golgi; adding it to the oligosaccharide chain on the protein; and exporting the molecule to the secretory vesicules.[4]

Congenital Disorders of Glycosylation

CDG are a disease family with more than 100 different members. CDG were defined by Jaeken and colleagues[5] in 1980. CDG types have been divided into four different groups, including defects in N-linked glycosylation, O-linked glycosylation, lipid-linked glycosylation, and combined glycosylation pathways.[2] For the clinician in general practice, the most frequent, important type is the group of N-linked glycosylation defects. The names of the different CDG are composed from the name of the gene hyphenated with CDG (eg, PMM2-CDG).The most common form is PMM2-CDG, which has more than 700 reported individuals. The second most common type is ALG6-CDG. Both disorders have a recognizable phenotype. In most cases, individuals with PMM2-CDG show hypotonia, strabismus, abnormal fat distribution,