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Diagnostic dilemma's

The congenital disorders of glycosylation are clinical chameleons

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The congenital disorders of glycosylation (CDG) are a fascinating and eclectic group of disorders with a multisystem phenotype. The largest impediment to diagnosing CDG is simply considering them in the first instance, which is no small task given their 'clinical mimicry'. Common clinical features associated with CDG involve developmental delay and intellectual impairment, ataxia, seizures, retinopathy, hepatic dysfunction, coagulopathies, failure to thrive, cardiomyopathy and pericardial effusion, hydrops fetalis, endocrine abnormalities, renal dysfunction, skeletal defects, early lethality, and dysmorphic features.[1] While the diagnosis of CDG may not lead to significant alterations in therapeutic management in most instances, an accurate diagnosis is imperative for natural history postulations and genetic counselling.

In CDG, hypoglycosylation of different glycoproteins and occasionally of other glycoconjugates leads to a variety of symptoms that ultimately affect multiple systems. Jaeken described the first CDG patients over 20 years ago, and in the last decade, more than 30 genetic glycosylation disorders mainly encompassing the N-linked and O-linked protein glycosylation pathways have been identified.[2] The CDG have been divided into two groups: type I defects, of which there are 13 subtypes (CDG-Ia to CDG-Im), and type II defects, of which there are 8 subtypes (CDG-IIa to CDG-II/COG8). The CDG are a 'booming field' of the inborn errors of metabolism.

An elegant example of the broadening CDG phenotype is given by Morava *et al*[3], on page XXX of this issue, who define a phenotype of an autosomal recessive cutis laxa (ARCL) associated with a combined N-linked and O-linked glycosylation defect. They describe a fascinating constellation of generalised neonatal cutis laxa that improves with time, joint hypermobility, decreased bone mineralisation, late closure of the anterior fontanels, progressive microcephaly, neuronal migration defects, seizures, hearing loss, transient feed intolerance, developmental and growth delay, and characteristic facial features.

ARCL is a genetically heterogeneous entity divided into two distinct groups, ARCL type I (OMIM 219100) and ARCL type II (OMIM219200). ARCL type I is a very severe disorder of elastic tissue marked by hernaea, visceral involvement, and early lethality. ARCL type II is likely to be a clinically and genetically heterogeneous condition. The cohort described by Morava *et al* displays many similarities to ARCL type II, and are likely to represent a subgroup of this broad umbrella terminology. Dermatological involvement as a major presenting feature is uncommon in CDG, with an ichthyosis-like skin disorder being described in CDG-If (OMIM 609180) and CDG-Im (OMIM 610768). Loose and wrinkled skin has been observed in CDG-IIe (OMIM 608779), but not as prominent as in patients with cutis laxa. CDG-IIe is secondary to a defect in the 7th subunit of the conserved oligomeric golgi complex (COG).[4] Like the patients described by Morava *et al*, deficiencies in COG exhibit abnormal N-linked and O-linked glycosylation. Progeroid Ehlers–Danlos syndrome (PEDS, OMIM 130070) is caused by defective galactosyltransferase-I activity, which results in defects in O-xylosyl-proteoglycans.[5] PEDS is characterised by wrinkled loose skin on the face, fine curly hair, scanty eyebrows and eyelashes, downslanting palpebral fissures, a distinctive facies, developmental delay, skeletal abnormalities, and the classical features of Ehlers–Danlos syndrome.[5] ARCL associated with a combined N-linked and O-linked glycosylation defect displays characteristic dysmorphology, neuroradiological pattern,

and clinical course, which differentiate it from other CDG with dermatological involvement.

Morava *et al*[3] describe a distinctive central nervous phenotype consisting of bilateral fronto-temporal pachygyria/polymicrogyria and delayed myelination with white matter anomalies. Some similarities are observed with the dystroglycanopathies such as Walker–Warburg syndrome (WWS OMIM 236670) and muscle–eye–brain disease (MEB OMIM 235280), which are a result of defective O-mannosylation of α-dystroglycan. WWS can display lissencephaly, hydrocephalus, severe cerebellar hypoplasia, and partial absence of the corpus callosum, while the neuroradiological features of MEB are less severe, and may involve fronto-parietal pachygyria, polymicrogyria, cerebellar hypoplasia, and flattening of the pons and brain stem.[6] However, cerebellar hypoplasia/atrophy, Dandy–Walker malformations, and global cerebral atrophy are more commonly associated with the N-linked CDG.

Morava *et al*[3] describe mild skeletal abnormalities in their cohort including delayed closure of the anterior fontanel and decreased bone mineralisation. The skeletal involvement of CDG can easily be overlooked in the face of a multisystem clinical phenotype; however, skeletal involvement can lead to significant morbidity, such as C1–C2 subluxation[7] or fractures secondary to osteopaenia and osteomalacia.[8] Less common manifestations include a 'dysostosis multiplex like phenotype',[9] and even a primary skeletal dysplasia has been reported in CDG-Ia,[10] CDG-Id, [11] and CDG-Ig.[12]

Dysmorphic features are a common reason to prompt referral to a clinical genetics clinic, thus highlighting the importance of the clinical geneticist in diagnosing the CDG. The 'CDG facies' constitutes a prominent forehead, triangular face, large floppy ears, strabismus, and thin upper lip. Peripheral dysmorphic features include inverted nipples, a striking lipodystrophy. These features are in contrast to the ARCL associated with a combined N-linked and O-linked glycosylation defect, which include late closure of the anterior fontanelle, microcephaly, midface hypoplasia, short nose with anteverted nares, small mouth, long philtrum, strabismus, and down-slanting palpebral fissures.[3,13]

Transferrin is a serum glycoprotein containing two N-glycosylation sites, attached to which are two biantenary complexes, carrying four sialic residue charges. Defects in glycosylation can alter the number of sialic acid residues and hence the charge of the molecule, thus altering the mobility of the transferrin isoforms under isoelectric focussing electrophoresis (IEF). Apolipoprotein C-III (Apo-CIII) carries a single O-glycosylation site and is not N-glycosylated, and Apo-CIII IEF can detect defects in O-glycosylation.[14] The importance of considering a combined N-linked and O-linked glycosylation defect is highlighted by the observations of a measurement of a normal transferrin IEF pattern in neonates with CDG-Ia.[15] Therefore a normal transferrin IEF pattern, without the concurrent performance of Apo-CIII IEF, can contribute to a missed diagnosis of a combined N-linked and O-linked glycosylation defects.

The patients presented by Morava *et al* contribute to the ever growing phenotype of the CDG, and highlight the point that they are under-diagnosed. While the patients presented in this cohort have a defined phenotype, combined N-linked and O-linked glycosylation defects should be explored in patients with isolated cutis laxa and in patients with an undiagnosed multisystem clinical phenotype. This work also raises the question: why is there such phenotypic heterogeneity among the combined N-linked and O-linked glycosylation defects? There also exists a need to refine the current CDG nomenclature as syndromes associated with a combined N-linked and O-linked glycosylation defect do not fit neatly into the type I or type II categories. The ever growing protean phenotype of the CDG creates challenges for the clinician as they are truly clinical chameleons■

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