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EDITORIAL

Quo vadis: the re-definition of "inborn metabolic diseases"

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How should we define or redefine inborn metabolic diseases (IMDs) in the era of genetic diagnostic revolution? Previously, it was relatively easy: IMDs were mostly inherited, and occasionally de novo, genetic disorders of the biosynthesis or breakdown of substances within specific pathways that were recognized by specific biochemical tests and sometimes treatable by metabolic intervention. Current challenges in the new era of emerging novel disorders are discussed and illustrated by examples of "classic" and novel-type IMDs.

The challenge of the definition is highlighted by the congenital disorders of glycosylation (CDGs). The number of inborn errors of glycosylation has increased exponentially in the last decade. But how should we define a "real" CDG? The expert literature does not agree on the exact number of CDG types; is it greater than 100, or fewer than 80 (Freeze et al. 2015; Rymen and Jaeken 2014; Scott et al. 2014) (Fig. 1). Are tissue-specific glycosylation defects CDGs? Where does one draw the line between secondary glycosylation disorders and CDG? Should the phenotype associated with mutations in *ATP6V0A2*, encoding a subunit of the lysosomal H^+-ATPase, be referred to as autosomal recessive cutis laxa syndrome type II (ARCL-2), or is it an IMD? Can it be classified as a CDG, even though there is no primary defect of a glycosylation-related enzyme (Kornak et al. 2008)? The same question can be raised about phosphoglucomutase 1 (PGM1) deficiency (Morava et al. 2015). If we were to define CDGs as all disorders with altered protein or lipid glycosylation, we would dramatically increase the number of disorders embraced by this term.

There are other emerging new inherited conditions in the category of intracellular trafficking. Additionally to Golgi trafficking defects, associated with abnormal glycosylation, novel metabolic diseases of trafficking include defects of copper metabolism, or functional defects disrupting endocytosis (Martinelli et al. 2013; Stockler et al. 2014), which are definitely affecting biochemical processes and the metabolism.

The difficulties have been exacerbated by the current shift towards genetics-based diagnostic approaches. Can we call a disease an IMD if there is no clear biochemical phenotype and no metabolic laboratory method to detect it? Would CDGs with only hematological manifestations, such as a sialic acid transporter defect (SLC35A1-CDG), or isolated haemoglobinuria, like paroxysmal nocturnal haemoglobinuria (MIM 300818) caused by somatic mutations in PIGA, be categorized as "true" IMDs (classical CDGs), or be excluded? Are these metabolic or hematological disorders (or both)? Who is the expert for these rare disease entities? Are these disorders to be diagnosed and followed up by the geneticist, the organ specialist or the metabolic specialist?

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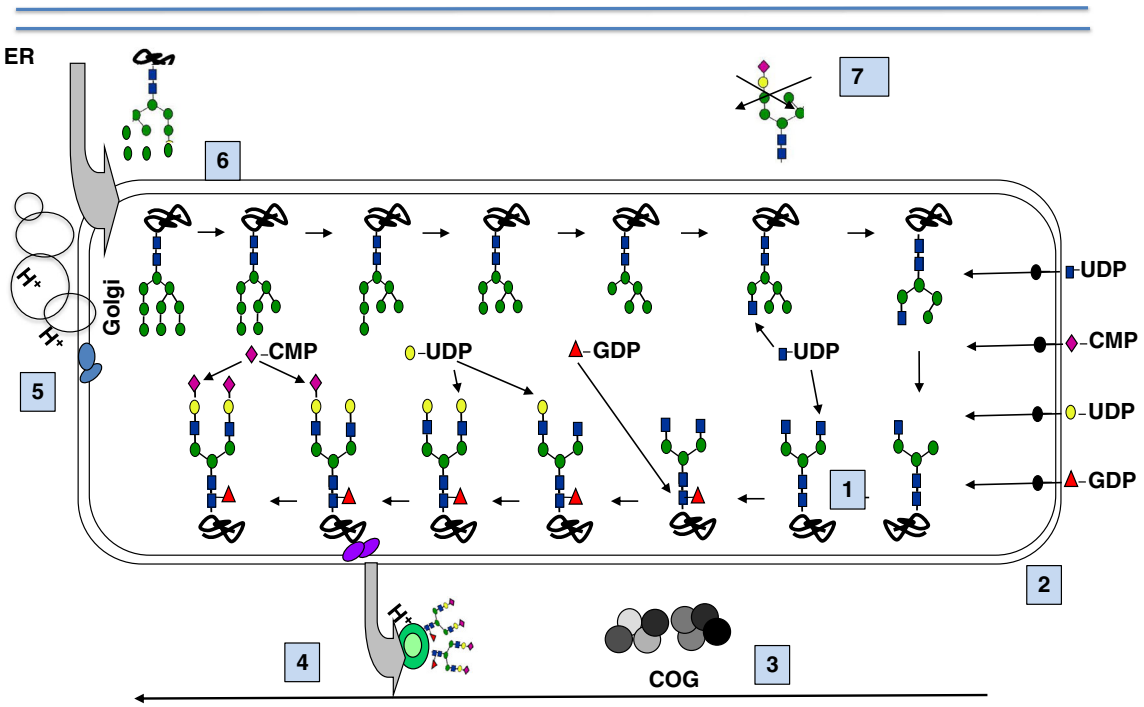

Fig. 1 Schematic representation of the glycosylation pathway linking the endoplasmatic reticulum to the Golgi apparatus. In this pathway, both classical and novel inborn errors of metabolism are known that all result in abnormal glycosylation. The classical inborn errors of metabolism that interfere with the step-by-step synthesis of glycoproteins in the different Golgi compartments (*1*) and the novel types involved in activated sugar transport through the Golgi membrane for glycoprotein processing (*2*), Golgi trafficking (*3*), vesicular transport between the ER to the Golgi system and retrograde transport (*4*, *5*), glycan maintenance. (*6*), and break down of abnormal glycans (*7*)

Other examples are found in mitochondrial disorders, and they go beyond the long-standing debate regarding whether or not defects in genes encoding mitochondrially targeted proteins and affecting mitochondrial function should be labelled as "primary" or "secondary" mitochondrial diseases (Schapira 2002, 2012), and is it possible to have secondary mitochondrial dysfunction in a "non-disease" (van de Ven et al. 2014). Often, we know very little about the novel genes we discover, only that they are associated with a metabolic condition. Proving that the gene mutation is pathogenic is more difficult and requires, at the very least, a reliable metabolic marker to use in functional experiments such as complementation studies. Elucidation of the gene defect underlying Sengers syndrome (MIM 212350) has raised more questions than answers about disease pathogenesis (Mayr et al. 2012). Is it a "straightforward" disorder of complex lipid biosynthesis? Or are mitochondrial reactive oxygen species-related mechanisms at play? MEGDEL syndrome (MIM 614725) has a similarly enigmatic background (Wortmann et al. 2012). A third disorder is the newly discovered Caseinolytic Peptidase B protein homologue (CLPB) deficiency, apparently a disorder of mitochondrial protein degradation associated with pleiotropic phenotypes (Kanabus et al. 2015; Wortmann et al. 2015). The underlying cellular pathways and the origin of the metabolic marker 3-methyl glutaconic acid, which unites these heterogeneous disorders, are still challenging (Wortmann et al. 2015; Kanabus et al. 2015).

The question of what is an IMD is not purely academic. This editorial arose out of a discussion on what articles SSIEM members would like to read in the JIMD. Should the Editorial Team consider, or reject, articles that discuss endocrine problems caused by an enzyme deficiency? Should we publish articles on skeletal dysplasias or connective tissue disorders that are caused by a disturbance in posttranslational modification in the endoplasmic reticulum? Which types of these conditions could be claimed to be IMDs and are thus of primary interest to the JIMD readers?

Challenges in the IMD field are not restricted to "new" disorders. We still lack quite basic knowledge regarding many "classic" disorders, including pathogenic mechanisms and biomarkers of disease progression. It is very difficult to perform prospective double-blind studies for rare life-threatening disorders, and efficacy in animal studies neither guarantees therapeutic efficiency nor effectively predicts adverse effects that might occur in humans. Cobalamin C deficiency is a good example; better understanding of the disease mechanism led investigators to question the importance of diet and simplified the treatment to focus on high-dosage OH-cobalamin therapy (Carrillo-Carrasco et al. 2008). Proof of the effects of such therapy on short- and long-term outcomes as well as the role

of novel players such as glutathione metabolism needs to be established for this still poorly understood disease (Pastore et al. 2014; Caterino et al. 2015).

Novel treatments, including small molecules, chaperone and gene therapies, are likely to improve management of many IMDs in the near future. Even relatively conventional treatments have many unanswered questions. Treatment studies for lysosomal disorders have been heavily influenced by the involvement of the pharmaceutical industry. Several studies have been performed on highly selected patient subgroups, sometimes with outlier (very mild or very severe) phenotypes, or on "leftover" patient groups. Treatment costs are high, and reimbursement is uneven, making an unbiased evaluation of possible therapeutic success and selecting specific therapies challenging.

There is much to discover in metabolic disease; to accomplish this goal, we need to accept a paradigm change. The presence of an abnormal metabolite (identifiable by "classical" techniques such as tandem MS, an enzyme assay or transferrin analysis) is no longer a prerequisite for a disease to be labelled as an IMD. In 2015, classification of a disorder as an IMD requires only that impairment of specific enzymes or biochemical pathways is intrinsic to the pathomechanism. If these cellular and biological processes are blocked or insufficient, they are suspected to underlie the disease phenotype. Parallel with next generation sequencing techniques, other rapidly evolving diagnostic techniques include proteomics, lipidomics, and glycomics. In most cases, we continue to target cell compartments. Certain organelles such as mitochondria, lysosomes, or peroxisomes have primary metabolic functions, and their genetic disorders are IMDs. Organelle-specific metabolic diagnostics can be used to complement, and in some cases replace, classical metabolic investigations. But IMDs do not stop with organelles. A good example is the new group of "complex lipid disorders" (Lamari et al. 2015), involving many different molecules, several cellular compartments, and the continuous remodelling of membranes (Saudubray et al. 2015).

In the end, some of these questions are futile and cannot address all the challenges of the genetic revolution. Many IMDs are multisystem disorders beyond the care of a single medical specialty. We need to continuously strengthen interdisciplinary collaboration, we need to work together, share the diagnosis and care of patients, and learn from each other. The strength of "metabolic specialists" is a detailed understanding of biochemical pathways in the body, the pathomechanisms related to disturbances in them, and the therapeutic consequences. Genetic analyses become more and more important in the diagnostic process but need to be complemented by biochemical investigations that sometimes have a higher diagnostic specificity and provide functional information on a phenotype level. Biochemical tests remain particularly important for disease monitoring. Many organelles such as mitochondria, peroxisomes, lysosomes, the endoplasmic reticulum, and the Golgi apparatus have primary metabolic functions, and it requires detailed biochemical knowledge to understand the diseases related to them. Metabolic specialists are the primary physicians for some classical disorders such as phenylketonuria or urea cycle disorders, where a specific treatment expertise is necessary, and they may have specific disease groups of special interest. But nobody "owns" their patients or the field of "inborn errors of metabolism." Just like medical geneticists, metabolic specialists have an increasing obligation to serve patients and colleagues in interdisciplinary networks. The complex phenotypes of patients with inherited metabolic diseases require the cooperation of many medical specialties to ensure optimal care. The metabolic physician, whose broad, cross-disciplinary training allows him or her to grasp the "big picture", is ideally positioned to serve as the principal caretaker or as a "case manager" for patients whose illness is due to a disruption of metabolic pathway(s).

A final question remains: which disorders can be declared unrelated to any cellular process or enzyme, and therefore are not an IMD? The JIMD will retain its focus on conditions affecting the biosynthesis or breakdown of substances within specific pathways, recognizable by specific biochemical tests. At the same time, the Editors will remain open for other genetic diseases that affect enzymes and pathways and are also interested in metabolism-based therapeutic interventions. Our metabolic playing field has indeed increased exponentially.

Conflict of interest None.

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