

Editorial

Congenital Disorders of Glycosylation

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Most plasma membrane and secretory proteins are glycosylated through N-linked or O-linked covalent bonding to complex carbohydrate molecules, oligosaccharides to form glycoproteins^[1]. N-linked glycosylation of proteins is a highly conserved modification process, which is initiated in the endoplasmic reticulum, and involves covalent linkage of oligosaccharides to the polypeptide through a coordinated and sequential set of enzymatic reactions^[2]. Aberrant glycosylation of proteins has recently been reported to cause many diseases, inherited as well as acquired disorders^[3,4]. Inherited defects of protein glycosylation, now termed as congenital disorders of glycosylation (CDG), are a rapidly enlarging group of inherited diseases with abnormal N-glycosylation of glycoconjugates^[5,6]. In classical CDG, the mannose incorporation into both protein-linked and dolichol-linked oligosaccharide is reduced, due to a defect in early steps of N-glycan biosynthesis.

Patients with CDG present with different clinical features according to age and the type of glycosylation defect. CDG-Ia is the classical type of CDG and is caused by deficiency of phosphomannomutase^[7]. It is a multivisceral disease with neurological (developmental retardation, hypotonia, cerebellar hypoplasia and peripheral neuropathy), gastrointestinal (diarrhea, failure to thrive and liver disease), renal (proximal tubulopathy) and cardiac (pericarditis) manifestations^[8,9]. Inverted nipples, unusual lipodystrophy, especially over buttocks and facial dysmorphism are useful clinical clues to diagnosis, but are not always present. In many cases, multiple organ failure can occur with resultant high mortality (15-20%). Contrary to CDG-Ia, CDG-Ib does not involve neurological impairment and the patients usually present with gastrointestinal complications^[9]. Hypoglycemia, vomiting, diarrhea and hepatomegaly are the common clinical features of CDG-Ib where loss of phosphomannose isomerase (PMI) is the notable

defect leading to non-glycosylation of proteins^[10]. CDG-Ic is the milder form of CDG-Ia, but is caused by a defect in glucosyl-transferase enzyme^[11]. CDG-Ic patients present at birth with ocular symptoms and show psychomotor retardation and developmental delay in the early months of life. CDG-Ic patients share the common clinical features of all CDG cases namely, liver abnormalities and decreased coagulation factors^[11]. CDG type-II is rare but has a more severe clinical course compared to CDG type I. CDG II patients present with severe psychomotor retardation, chronic feeding difficulties, dysmorphic features and epilepsy^[12]. A defect in Golgi enzyme N-acetylglucosaminyl-transferase II is a key feature of this group of CDG. Inverted nipples, skin lipodystrophy, peripheral neuropathy and cerebellar ataxia, the common features of CDG-Ia patients are not observed in CDG II.

Due to severe glycosylation defects, a number of serum glycoproteins occur in hypo-glycosylated or non-glycosylated forms in CDG patients and have served as useful diagnostic tools for CDG^[13]. Detection of serum transferrin profiles through isoelectric focusing (IEF) is a useful screening test. However, enzyme studies and mutation analysis should be used to confirm the exact defect because IEF will not identify all defects. Based on clinical and laboratory findings, CDG have been reported from various parts of the world including Asia, Europe and the Americas, but remains to be documented in the Middle East.

No treatment has been found to be effective in CDG patients yet. However, patients with CDG-Ib defect have shown significant improvement when treated with oral mannose^[14] emphasizing the importance of recognizing these patients early.

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