

Review Article

Congenital Disorders of Glycosylation: A Review

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ABSTRACT

Congenital disorders of glycosylation (CDG) are a group of newly recognized autosomal recessive disorders that cause serious neurological and other health complications due to defective glycoprotein biosynthesis. Based on clinical and biochemical peculiarities CDG can be classified into CDG type-I and CDG type-II. CDG Ia patients have dysmorphic features, developmental retardation and cerebellar hypoplasia, and show deficiency of phosphomannomutase (PMM), a key enzyme required for protein glycosylation. CDG Ib, patients have severe liver disease, enteropathy, and hyperinsulinaemic hypoglycaemia but no neurological involvement and is caused by deficiency of mannose-6-

phosphate isomerase (MPI), a potentially treatable disorder. CDG Ic is a multivisceral form of CDG and is caused by deficiency of glucosyl transferase. In contrast to CDG type-I, patients with CDG type-II have a more severe psychomotor retardation but no peripheral neuropathy or cerebellar ataxia and show a deficiency of N-acetyl-glucosaminyl transferase. CDG have been widely reported from different parts of the world but remain to be identified in the Middle East. This article is intended to introduce the main characteristics of CDG to health care professionals in the Middle East countries where this newly characterized group of genetic diseases might be prevalent but remains undiagnosed.

KEYWORDS: genetics, glycosylation disorders, Middle East, serum proteins, transferrin

INTRODUCTION

The congenital disorders of glycosylation (CDG) form a newly recognized group of inherited metabolic disorders characterized by deficiency of N-glycan moiety in glycoproteins. CDG are autosomal recessive disorders that affect the nervous system and other organs including liver, kidney, adipose tissue and genitalia. CDG were documented by Jaeken and coworkers^[1] in 1980 and thereafter CDG have been reported from various parts of the world including East Asia, USA and Europe^[2,3]. However this group of genetic diseases remains to be reported from the Middle East. CDG patients reported so far, present with different clinical features according to the age and the type of glycosylation defect. The incidence of autosomal recessive disorders with or without neurological complications is apparently high in Arab countries including Kuwait, however CDG have not yet been reported from the Middle East. Heterogeneity and severity of CDG underscore the need for rapid diagnosis to ensure better management and timely treatment of patients. Therefore, the main objective of this article is to familiarize the general pediatricians, pediatric neurologists and geneticists in the Middle East countries, with the biochemical and clinical

characteristics of CDG. CDG is a group of genetic disorders that might be prevalent in Arab populations, but has remained unidentified.

GLYCOSYLATION OF PROTEINS

Glycoproteins are important secretory molecules and integral components of plasma membranes in humans. Glycosylation is a complex process of modification of newly synthesized peptides destined to act as structural or secretory proteins^[4]. The glycosylation pathways occur in the endoplasmic reticulum and Golgi complex and involve covalent linking of O- and N-oligosaccharides to proteins. N-oligosaccharides are the predominant carbohydrate complexes found in serum glycoproteins and contain a high percentage of mannose^[5]. The biosynthesis of N-oligosaccharides involves an orderly arrangement of sugar moieties such as mannose, N-acetyl-glucosamine, glucose and sialic acid into a large precursor molecule which is then linked to dolichol pyrophosphate (Fig. 1). The process of protein glycosylation is tightly regulated by enzymes involved in biosynthesis of oligosaccharide precursor sugar molecules such as mannose, and by enzymes such as glycosyltransferases that coordinate the sequential transfer of

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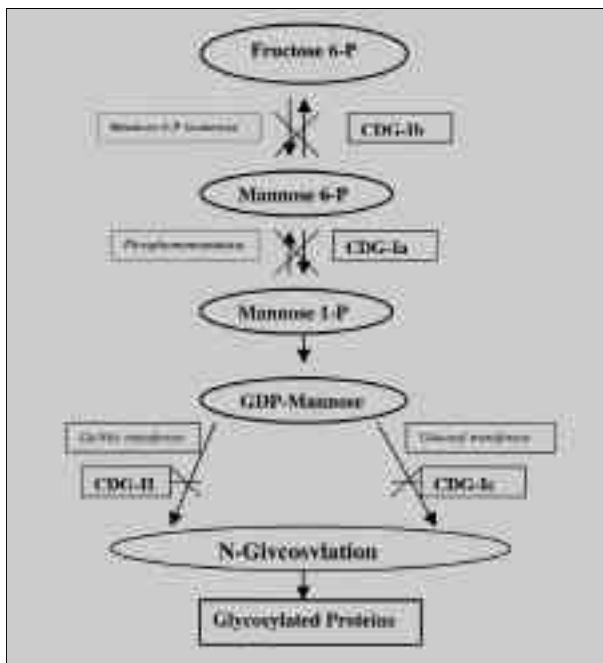


Fig. 1: Schematic of mannose pathway in protein glycosylation and related disorders

oligosaccharides to the nascent polypeptide chain. Biosynthesis of mannose-rich oligosaccharides requires formation of GDPmannose from mannose 1-P. Cellular pool of Mannose 1-P is generated from mannose and fructose through their inter-conversions by specific enzymes (Fig. 1) such as MPI and PMM. Mannose-rich oligosaccharides are then N-linked to asparagine (Asn) residue on polypeptide through enzyme-catalyzed process of N-glycosylation. Inherited or acquired deficiency of enzymes involved in biosynthesis of N-oligosaccharides and their binding to amino acid residue causes disorders of glycosylation^[6]. Fig. 1 illustrates that different types of CDG can occur due to deficiency of enzymes involved in synthesis of mannose 1-P or transfer of oligosaccharide to the protein.

CLASSIFICATION OF CDG AND CLINICAL FEATURES

On the basis of biochemical defect and clinical features of patients^[7], CDG can now be divided into two main groups described as follows:

CDG type-I Disorders: CDG type-I further has three subtypes each with a specific glycosylation defect and peculiar clinical features^[8].

CDG-Ia, the most frequent type, is a multivisceral disorder affecting the nervous system, liver, kidney, heart, adipose tissue, bone, and genitalia^[9]. Deficiency of phosphomannomutase (PMM), an enzyme involved in protein glycosylation, has been identified as the underlying cause of CDG-Ia^[10]. CDG-Ia is the classical type of CDG and patients show developmental retardation, muscular

hypotonia, inverted nipples, abnormal fat distribution, and cerebellar hypoplasia. Skin lipodystrophy, inverted nipples and fat dimples due to abnormal fat distribution are the distinguishing features found in CDG-Ia patients only. There is generally a mild to moderate hepatomegaly and occasionally cardiomyopathy. Areflexia and retinopathy have also been reported as frequent features after the first year of age in CDG-Ia patients. In older patients with CDG-Ia syndrome, limb joint restrictions, kyphosis and delayed puberty are also observed. Diarrhoea, pericarditis, liver disease and proximal tubulopathy are also observed in some patients.

CDG-Ib is a unique form of CDG as patients do not show neurological impairment, however gastrointestinal complications are serious^[8]. Common symptoms are severe hypoglycemia, protein-losing enteropathy, vomiting, diarrhoea and congenital hepatic fibrosis. These symptoms appear as early as 3 months of age and death in these patients is largely due to liver failure, caused by steatosis or liver cirrhosis. Renal hyperechogenicity has also been reported in some CDG-Ib patients. Deficiency of phosphomannose isomerase (PMI) is the notable defect leading to non-glycosylation of proteins^[11].

CDG-Ic is the milder form of CDG-Ia but is caused by a defect in glucosyl transferase enzyme^[12,13]. CDG-Ic patients have developmental delay in early months of life, show psychomotor retardation and have seizures^[14]. CDG-Ic patients present at birth with ocular findings and share the common clinical features of all groups of CDG namely, liver abnormalities and decreased coagulation factors. Two other CDG - type I forms (form Id and Ie) have been reported, however the exact enzyme defect and clinical characteristics remain to be clarified^[15,16].

CDG type-II Disorders: CDG type-II is a rare form of CDG but clinical course is severe^[17]. Only a few cases of this most serious form of CDG have been studied so far. The patients show severe psychomotor retardation without peripheral neuropathy but have a normal cerebellum. Chronic feeding difficulties, dysmorphic features and epilepsy are also observed in these patients. Inverted nipples, skin lipodystrophy and cerebellar ataxia, the common features of CDG-Ia patients are not observed in CDG II. A defect in Golgi enzyme N-acetylglucosaminyl transferase II is key feature of this group of CDG (Table 1).

BIOCHEMICAL AND MOLECULAR BASIS OF CDG

CDG are caused by abnormal N-glycosylation, a process initiated in the endoplasmic reticulum for

biosynthesis of glycoproteins^[4,6]. In CDG, the mannose

transferrin isoforms in CDG lack one complete oligosaccharide structure (mono-oligosaccharide) or both oligosaccharide structures (α -oligosaccharide), but not the sialic acids, as presumed on the basis of IEF methods. Advantages of the LC-MS method include improved sensitivity, minimal sample preparation, and an analysis time of < 10 min. Moreover, the nature of the oligosaccharide defect in CDG is accurately reflected by mass resolution^[24].

Since the differentiation of hypoglycosylated forms of glycoproteins can sometimes be difficult in patients with milder form of CDG, assay of PMM and MPI enzyme activities are used to differentiate CDG 1a from CDG 1b. The enzymatic deficiencies and the corresponding gene mutations can be demonstrated in leukocytes and in cultured skin fibroblasts from patients. CDG 1c and CDG type-II are easily diagnosed by western blot analysis^[22] and demonstration of glucosyl-transferase and glucosamine-N-acetyl-transferase deficiencies and related gene mutations. Attempts for pre-natal diagnosis of CDG have been unsuccessful until recently due to indistinguishable IEF pattern of transferrin in fetal blood. Charlwood and coworkers^[25] have successfully carried out the first prenatal diagnosis of CDG 1a on the basis of PMM enzyme assay in chorionic villi or cultured amniotic fluid cells and genetic linkage analysis of CDG I locus on chromosome 16.

TREATMENT

Though, a vast number of reports on various aspects of CDG have emerged in last ten years, there is as yet no effective treatment for CDG patients. In vitro studies on fibroblasts from patients with PMM deficiency provided some hope for oral mannose supplementation as a therapy, however oral or intravenous mannose did not improve the biochemical or clinical abnormalities in CDG-1a patients. On the other hand mannose administration has a potential therapeutic importance in CDG-1b, a lethal defect with PMI deficiency^[26]. Oral administration of mannose in a dose of 100 mg/kg body weight three times a day (increased to 150 mg/kg body weight after 8 months), stopped gastrointestinal bleeding and diarrhea in a 6 year old CDG-1b patient and normalized IEF pattern of serum transferrin. Unfortunately the number of CDG-1b patients reported in literature with or without mannose treatment is not large enough to validate mannose treatment as a universally accepted mode of treating PMI deficiency. No efficient treatment is available for CDG-II patients.

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