Review

Congenital disorders involving defective N-glycosylation of proteins

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Abstract. This review deals with several of the main autosomal recessive congenital disorders involving defective N-glycosylation of proteins (the addition of glycans linked to the polypeptide chain by a β-linkage between the anomeric carbon of N-acetylglucosamine and the amido group of L-asparagine). These congenital disorders of glycosylation (CDG, previously known as carbohydrate-deficient glycoprotein syndromes) are a group of multisystemic diseases often involving severe psychomotor retardation. Six distinct variants of CDG in group I (types Ia–If) have been described to date and the defects have been localized to deficiencies in the assembly of the dolichylpyrophosphate-linked oligosaccharide N-glycan precursor and its transfer to asparagine residues on the nascent polypeptides. Two variants of CDG group II (types IIa and IIb) have been identified as defects in the processing of protein-bound N-glycans. Hereditary erythroblastic multinuclearity with a positive acidified-serum lysis test (HEMPAS; congenital dyserythropoietic anemia type II) presents as a relatively mild dyserythropoietic anemia. The genetic defect in most cases of HEM-PAS is not known, but α-3/6-mannosidase II is involved in at least some patients. Leukocyte adhesion deficiency type II (LAD II) is a rare disorder characterized by recurrent infections, persistent leukocytosis and severe mental and growth retardation. LAD II is due to lack of availability of GDP-fucose. The study of these diseases and of relevant animal models has provided strong evidence that N-glycans are essential for normal mammalian development.

Key words. Glycosylation; N-glycans; congenital disease; congenital disorders of glycosylation; congenital dyserythropoietic anemia; leukocyte adhesion deficiency; mannose metabolism; fucose metabolism.

Introduction

A glycoconjugate is a covalent complex between carbohydrate and non-carbohydrate moieties. The non-carbohydrate moiety may be a protein, peptide, amino acid, lipid or some other aglycone. This review will deal with congenital diseases involving defects in the glycosylation of proteins. Glycans can be conjugated to amino acids either by N-glycosyl or O-glycosyl linkages [1]. The only N-glycan in animals involves a beta-linkage between the anomeric carbon of N-acetylglucosamine (GlcNAc) and the amido group of L-asparagine (Asn) although other N-glycan linkages have been found in bacterial glycoproteins. Several O-glycan linkages are present in animals. The alpha-linkage between the anomeric carbon of N-acetylgalactosamine (GalNAc) and the hydroxyl group of either serine (Ser) or threonine (Thr) was first described in mucins but is also commonly found in non-mucinous glycoproteins. Other common O-glycan linkages in animals are the beta-linkage between xylose (Xyl) and the hydroxyl group of Ser (characteristic of proteoglycans) and the beta-linkage between galactose (Gal) and the hydroxyl group of hydroxylysine (characteristic of the collagens). Proteoglycans are a subclass of glycoproteins.
in which the carbohydrate moieties are polysaccharides that contain amino sugars (glycosaminoglycans). Carbohydrate macromolecules usually consist of various building blocks (monosaccharides such as mannose, galactose, GalNAc, etc.) that can be linked together in several different ways (the anomeric carbon of one sugar can be attached in alpha- or beta-linkage to one of several carbons of the linking sugar). This allows the structure to become branched. Whereas the other major biological macromolecules (proteins, nucleic acids) are linear and are synthesized by a linear template mechanism, large carbohydrates must be made on an assembly line (the endoplasmic reticulum-Golgi apparatus) along which various enzymes add and remove sugars. The sugar sequences and branching patterns are controlled not by copying a template but by the substrate specificities of these enzymes (mainly glycosyltransferases and glycosidases). The diversity of linkages and branching patterns between monomer building blocks conveys on carbohydrates the ability to carry an enormous amount of information in very compact structures [2]. The cell surface is covered with protein- and lipid-bound carbohydrate structures that vary significantly between cell types and at different stages of mammalian development. There is considerable evidence that these carbohydrates play important roles in the interaction of a cell with its cellular and fluid environment [3–5]. The essential role of glycoproteins and proteoglycans in development has been demonstrated by studies on mice with null mutations in various glycosyltransferases and glycosidases [6–14], on mutant *Drosophila melanogaster* [15] and *Caenorhabditis elegans* [16–19], and on human congenital diseases with defects in the glycosylation of proteins [20, 21]. This review will deal with several of the main autosomal recessive congenital disorders involving defects in the synthesis of Asn-linked glycans (tables 1, 2), congenital disorders of glycosylation (CDG), congenital dyserythropoietic anemia type II, and leukocyte adhesion deficiency type II. Other defects in glycosylation are listed in tables 1 and 3. Since at least 0.5–1% of the transcribed human genome is devoted to the production of proteins involved in the synthesis, degradation, and function of glycoconjugates [11], many other such congenital diseases may exist.

**Congenital Disorders of Glycosylation**

CDG (previously known as carbohydrate-deficient glycoprotein syndromes) are a group of congenital multisystemic diseases characterized by defective N-glycosylation. The discovery of these diseases was based on the observation by Jaeken et al. [22] of decreased serum thyroxine-binding globulin and increased arylsulfatase A activity in two patients with familial psychomotor retardation. In 1984, Jaeken et al. [23] reported sialic acid deficiency in serum and cerebrospinal fluid transferrin from identical twin sisters with demyelinating disease, demonstrating for the first time that this new syndrome was due to defective protein glycosylation. There were about 280 patients with this disease worldwide as of October 1998 [24]. In 1999, at a meeting held in Belgium, a new classification and nomenclature for CDG was proposed [25, 26]. Six distinct variants of CDG in group I have been described to date (types Ia–If; table 2) and the defects have been localized to deficiencies in the assembly of the dolichol-pyrophosphate-linked oligosaccharide N-glycan precursor and its transfer to asparagine residues on the nascent polypeptides. Two variants of CDG group II (types IIa and IIb; table 2) have been identified as defects in the processing of protein-bound N-glycans. CDG patients in which the defect has not yet been determined (table 2) will not be discussed here.

**CDG group I (CDG-I)**

The following discussion is based primarily on papers published prior to the separation of CDG group I patients into separate types. Since CDG-Ia is the most common type of CDG-I, the discussion of clinical and pathological features refers primarily to CDG-Ia patients. However, the section on clinical biochemistry is relevant to all CDG-I types.

**Clinical and pathological features**

CDG-I occurs worldwide and affects both sexes [27–34]. The patients show moderate to severe neurological disease, a characteristic dysmorphism, and variable involvement of other organs [24, 27, 32, 35–38]. In the neonatal period, the patients may show slow head movements, and in infancy, alternating internal strabismus, abnormal eye movements, axial hypotonia and hyporeflexia. Feeding problems, vomiting and diarrhea may occur, resulting in severe developmental delay and failure to thrive [39, 40]. Infants may show a distinctive lipodystrophy (peculiar distribution of subcutaneous fat), nipple retraction, and hypogonadism. Some infants show liver failure, cardiac insufficiency, pericardial effusion [41–43], nephrotic syndrome, and multiorgan failure [43–46]. Older children usually develop cerebellar ataxia and marked psychomotor retardation [47]. Retinitis pigmentosa [48, 49], joint contractures, skeletal deformities [50], stroke-like episodes, epilepsy, and peripheral neuropathy may also develop. About 20% of the patients die within the first year. Some adults show premature aging [51]. Language and motor development are severely delayed and walking without support is rarely achieved. The IQ ranges from 40 to 60 and the children usually have an extroverted and cheerful disposition.