

The CDG syndrome

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Abstract

The congenital disorders of glycosylation or carbohydrate-deficient glycoprotein (CDG) syndrome is a group of autosomal recessive diseases that affect the synthesis of glycoproteins. These diseases (frequency estimated to be 1/50,000-1/100,000) are characterized by neurological involvement that can be associated with multivisceral involvement. CDG syndromes are associated with different enzymatic deficits of which the most common is a phosphomannomutase deficit (corresponding to CDG Ia and representing 70% of the CDG syndromes). Psychomotor retardation is the most constant sign. The other signs often associated to various degrees are: lipocutaneous abnormalities (peau d'orange), olivopontocerebellar atrophy, skeletal anomalies, inverted nipples, coagulation disorders, and hepatic cytolysis and fibrosis. The biological diagnosis is based on the demonstration of abnormal glycosylation of serum glycoproteins, the measurement of leukocyte enzyme activities responsible and the search for mutations in the corresponding genes. The prenatal diagnosis of CDG syndrome can be achieved, once the diagnosis is confirmed in the index case.

Keywords

Carbohydrate-deficient glycoprotein, glycosylations disorder, phosphomannomutase deficiency

Name of the disease and synonyms

CDG syndrome

Congenital disorders of glycosylation

Previously Carbohydrate-deficient glycosylation syndrome

Definition/Classification

CDG syndrome represents a group of innate diseases affecting the synthesis of glycoproteins; their classification is based on the level of the limiting step of glycosylation.

CDG I

(upstream from the transfer of oligosaccharide onto the peptide chain) is the most common, with more than 500 cases described world-wide and more than 80 families in France. It corresponds to the partial-to-total absence of the glycan chains of serum N-glycoproteins.

CDG Ia

CDG Ia is an autosomal recessive disease characterized by a deficit in phosphomannomutase (PMM) activity and

mutations in the *PMM2* gene located on chromosome 16p13.

Only a limited number of cases of the other CDG I have been reported:

CDG Ib

CDG Ib is associated with a deficit in phosphomannose isomerase (*PMI* gene); it can be treated with mannose per os.

CDG Ic

CDG Ic presents a deficit in one of the glucosyltransferases of the endoplasmic reticulum (dolichyl-P-Glc:Man9GlcNAc2-PP-dolichyl alpha1,3 glucosyltransferase); it is characterized by mutations in the apoptosis-linked gene *hALG6*.

CDG Id

CDG Id is deficient in one of the mannosyltransferases of the endoplasmic reticulum (dolichyl-P-Man:Man5GlcNAc2-PP-dolichyl alpha1,3 mannosyltransferase); it is characterized by mutations in the *hALG3* gene.

CDG Ie

CDG Ie has a deficit in dolichyl-phosphate-mannose (Dol-P-Man) synthase of the endoplasmic reticulum; it is characterized by mutations in the *DPM1* gene.

CDG If

CDG If is associated with a deficit in Lec35, a protein whose role is not totally clear; it is characterized by mutations in the *Lec35* gene.

CDG Ig

CDG Ig presents a deficit in one of the mannosyltransferases of the endoplasmic reticulum (dolichyl-P-Man:Man7GlcNAc2-PP-dolichyl alpha1,6 mannosyltransferase); it is characterized by mutations in the *hALG12* gene.

Other new types of CDG deficiencies with limited cases described have been recently reported: CDG Ih, li and lh. These CDG types are caused by a defect in an endoplasmic reticulum-Golgi shuttle protein carrying multiple glycosyltransferases and nucleotide-sugar transporters. The corresponding genes have been identified.

CDG II

(downstream from the transfer of the oligosaccharide onto the peptide chain) is currently comprised of:

CDG II a

CDG II a is attributable to a deficit in UDP-GlcNAc:alpha-6-Dmannoside beta 1,2-N-Acetyl glucosaminyltransferase II (GnT II) of the median

compartment of the Golgi apparatus and mutations in the *MGAT2* gene.

CDG IIb

CDG IIb is attributable to a deficit in glucosidase I of the endoplasmic reticulum and mutations in the corresponding gene.

CDG IIc

CDG IIc (formerly called Leucocyte Adhesion Deficiency II; LAD II) is a deficit in the fucose transporter from the cytosolic compartment to the lumen of the Golgi apparatus; it is characterized by a mutation in the corresponding gene. It can be treated with fucose per os.

CDG IId

CDG IId is a deficit in galactosyltransferase of median Golgi, it is characterized by mutations in *GALT1* gene

CDGx

CDGx corresponds to patients whose deficit is unknown.

Clinical description

The clinical picture varies according to the type and is heterogeneous.

CDG Ia in its usual form is very characteristic and associated as of birth with an internal strabismus, marked hypotonia, inverted nipples and a very characteristic dysmorphism (almond-shaped eyes and large forehead). Atrophied cerebellum and/or cerebral trunk (olivopontocerebellar atrophy) are present. The first months of life see the appearance of lipocutaneous anomalies (peau d'orange, infiltration of the external face of the thighs and buttocks) that can already be present at birth, very frequently pigmentary retinitis and moderate hepatomegaly with cytotoxicity in association with quasi-constant hepatic fibrosis. Cardiac involvement (pericarditis, cardiomyopathy) is common and often responsible for death in the first or second year of life. Other manifestations can also be seen: renal, diverse endocrine (hypoglycemia due to hyperinsulinemia, hypogonadism, electrolyte loss), coagulation disorders. Sometimes, the disease can apparently start with one symptom or another. When seen late, the cutaneous signs have a tendency to disappear and the neurological manifestations tend to predominate (psychomotor retardation, peripheral neuropathy, ataxia).

CDG Ib has no neurological manifestations but hepatodigestive symptoms predominate (hepatic fibrosis, exsudative enteropathy, recurrent episodes of angiocolitis, hepatic cytotoxicity, coagulation disorders) and short-term fasting hypoglycemia that stimulates hyperinsulinism and can reveal the disease.

The other types (c, d and e) are too rare to describe the symptomatology, which seems to be primarily neurological (mental retardation, convulsions or grand-mal epilepsy).

Diagnostic criteria

The association of neurological signs, pigmentary retinitis, cutaneous signs and hepatodigestive signs (cytolysis, fibrosis) is highly suggestive of a CDG syndrome.

The diagnosis is based on the demonstration of serum N-glycoprotein glycosylation anomalies (isoelectrofocalization of serum transferrin or Western blot of different serum glycoproteins) and dosage of the responsible cellular (leukocytes or fibroblasts) enzymes, and the search for the corresponding mutations. Congenital galactosemia and fructose intolerance are considered to be secondary CDG syndromes since the serum glycoproteins present the same glycosylation anomalies.

Prenatal diagnosis

The prenatal diagnosis of CDG syndrome can be achieved, once the diagnosis is confirmed in the index case by searching for mutations in the corresponding gene.

Management

CDG Ib can be treated orally with mannose and CDG IIc with fucose. Monitoring of mannose uptake by blood assay is recommended

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