Syndrome of the month

Carbohydrate deficient glycoprotein (CDG) syndrome type I

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CDG syndrome type I is a genetic, multisystemic disorder characterised by a partial deficiency of the N-linked glycans of secretory glycoproteins, lysosomal enzymes, and probably also membranous glycoproteins. The first patients were reported in 1980.[1] The basic defect was elucidated only in 1995 as a phosphomannomutase deficiency.[2] As of February 1996 some 200 patients worldwide (published and unpublished) were known to the authors. Since the N-linked glycoproteins play important roles in every organ and biochemical system of the body, it is no wonder that this syndrome is one of the most complex metabolic diseases known, with an extremely broad biochemical as well as clinical spectrum.[3–6]

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Clinical presentation

For those familiar with the disease it can often be diagnosed in the first days of life. The nervous system is affected in the great majority of known patients and all other organs are involved in a variable way. The neurological picture comprises alternating internal strabismus, abnormal (roving) eye movements, axial hypotonia, psychomotor retardation (usually severe), ataxia, and often hyporeflexia. After infancy, as a rule there are retinitis pigmentosa, joint contractures, stroke–like episodes (in about 50%), and sometimes epilepsy. Only rarely do these patients achieve walking without support, but there is no regression.

Other features are mild facial dysmorphism (fig 1), in particular large, somewhat dysplastic ears, abnormal subcutaneous adipose tissue distribution (fat pads, "orange peel" skin, "tal-

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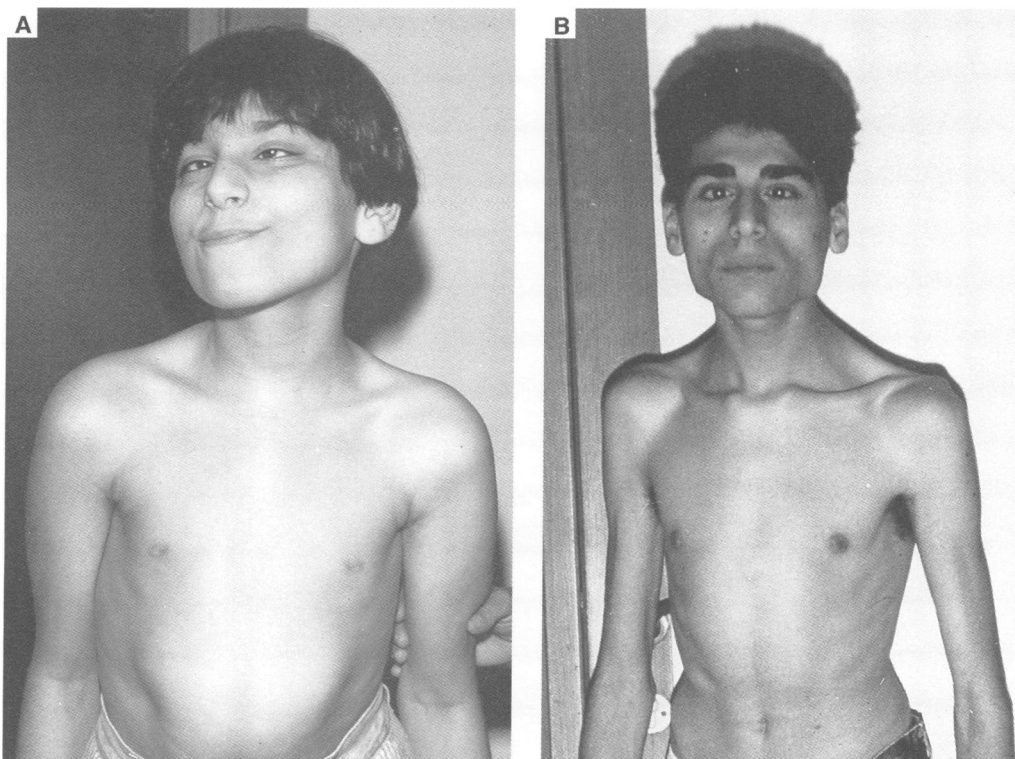
Figure 1 Sibs with CDG syndrome type I. (A) A girl aged 16 years; note strabismus and absence of breast development owing to hypogonadism. (B) Her brother aged 18 years.
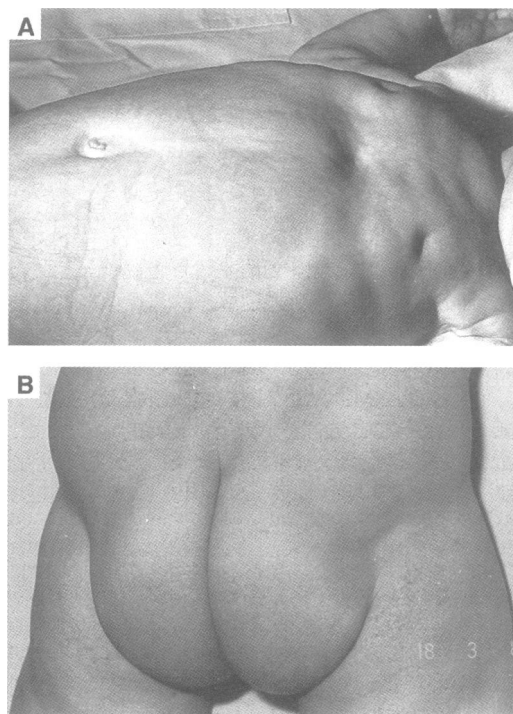
Figure 2   Typical features of CDG syndrome type I: (A) inverted nipples, (B) fat pads on the buttocks.

low") (fig 2), as well as dystrophic extremities, mild to moderate hepatomegaly, skeletal abnormalities, hypogonadism, and proteinuria. It is important to note that dysmorphism can be minimal. Some infants develop pericardial effusion or cardiomyopathy or both. The patients have often an extrovert and cheerful personality.

About 20% have died during the first years of life owing to severe infection, multiorgan failure, liver failure, nephrotic syndrome,[7 8] cardiac insufficiency, or in status epilepticus.[9] Postmortem findings include olivopontocerebellar hypoplasia, loss of neurons, and gliosis in the cerebral cortex, basal ganglia, and thalamus, involvement of the spinal cord,[9] renal cysts, fibrosis of the testes, and lymph node abnormalities. The peripheral nerves show decreased myelin and multivacuolar inclusions in the Schwann cells. The fibroblasts show signs of premature aging, cytoplasmic inclusions (fig 3), and dilated endoplasmic reticulum. Liver pathology is characterised by fibrosis, steatosis, and glycogen storage, and electron microscopy shows myelin-like and granular lysosomal inclusions and dilated endoplasmic reticulum in the hepatocytes.

Biochemical features and basic defect

A large number of serum glycoproteins are abnormal including transport proteins, glycoprotein hormones, complement factors, lysosomal and other enzymes, enzyme inhibitors, and others. It was found that these patients have a unique coagulopathy (with a marked factor XI deficiency)[10] as well as a new endocrinological entity.[11 12] In general, the glycoprotein concentrations or enzyme activities in serum are decreased but some are increased (for example, follicle stimulating hormone, arylsulphatase A) and others are normal (for example, transferrin). Isoelectric focusing of these glycoproteins shows a cathodal shift. This is because of a partial deficiency of sialic acid,
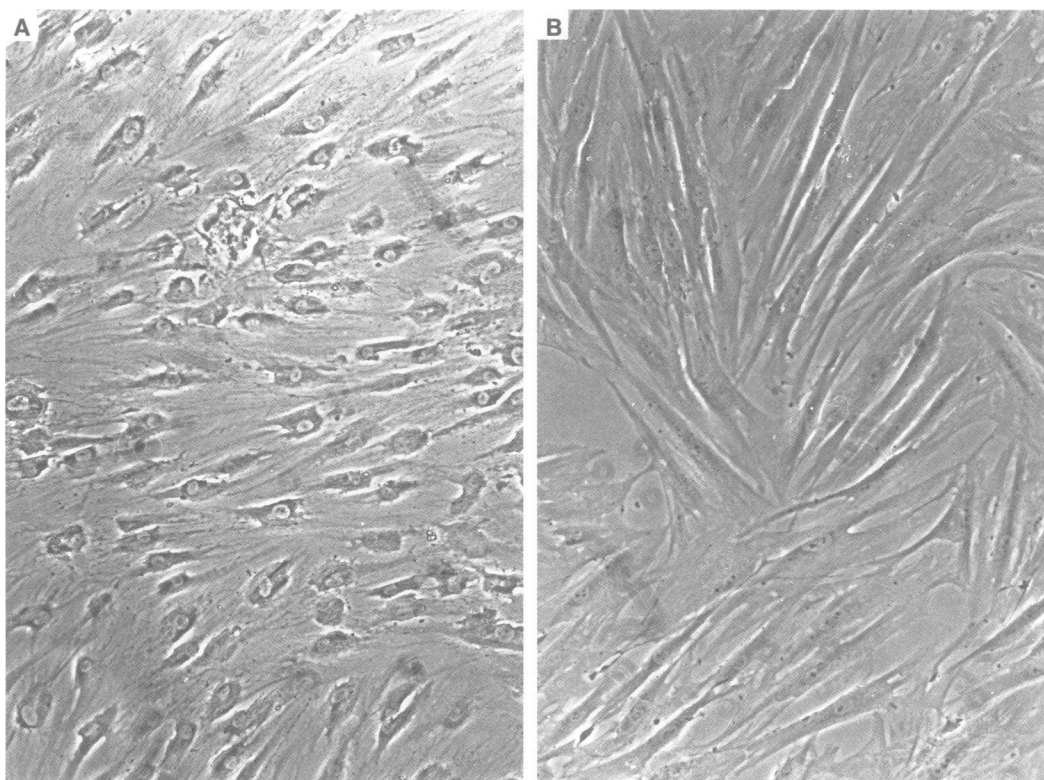

Figure 3   Cultured fibroblasts from patient with CDG syndrome type I showing (A) features of premature aging (inclusions and ballooning) compared with control (B).

a negatively charged sugar. Moreover, these patients have, to various extents, decreased serum levels of copper, iron, zinc, cholesterol, cortisol, total thyroxine (T$_4$), and tri-iodo-thyronine, most probably as a consequence of the decreased levels of transport proteins. Other non-glycoprotein abnormalities are hypoalbuminaemia and increased serum levels of growth hormone and insulin associated with normal or subnormal growth and mostly normal glycaemia. These endocrinological abnormalities are indicative of defects in receptors (membrane glycoproteins). In cultured skin fibroblasts, aberrant expression has been found of the genes for the small proteoglycans decorin and biglycan.[13]

The partial deficiency of sialic acid in serum transferrin was first reported in 1984.[14] Subsequently galactose and N-acetylglucosamine were also found to be deficient.[15 16] In 1992 and 1993 Japanese workers showed that the number of glycans on serum transferrin was decreased, pointing to a disturbance in the early steps of glycosylation, possibly in the formation of the dolicholpyrophosphate oligosaccharide precursor or in its transfer to the acceptor protein.[17 18] Hence a decreased incorporation was found of [^{3}H] mannose into N-linked oligosaccharides and their lipid precursors in fibroblasts of patients with CDG syndrome type I.[19 20] Finally, phosphomannomutase deficiency was shown to be the major cause of the CDG syndrome type I[2] (unpublished observations). Phosphomannomutase converts mannose-6-phosphate into mannose-1-phosphate, which is then converted to GDP-mannose. This compound is the donor of the nine mannose units needed for the synthesis of the dolicholpyrophosphate oligosaccharide in the endoplasmic reticulum. Phosphomannomutase has been well characterised in yeast where it is encoded by the SEC53 gene. It is a protein that acts as a dimer and shows phosphomannomutase activity in yeast and *E coli*.[21] No published reports are available on phosphomannomutase activity in man. Efforts to clone and map the human homologue of SEC53 are under way.

Diagnosis

CDG syndrome type I should be considered in any unexplained neurological syndrome including psychomotor retardation and, in infancy, axial hypotonia, particularly when associated with various combinations of the above mentioned clinical and biochemical abnormalities. Particularly suggestive are unexplained feeding problems with failure to thrive, abnormal subcutaneous fat distribution, retracted nipples, unexplained liver fibrosis, and decreased coagulation factor XI and antithrombin III. However, as said above, dysmorphic features may be minimal and it seems that even significant encephalopathy may be absent. Some patients have received a diagnosis of leprechaunism, lipodystrophy, Smith-Lemli-Opitz syndrome, a peroxisomal disorder, or Marfan syndrome. Owing to the partial thyroxine binding globulin deficiency, some of these

patients can be detected through neonatal screening for congenital hypothyroidism with T$_4$ measurement.

The diagnosis of CDG syndrome type I is usually made by isoelectric focusing and immunofixation of serum transferrin. Normal serum transferrin is mainly composed of tetrasialotransferrin besides small amounts of mono-, di, tri-, penta-, and hexasialotransferrin. The partial deficiency of sialic acid in CDG syndrome type I causes a cathodal shift resulting in a marked increase of both asialo- and disialotransferrin, and a decrease of tetra-, penta-, and hexasialotransferrin. These changes can be measured by densitometry. The carbohydrate deficient transferrin (CDT) assay enables the quantification of the total sialic acid deficient serum transferrin.[22] It should be noted that similar transferrin changes are found in chronic alcoholism,[23] galactosaemia,[24-26] and fructosaemia.[27]

The diagnosis is confirmed by finding decreased phosphomannomutase activity in leucocytes, fibroblasts, or liver. Heterozygote detection is now possible as well as prenatal diagnosis, since the enzyme is active in amniocytes.[2] Remarkably, in the fetus with CDG syndrome type I, transferrin isoelectric focusing and other tests used for the detection of the glycosylation defect show normal results.[28]

Three other CDG syndrome types have been reported each in only two families: type II resulting from a Golgi localised N-acetyl-glucosaminyltransferase II deficiency,[29] and types III[30] and IV[31] with an unknown basic defect. All three show a cathodal shift on serum transferrin isoelectric focusing different from type I.

Genetics

CDG syndrome type I is inherited in an autosomal recessive mode. The CDG syndrome type I locus has recently been mapped by Martinsson *et al*[32] to chromosome 16p, to a 13 cM interval between markers D16S406 and S16S500.

We have analysed this region in 17 families of Belgian, Dutch, French, German, Canadian, and Italian origin. Linkage to the region between D16S406 and S16S500 was confirmed in 10 of 11 informative families. In one family with two affected sibs, the disease was not linked to chromosome 16p.[33]

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