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Review

Carbohydrate-deficient glycoprotein syndrome type IA (phosphomannomutase-deficiency)

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Abstract

The carbohydrate-deficient glycoprotein or CDG syndromes (OMIM 212065) are a recently delineated group of genetic, multisystem diseases with variable dysmorphic features. The known CDG syndromes are characterized by a partial deficiency of the *N*-linked glycans of secretory glycoproteins, lysosomal enzymes, and probably also membranous glycoproteins. Due to the deficiency of terminal *N*-acetylneuraminic acid or sialic acid, the glycan changes can be observed in serum transferrin or other glycoproteins using isoelectrofocusing with immunofixation as the most widely used diagnostic technique. Most patients show a serum sialotransferrin pattern characterized by increased di- and asialotransferrin bands (type I pattern). The majority of patients with type I are phosphomannomutase deficient (type IA), while in a few other patients, deficiencies of phosphomannose isomerase (type IB) or endoplasmic reticulum glucosyltransferase (type IC) have been demonstrated. This review is an update on CDG syndrome type IA.

Keywords: Carbohydrate-deficient glycoprotein syndrome; Glycoprotein; *N*-Glycosylation; Serum transferrin; Phosphomannomutase deficiency

Contents

Abbreviations: APTS, 9-aminopyrene-1,4,6-trisulfonate; CDG, carbohydrate-deficient glycoprotein; CDGS, carbohydrate-deficient glycoprotein syndrome; Dol, dolichol; ER, endoplasmic reticulum; EST, expressed sequence tag; GDP, guanosine diphosphate; CDT, carbohydrate-deficient transferrin; GC, guanosine-cytosine; CpG, cytidine-phosphate-guanine; GnT, *N*-acetylglucosaminyltransferase; GPI, glycosyl phosphatidylinositol; IEF, isoelectrofocusing; Man1P, mannose 1-phosphate; Man6P, mannose 6-phosphate; PMM, phosphomannomutase

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1. Introduction

The CDG syndromes are a family of genetic disorders characterized by a deficiency of the glycan moiety of glycoproteins. Only defects in *N*-glycan synthesis have been characterized in CDG syndromes to date. The synthesis of *N*-glycans occurs over three cellular compartments: a cytosolic compartment, the endoplasmic reticulum (ER) and the Golgi apparatus. Some forty (enzymatic and transport) steps are involved. The first part of this pathway comprises the synthesis of guanosine diphosphate (GDP)-mannose from fructose 6-phosphate, an intermediate of the glycolytic pathway. On the cytoplasmic side and subsequently on the lumenal side of the ER a dolichyl-pyrophosphate oligosaccharide (Dol-pyrophosphate-GlcNAc2-Man9-Glc3) precursor is gradually assembled. Subsequently, the oligosaccharide moiety is transferred to selected asparagines of nascent proteins by the oligosaccharyltransferase complex. In the third part, the three glucoses and six mannoses are removed and replaced by two or more residues each of *N*-acetylglucosamine, galactose and sialic acid, in that order, in the Golgi apparatus. In some glycoproteins (lysosomal enzymes) only the three glucose residues are removed and the resulting glycoproteins retain a high number of mannoses on most of their glycans. This is followed by phosphorylation of mannoses, binding of the enzymes to mannose 6-phosphate (Man6P) insulin-like growth factor II receptors and uptake in the lysosomes [1,2].

Glycans are very important for the metabolism, structure and function of glycoproteins and other glycoconjugates [2–4] as evidenced by the severe diseases resulting from defects in their synthesis. The discovery of these diseases was based on the observation by Jaeken et al. [5] of unusual serum protein abnormalities in the two princeps patients, namely, a decrease of thyroxine-binding globulin and an increase of arylsulfatase A activity. The search for a defect as a common feature of these and other proteins finally attracted attention to the glycan moiety since sialic acid deficiency in serum transferrin was strongly suggested by isoelectrofocusing (IEF) [6]. As of October 1998, about 280 patients world-wide (published and unpublished) were known to the authors [7–23]. IEF of serum transferrin remains the cornerstone of the diagnosis of these diseases [6]. Deficiency of the terminal, negatively charged sialic acid results in a cathodal shift of the IEF pattern. Three diseases associated with a type I pattern have been well characterized at the enzymatic level: phosphomannomutase (PMM) and phosphomannose isomerase (PMI) deficiency (CDGS type IA and type IB, respectively), both pre-endoplasmic reticulum (ER) disorders, and ER glucosyltransferase deficiency (CDGS type IC; also called type V). In a considerable number of patients, the basic defect still remains to be determined. This review is limited to CDGS type IA.

2. Clinical presentation

CDGS type IA occurs world-wide [24–28] and affects both sexes equally [29]. There exists a great variability in clinical expression even among affected siblings. The clinical presentation includes three main features: a moderate to severe neurological disease, a more-or-less typical dysmorphy, and a variable involvement of different organs. The diagnosis can be made in the first days of life. The neurological picture comprises abnormal slow rolling horizontal or vertical eye movements combined with slow head movements in the neonatal period, alternating internal strabismus, axial hypotonia and hyporeflexia. Later, ataxia as well as a marked psychomotor retardation generally becomes obvious [20]. After infancy, retinitis pigmentosa [30,31], joint contractures, stroke-like episodes (in about 50% of the cases), and

sometimes epilepsy develop. During the first year(s) of life there are variable feeding problems that can result in severe failure to thrive and that can necessitate nasogastric tube feeding or feeding via gastrostomy [32].

A minority of infants have severe organ problems, such as liver failure, cardiac insufficiency, nephrotic syndrome or multiorgan failure [17,33–35]. Together with severe infections, these are the main causes of death. Overall mortality is about 20% occurring mostly in the first years of life. Some adults show striking premature aging [36]. Only rarely do these patients achieve walking without support, but, as a rule there, is no regression. Their IQ ranges from 40 to 60 and they mostly have an extrovert and cheerful personality.

3. Biochemical features

3.1. Glycoprotein abnormalities

Numerous glycoproteins demonstrate an abnormal protein heterogeneity. In serum, data have been reported on transport proteins [5,6,37–39], coagulation and anticoagulation factors [37–44], hormones [5,45–47], lysosomal and other enzymes [5,48–52], as well as glycoproteins [37,53–58]. Information is also available on glycoproteins in cerebrospinal fluid [6,59,60], leukocytes [48], fibroblasts and liver [56,61]. Most glycoprotein concentrations or enzyme activities in serum are decreased; others are increased (e.g. several lysosomal enzyme activities [48]) or normal (e.g. transferrin, immunoglobulins [62]).

Human serum transferrin is involved in iron metabolism; it contains 679 amino acid residues and has a molecular mass of 75 143 kilodalton (kDa) with an *N*-terminal domain (residues 1–336) and a C-terminal domain (residues 337–679). There are two glycosylation sites located on residues 413 and 611 with mostly biantennary *N*-acetyllactosamine-type glycans [63,64] and a small amount of tri- and tetra-antennary *N*-acetyllactosamine type glycans [65,66]. Due to the heterogeneity of the glycan structures [67], serum transferrin consists of a pool of glycovariants detectable by immuno-isoelectrofocusing [68] using monospecific anti-transferrin antibody. Table 1A and B list the glycovariant composition of transferrin (%) in control sera ($n=96$) and serum of CDGS type IA patients ($n=26$), respectively. Data were obtained by IEF of iron-saturated transferrin separated on agarose gels in a pH gradient 5.0–7.0 using the Pharmacia PhastSystem followed by densitometry. Prominent asialo- and disialotransferrins and decreased tetra-, penta- and hexasialotransferrins are observed in the patients sera [6,25,37,54,56]. Mono- and trisialotransferrin composition remain unchanged.

Electrospray ionization-mass spectrometry (ESI/MS) of whole serum transferrin from CDGS type IA patients revealed both the normal and a smaller glycovariant that correlated with tetra- and disialo-

Table 1
Percentile values and range of sialotransferrin fractions (expressed as %) in serum from control patients (A, $n=96$), and patients with CDG syndrome type IA (B, $n=26$) as indicated by the number of sialic acids per transferrin molecule

	0	1	2	3	4	5	6
(A)							
P25	0	0	2.9	8.6	52.8	20.7	4.3
P50	0	1.1	3.5	9.8	55.9	22.7	5.1
P75	0	2.5	4.1	12	59.3	25.6	6.1
Range	0–1.4	0–5.3	1–7.2	3.7–17.1	45.8–72.9	10.2–29.9	0–9
(B)							
P25	5.6	1.5	27.7	8.6	28.3	6.8	0.3
P50	8.5	2.3	30.9	10.8	34.8	9.3	1.6
P75	13.8	3.6	34.7	12	39.7	12	2.6
Range	1.7–28.5	0–5.1	14.3–37.1	6.4–18.7	17.5–56.5	5.3–17	0–5.5

transferrin [69]. This was confirmed by Yamashita et al. [70,71] who also demonstrated by ESI/MS that the non-glycosylation site in the disialotransferrin isoform was not specific. Complex oligosaccharide isomers can be analyzed as 9-aminopyren-1,4,6-trisulfonate (APTS) derivatives by capillary electrophoresis with laser-induced fluorescence detection [72]. Fig. 1A shows the electropherogram of APTS-labeled glycans obtained after enzymatic release from 200 μg purified control serum transferrin in the presence of 2 nmol maltose (reference substance) according to the eCAP *N*-linked Oligosaccharide Profiling Kit procedure (Beckman, USA). The arrow indicates the main glycan fraction corresponding to the biantennary glycan resulting from tetrasialotransferrin. The electropherogram in Fig. 1B shows the APTS-labeled glycans released from serum transferrin of a CDGS type IA patient. The migration time of the main glycan fraction with respect to maltose is the same as in Fig. 1A suggesting a biantennary glycan structure also for the disialotransferrin fraction [70,71,73].

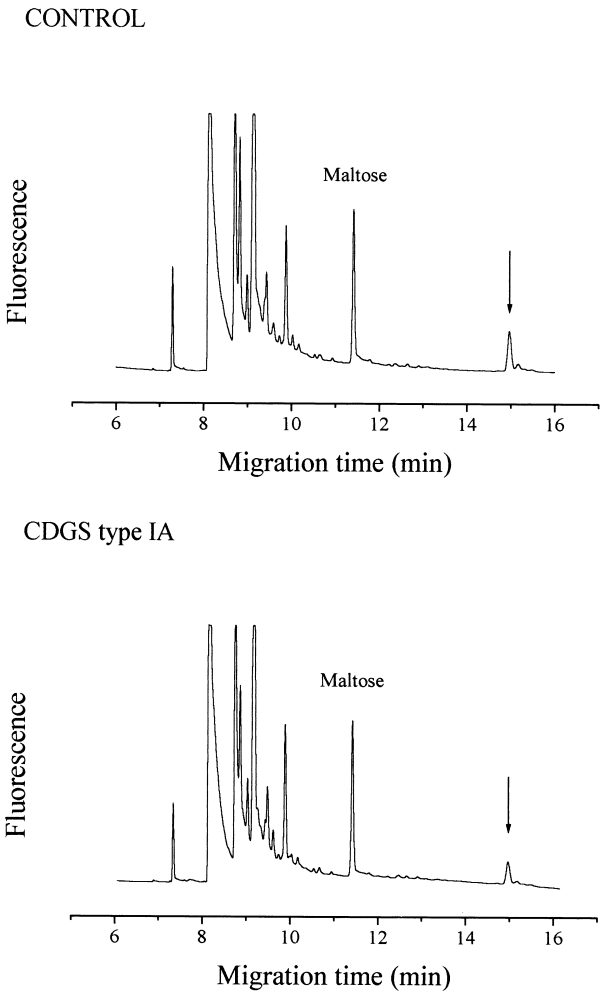

Fig. 1. Capillary gel electrophoretic separation of maltose (reference substance) and the *N*-linked oligosaccharides released from serum transferrin by the eCAP *N*-linked Oligosaccharide Profiling Kit procedure (Beckman, USA). Arrows indicate the main glycan fraction for a control (A), and a type IA patient (B). (See text.)

Remarkably, in serum of preterm infants with PMM deficiency (postmenstrual age <37 weeks) a normal IEF pattern of β-hexosaminidase, α1-antitrypsin, and transferrin has been observed [74].

3.2. Phosphomannomutase deficiency

N-Linked oligosaccharides on serum transferrin of patients have a normal structure, but their total number is decreased. This suggested a disturbance in the first steps of the pathway comprising the synthesis of GDP-mannose from fructose 6-phosphate (Fig. 2), the formation of the dolichyl-pyrophosphate oligosaccharide precursor or its transfer to the acceptor protein [69,71,75]. It was also found that fibroblasts from patients with CDGS type IA incorporate less [^{3}H]mannose into glycoprotein glycans and contain truncated dolichol-linked oligosaccharide precursors [75–78]. Defects in the synthesis of Man6P from glucose [79], in the synthesis of dolichyl-phosphate and *N*-acetylglucosaminyl pyrophosphoryldolichol [80] as well as a deficiency of *N*-oligosaccharyltransferase activity [81] were excluded. Finally, phosphomannomutase (PMM) deficiency was identified [82] (Fig. 2). This defect causes a reduced production of mannose 1-phosphate (Man1P), GDP-mannose, GDP-fucose and dolichyl-phosphomannose, but not an increase of the substrate Man6P [77,83]. Moreover, mannose levels are reduced in serum of these patients [84]. It seems that approximately 80% [26,85] of the CDSG type I patients have PMM deficiency.

It has been shown recently that in rat [86,87] as well as in man two different PMM isozymes exist: PMM1, encoded by chromosome 22q13 [88–90] and PMM2, encoded by chromosome 16p13 [91]. They share about 66% sequence identity and are homologous to PMMs from *S. cerevisiae* (also known as SEC53) and *C. albicans*.

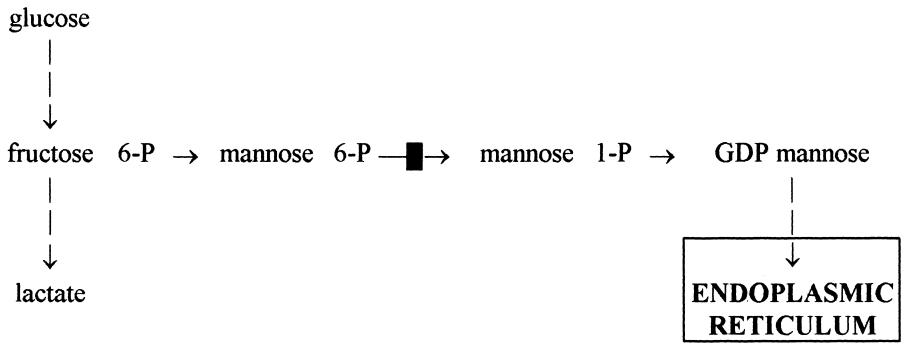

Fig. 2. Part of the *N*-glycosylation pathway. Vertical bar indicates the location of PMM deficiency.

Human PMM1 and PMM2 have been overexpressed in *E. coli* and their kinetic properties have been investigated [86–88]. Like most phosphomutases, eukaryotic PMMs require a bisphosphate cofactor (1,6-bisphosphate of glucose or mannose in the case of PMM), that phosphorylates the catalytic site. Man6P is first converted into mannose 1,6-bisphosphate which is then transformed into Man1P. Human PMM, as well as yeast PMM are homodimers with subunits of 30 kDa [86,92]. The human PMM1 and the yeast PMM have approximately equal activity in converting glucose 1-phosphate to glucose 6-phosphate as in converting Man1P to Man6P, whereas PMM2 acts 20 times more rapidly as a phosphomannomutase than as a phosphoglucomutase [87]. In addition, PMM1 though not PMM2, acts as a hexose 1,6-bisphosphatase which hydrolyzes both mannose 1,6-bisphosphate and glucose 1,6-bisphosphate at a rate corresponding to about 3% of its mutase activity. PMM2 is therefore more specific than PMM1, both in terms of substrate recognition and in the kind of reaction that is catalyzed. PMM2 also has a significantly higher affinity for its hexose bisphosphate cofactor than PMM1 [86].

The distributions of PMM1 and PMM2 in different tissues have been studied in rat, based on differences in their kinetic properties as well as on their reactivity to antibodies raised against the two human isozymes. PMM1 activity appears to be more restricted to the brain and to the lungs, where it constitutes about 65 and 10%, respectively, of the total PMM activity. PMM2, however, is more widely distributed and appears to be responsible for more than 97% of the activity in other tissues, including cerebellum [87]. The finding that the PMM activity of one patient with CDGS type IA was below the detection level both in liver and in skeletal muscle argues also for PMM2 being the only isozyme expressed in these two tissues in man (Van Schaftingen, unpublished data).

The finding of very low activities ($< 5\%$ of the normal activity) in liver, leukocytes, fibroblasts or lymphoblasts of the majority of patients with CDGS type IA indicates that most of the mutations are particularly severe, a finding which is likely confirmed by observations on mutant proteins expressed in bacterial systems [87]. In some patients, activities were up to 25% higher in fibroblasts or lymphocytes than in leukocytes [26,93]. It is not known presently whether this high activity in fibroblasts or lymphoblasts results from abnormal expression of PMM1 or from overexpression of a partially active enzyme.

4. Molecular biology of the *PMM2* gene

CDGS type IA is inherited in an autosomal recessive manner and the gene has been localized to chromosome 16p13 by linkage analysis [94,95]. Fine mapping of the disease locus was obtained by haplotype and linkage disequilibrium analysis in Scandinavian families [96]. By observing critical cross-overs in carriers identified by measuring PMM activities in siblings of patients, Schollen et al. [97] located the gene between markers D16S404 and D16S406. The identification of the *PMM2* gene on chromosome 16p13 and the identification of mutations in this gene that segregate with the disease [91] gave final support to the biochemical evidence that PMM deficiency is the basis for CDGS type IA [24,82]. The human *PMM2* gene [91] and the *PMM1* gene (OMIM 601786) [88] were identified on the basis of the sequence similarity

of a number of expressed sequence tags (ESTs) in the public database with the sequence of yeast PMM or SEC53. The cDNA of PMM2 has an open reading frame of 738 base pairs and encodes a protein of 246 amino acids. The protein has been expressed in vitro, and shown to have PMM activity. The degree of identity with yeast SEC53 is slightly higher for PMM2 than for PMM1 [88,91]. The *PMM2* gene consists of eight exons spanning approximately 20 kilobases of genomic DNA [91,97]. An analysis of the sequence of the 5′ region of the gene suggests that *PMM2* has a housekeeping promoter; which is expected for an enzyme with a very fundamental role in post-translational processing. However, the variable expression suggests that the basal expression can be modulated in a tissue-specific manner.

Molecular analysis of the *PMM2* gene has led to the identification of a large number of mutations which are generally of the missense type ([91,93], T. Martinsson; N. Seta; V. Cormier-Daire, unpublished data). The mutations are numbered according to their position in the cDNA (Genbank accession no. 85773) [91] (Fig. 3).

The most intriguing observation is the total lack of patients homozygous for the most frequent mutation: R141H [93] (T. Martinsson, unpublished data). On the other hand, patients homozygous for the relatively frequent F119L mutation were found [93,98] as well as one patient homozygous for the D65Y mutation [93]. Thus, it is suggested that the R141H mutation is a severe mutation, and homozygosity may not be compatible with life. It might also give rise to a different phenotype or no phenotype at all.

Due to the extensive allelic heterogeneity revealed by the mutation analysis, only limited inferences can be made from the genotype–phenotype comparison. There is no clear correlation between the PMM activities and the genotype in 6 and 14 patients with the R141H/P113L and R141H/F119L combinations, respectively. A remarkable observation is the high mortality in the patients with the D188G/R141H genotype where four of five patients died before the age of 2 years, while the fifth patient, now 10 years of age, is severely affected. The twin patients described originally [5] are now 22 years old and relatively well, and have the R141H/P113L genotype. The R123G mutation is observed in two Spanish patients with pubertal development, which is not normally seen in CDGS type IA. There is a relatively high residual PMM activity in fibroblasts of the D65Y/D65Y patient [93]. However, the same D65Y mutation, in combination with the R141H mutation was found in a patient with a severe phenotype, who died at a very young age [93]. There is emerging data on adult cases of CDGS type IA. A 35-year-old patient, with a typical history of CDGS type IA was homozygous for the F119L mutation [93,98]. French investigators identified two patients 30 and 33 years of age with the C9Y/R141H genotype (N. Seta; V. Cormier-Daire, unpublished data).

Northern analysis of human tissues showed high-

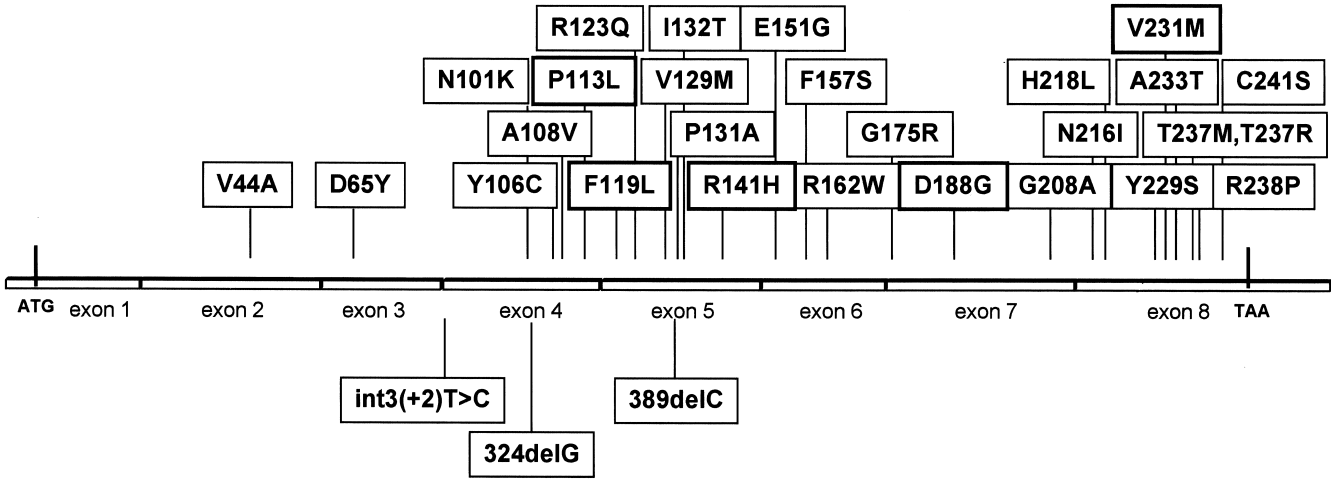

Fig. 3. Schematic diagram of *PMM2* cDNA, indicating the various mutations found in the gene on the exons. Mutations that have been relatively frequently encountered are indicated in boxes bordered by the thicker lines.

est expression of the PMM2 gene in pancreas and liver, two organs that both have a high production of secreted proteins. The gene is also expressed in kidney and placenta, and to a lesser extent in skeletal muscle and heart, and weakly in brain. On Northern blots, no expression is detected in lung [91]. The expression pattern of PMM1 is different from the pattern obtained for PMM2. In brain PMM1 is highly expressed [88]. It is not clear at present how these levels of expression would correlate to the clinical picture, in which brain is one of the most severely affected organs. Immunohistological data are not available yet.

In the course of the mapping experiments, a processed pseudogene was identified on chromosome 18 [97] that closely related to *PMM2*. When compared to *PMM2*, several base substitutions and single base insertions or deletions are present, suggesting that this processed pseudogene (*PMM2ψ*) has been inactivated by mutations. Remarkably, several base substitutions in *PMM2* that are associated with disease, are also present at the corresponding positions in the *PMM2ψ*. Thus, mutations that occur at a slow rate in the active gene in the population have also accumulated in the processed pseudogene. This is an important observation, because these mutations might interfere with certain mutation detection strategies, e.g. dot blot analysis. Therefore probes need to be designed carefully.

5. Diagnosis

The CDGS type IA is diagnosed by IEF and immunofixation of serum transferrin [6,25] or transferrin obtained from dried blood spots [99] (Table 1B). When an abnormal pattern is observed, IEF of another glycoprotein (e.g. β-hexosaminidase, thyroxine-binding globulin) is required to eliminate protein variation [100]. Further confirmation should be obtained by finding decreased PMM activity in leukocytes or fibroblasts [26,78,82]. It must be kept in mind that cord sera from controls show increased asialo-, mono- and disialotransferrin fractions [101]. A saturation by iron is required to produce the typical IEF pattern [102]. EDTA plasma can produce deviating patterns [19], only serum or heparin plasma should be used. The determination of carbohydrate-deficient transferrin (CDT) in also used as screening test. This method, initially developed for diagnosing alcohol abuse, measures the total concentration of cathodal isotransferrins in serum, while the normal components are retained by the anion exchanger. In this case, the microanion exchange chromatography of transferrin is followed by a transferrin radioimmunoassay of the eluate [103,104]. Except when rare genetic D variants of transferrin are present, increased concentrations of CDT indicate a reduction of its sialic acid content [52,105]. However, the CDT test provides only limited information for the diagnosis of CDG syndromes because the distribution of the abnormal glycovariants remains unknown.

A diagnosis of CDGS type IA should be completed by mutational analysis. Given the frequency of the R141H, F119L and P113L mutations, the obvious approach is to search for these mutations first. Due to this heterogeneity, PMM assays are still useful for diagnosis. However, in some cases, the activity found in fibroblasts or in lymphoblasts still represents up to about 30% of the control value, whereas in other samples derived from the same patients or from other patients with the same genotype, the activity was less than 5% of the control activity [93]. This problem has not been encountered in assays performed with fresh material such as leukocytes or liver. In the latter cases, a profound deficiency has nearly always been observed. PMM measurements are also useful for the identification of carriers. If cells from an affected child are not available, indirect evidence can be obtained from the PMM activities in leukocytes from the parents [106]. In view of the genetic heterogeneity, prenatal testing should only be offered to families with a documented PMM deficiency and mutations in PMM2.

6. Conclusion

No efficient treatment is available at present. Although mannose is able to correct glycosylation in vitro in fibroblasts with PMM deficiency [77,107,108], in vivo trials with oral and intravenous mannose did not cause any clinical or biochemical improvement [19,109–111].

CDGS type IA has a broad phenotype. Recently, a

female CDGS type IA patient presented with approximately 10% of the normal PMM activity, but with very mild clinical symptoms [112]. Extensive screening is therefore recommended by performing serum sialotransferrin IEF analysis also in patients with only mild psychomotor retardation and no or only minor dysmorphy.

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