Review

The clinical spectrum of phosphomannomutase 2 deficiency (CDG-Ia)

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A B S T R A C T

Congenital disorders of glycosylation are a clinically and genetically heterogeneous group of disorders resulting from abnormal glycosylation of various glycoconjugates. The first description of congenital disorders of glycosylation was published in the early 80s and once screening tests for glycosylation disorders (CDGs) became readily available, CDG-Ia became the most frequently diagnosed CDG subtype. CDG-Ia is pan-ethnic and the spectrum of the clinical manifestations is still evolving: it spans from severe hydrops fetalis and fetal loss to a (nearly) normal phenotype. However, the most common presentation in infancy is of a multisystem disorder with central nervous system involvement.

1. Introduction

Congenital disorders of glycosylation (CDG) are a rapidly enlarging group of (neuro)metabolic disorders. The first patients were described by the Belgian paediatrician Professor Jaak Jaeken in 1980 [1] and it took 15 years for the biochemical basis to be unravelled, and the defective enzyme, phosphomannomutase (PMM) identified [2]. It was then understood, that a deficiency of this cytosolic enzyme leads to an early disruption of the N-glycan assembly of glycoproteins. Another two years later, the gene was cloned and the diagnosis of so called ‘CDG-Ia’ (OMIM # 212065) could be confirmed by mutational studies [3]. Most of CDG subtypes including CDG-Ia are inherited as autosomal recessives.

When CDG was first described it was known as disialotransferrin developmental deficiency or carbohydrate deficient glycoprotein syndrome or Jaeken’s disease, clinicians looked out for patients presenting with similar symptoms as originally described. This was a combination of developmental delay, peculiar fat pads, cerebellar hypoplasia and inverted nipples [4]. However, once a powerful screening test (transferrin isoelectric focusing) was established in 1984 [5] and was applied on a broader population, it soon became evident, that CDG-Ia is a multisystem disorder with a highly variable phenotype.

It was thought that the course of patients with CDG-Ia will usually progress through four stages: the infantile multisystemic stage, the childhood ataxia-mental retardation stage, the teenage leg atrophy stage and the adult hypogonadal stage [14]. This still applies to the majority of CDG-Ia patients that survive the early years but the mortality is as high as 20% in CDG-Ia patients with the so called ‘visceral’ form, presenting with a combination of neurological and extraneurological manifestations; lethality is often attributed to (multi) organ failure [12].

It is now realised that almost any organ system can be affected in CDG-Ia patients and the combination and severity of the different signs and symptoms can vary widely. Clinical variability is not only seen in patients with the same PMM2 genotypes, but even between affected siblings and monozygotic twins [15–18], suggesting an additional impact of both environmental and other genetic factors.

3. Organ specific involvement

Table 1 summarises clinical signs and symptoms of CDG-Ia.

Abbreviations: AT III, Antithrombin III; CDG, Congenital disorders of glycosylation; CDG-Ia, Congenital disorders of glycosylation type Ia; CDT, Carbohydrate-deficient transferrin; ER, Endoplasmatic reticulum; Glc, Glucose; GlcNAc, N-acetylglucosamine; IEF, Isoelectric focusing; LLO, Lipid linked oligosaccharide; PMM, Phosphomannomutase; PMM1, Isoenzyme 1 of Phosphomannomutase; PMM2, Isoenzyme 2 of Phosphomannomutase

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Clinical features of CDG-Ia patients.

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### 3.1. Central and peripheral nervous system

Several reviews on the neurological presentation of CDG-Ia have been published [19–21].

Psychomotor development is usually delayed in CDG-Ia patients and this becomes evident in the first months of life. Truncal muscular hypotonia and weakness of the legs contributes to the delay in developmental milestones. Signs of cerebellar ataxia, due to a small cerebellum manifest in early childhood. The cerebellum might be reported as normal in very young CDG-Ia children, but on serial imaging it was shown, that the development of the cerebellum was delayed or even arrested. This is most probably due to abnormal glycosylation of key factors that play a role in the maturation of the cerebellum [18,22]. On the other hand the complete loss of the Purkinje cells and subtotal loss of granule cells throughout the cerebellum has been seen on autopsies, reflecting progressive degeneration [23]. Cerebellar atrophy has been documented as early as at the age of 1 month in a neonate with CDG-Ia consistent with wide variation in the onset of atrophy [24]. Absence of cerebellar hypoplasia/atrophy does not exclude CDG-Ia [25]. Supratentorial abnormalities include global atrophy and hydrocephalus [19]. Acquired microcephaly is commonly seen [53].

The majority of older CDG-Ia patients are wheelchair bound. Deep tendon reflexes are usually diminished from an early age and often cannot be elicited in later life. Accordingly, nerve conduction velocities are reduced. On nerve biopsies, multivacular inclusions of the Schwann cells were seen [26]. CDG-Ia patients have epilepsy of various types and usually the seizures can be well controlled.

In late infancy, communication is frequently difficult with dissociation between comprehension and expression: The level of comprehension is underestimated because of difficulties in expressive language compounded by dyspraxia and dysarthria. Their intelligence is very variable, and borderline or normal ability has been reported [9,27–31]. Neurological regression is usually not seen in CDG-Ia, with the exception of those patients developing secondary neurological sequelae after stroke-like episodes. The latter can result in sudden unconsciousness, convulsions, transient blindness or hemiplegia which might be reversible (in the majority of cases). The aetiology of the stroke-like episodes is not understood and is most probably multifactorial. In a patient who had had two stroke episodes, magnetic resonance imaging (MRI) findings revealed in one an ischemic stroke, and the other demonstrated marked oedema followed by focal necrosis [32]. In another case, after a stroke-like episode, magnetic resonance spectroscopy showed a decrease of the N-aspartylaspartate peak, consistent with neuronal loss [21,33]. Episodes of stupor and coma might be triggered by infections or strokes (personal observation).

Individuals with CDG-Ia are usually very social, of warm character and extroverted.

### 3.2. Gastrointestinal tract and liver

Failure to thrive is a very common feature of CDG-Ia and the majority of patients will benefit from nasogastric or gastrostomy feedings especially in the early years. Many patients have been investigated for malabsorption with usually negative results. Protein-losing enteropathy may contribute to low albumin concentrations [34] and renal tubular acidosis, nephritic syndrome and/or tubulopathy might aggravate the failure to thrive. Hepatopathy with recurrent increased plasma transaminases and hepatomegaly are particularly seen during intercurrent illnesses. On liver biopsy, steatosis, fibrosis and enlargement of the portal tracts has been reported [34]. We have previously shown lysosomal inclusions that spare Kupffer cells [35]. CDG-Ia patients have died in liver failure and autopsy showed micronodular cirrhosis and lamellar inclusions in the lysosomes of the hepatocytes [35,36].

### 3.3. Kidney

There are only limited reports on kidney abnormalities in CDG-Ia, however bilateral hyperchoic kidneys are often seen on ultrasound [37]. Enlarged kidneys [38], renal cysts [39] and microcystic renal changes with congenital nephrotic syndrome of diffuse mesangial sclerosis type have been reported [25,36,40]. It is thought, that the microcystic changes of the renal parenchyma of neonatal onset, might be due to ciliary dysfunction secondary to alteration of tubular glycoproteins [37]. Even though, these changes are commonly seen in CDG-Ia, the renal function seems to be well preserved in the long term (personal observation).

### 3.4. Heart

In 1992, Clayton et al. described hypertrophic obstructive cardiomyopathy as a new feature in CDG-Ia [41]. Since then several CDG-Ia patients, usually at young age, have been reported with (hypertrophic or dilative) cardiomyopathy, pericardial effusions or even myocardial infarct and cardiac tamponade [24,42–45]. Treatment of the pericardial effusions might be difficult and diuretics, albumin infusions or corticosteroids have been given, in some cases followed by pericardial-pleural shunting [46].

### 3.5. Eyes

Roving eye movements and squint is often seen in very young CDG-Ia children. They have deficient eye abduction but interestingly, the squint often corrects itself, so that any early surgical intervention should be avoided. Visual maturation in CDG-Ia may be delayed and progressive myopia has also been described [47]. Retinitis pigment-
tos as a result of progressive tapetoretinal degeneration is predominantly seen in older CDG-Ia patients [48–50]. Despite progressive deterioration of the electoretinogram (ERG), central vision may be preserved [51]. Transient blindness may occur after suffering from a metabolic stroke but there is a chance for full recovery (personal observations).

3.6. Endocrine system

CDG-Ia patients usually have normal fetal growth. A study of 25 Danish CDG-Ia patients with the same genotype (R141H/F119L) documented immediate postnatal onset of growth failure with a decline in weight and length from early on with no prepubertal catch up [52]. The cause of the faltering growth is not well understood and is likely to be multifactorial.

In CDG-Ia free serum thyroxin is typically decreased, with increased thyroid-stimulating hormone but decreased thyroxin binding globulin. Generally, hypergonadotropic hypogonadism occurs in females. Levels for GH, FSH and prolactin fluctuate [54]. Persistent hyperinsulinaemic hypoglycaemia in CDG-Ia has been shown to be diazoxide responsive, as in patients with CDG-Ib [55]. Histology of the pancreas showed no focal abnormalities [56,57].

3.7. Skeletal system

Typically, CDG-Ia patients have long fusiform phalanges of the fingers. Large limb joints can be restricted, contrasting with the muscular hypotonia but consistent with reduced movements in utero.

Various deformities including kyphosis, kyphoscoliosis and chest deformities may develop in young teenagers. Progressive paresis caused by spinal cord compression due to atlantoaxial subluxation is a rare but serious complication in patients with CDG-Ia [59]. Osteopenia, revealed on skeletal radiography and densitometry, may need early treatment [14,16,60]. A recent review by Coman et al. lists the diverse range of skeletal abnormalities in CDG-Ia patients [58] including “dysostosis multiplex-like phenotype” [61] and the radiological changes reminiscent of type II collagenopathy [62].

3.8. Skin and hair

Abnormal distribution of subcutaneous fat, or tough (“peau d’orange”) or puffy skin and subcutaneous tissue, is usually present at birth. Often lipodystrophy is seen on the buttocks, which might disappear with time. Silengo et al. described hair abnormalities in CDG-Ia, being sparse and course textured, lacked lustre, growing slowly. Microscopically, trichorrhexis nodosa and pili torti was seen [63].

4. Dysmorphic features

CDG-Ia patients have rather subtle facial dysmorphism; in particular large somewhat dysplastic ears, high forehead, triangular face and thin upper lip [64]. Commonly seen, however not diagnostic, is the presence of inverted nipples, which might be displaced laterally and can normalise with age. Abnormal fat distribution may be localised or generalised.

5. Mortality in CDG-Ia

It is estimated, that about 20% of CDG-Ia patients die in the first years of life, particularly those, who present with the “visceral” form [64]. Sudden death may occur at older age, despite patients having apparently been very stable (personal observation).

6. Neonatal onset

Although CDG-Ia patients are usually born after an uneventful pregnancy with good birth weight, several cases of hydrops fetalis have been reported [65,66]. Pericardial fluid accumulation and ascites were also observed in a few young patients with CDG type Ia, developing life-threatening extravascular fluid accumulation as reported by Truin et al. in three children: one patient was successfully treated with a pericardial-pleural shunt. Pericardial fluid accumulation and generalised oedema resolved temporarily in the other two children on regular albumin infusions and the use of diuretics. However, in one of those children, severe extravascular fluid accumulation subsequently progressed leading to decompensation and death. The abdominal fluid and pericardial fluid have a high extracellular protein concentration and increased cytokine concentrations, consistent with a local activation of the cytokine pathways and subsequent protein transport through the endothelial surface to the extravascular space [46].

Another CDG-Ia baby presented early with hypertrophic non-obstructive cardiomyopathy with marked peripheral oedema. Although hydrops fetalis was suspected it was not confirmed as there was no ascites and pleural effusions. In another case, the most striking clinical problems were therapy-resistant arterial hypertension and recurrent pericardial and pleural effusions. Persistent congenital thrombocytopenia, hyperferritinaemia activated macrophages were noted [67].

A very rare condition called mirror syndrome (fetal hydrops with subsequent oedema in the pregnant woman) has been reported in a woman in two pregnancies complicated by this syndrome. Congenital disorder of glycosylation type Ia (CDG-Ia) was identified as the underlying disease in the foetus in both cases [68].

7. CDG-Ia in adulthood

There is still scant recognition of adults with CDG-Ia. In adolescence and adulthood, the condition appears to be static without -regression. Patients have moderate mental retardation, ataxia, retinitis pigmentosa, peripheral neuropathy, kyphoscoliosis, and endocrinopathies. Adult female CDG-Ia patients have signs of hypogonadism, whereas male patients appear to have a normal puberty. They may have decreased testicular volume and testicular atrophy [54,69]. Skeletal problems include significant kyphoscoliosis, joint contractures, and osteopenia. Muscle wasting seems to be secondary to progressive neuropathy. As in childhood, the severity of the disease is broad but the majority of CDG-Ia adults will not be independent [14,16,70,71].

8. Differential diagnosis

As CDG-Ia has such a variable phenotype, it is not surprising, that it can mimic other (metabolic) diseases suchlike peroxisomal or mitochondrial disorders. Clinical overlap has been reported with two patients with a classical symptoms of MELAS (mitochondrial encephalopathy, lactic acidosis and stroke like episodes) and in another patient thought to have NARP (neuropathy, ataxia and retinitis pigmentosa). All three patients were later diagnosed as CDG-Ia [72]. Clinical overlap can be seen with Joubert syndrome [73], pontocerebellar hypoplasia type I–VI, Hoyeraal–Hreidarsson syndrome, X-linked mental retardation with cerebellar hypoplasia and distinctive facial appearance syndrome, Arima and COACH syndrome.

9. Biochemical features

In CDG-Ia, large numbers of serum glycoproteins are abnormally glycosylated, have reduced concentrations or activities. The
glycans. Hypoglycosylation of transferrin results in partial de-oligosaccharide branches (tetrasialotransferrin) on two N-linked Glycoforms of transferrin or other N-glycoproteins can be separated N-glycosylation is still the isoelectric focusing (IEF) of transferrin.

10. Diagnosis

10.1. Analysis of hypoglycosylated transferrin

The most commonly used screening test for congenital disorders of N-glycosylation is still the isoelectric focusing (IEF) of transferrin. Glycoforms of transferrin or other N-glycoproteins can be separated and visualised by IEF or by Western blotting/immunoprecipitation [85]. The predominant glycoform of transferrin contains four oligosaccharide branches (tetrasialotransferrin) on two N-linked glycans. Hypoglycosylation of transferrin results in partial deficiency of the terminal, negatively charged sialic acid, and hence in a cathodal shift. In patients with CDG-I, there is an increase of the a- and disialotransferrin glycoform and reduction of tetrasialotransferrin. IEF of transferrin can differentiate between CDG-I (due to defects in the assembly of dolichol-lipid linked oligosaccharides) and CDG-II pattern, the latter observed in N-glycoprotein trimming and processing. A false positive IEF pattern may be seen in secondary disorders of glycosylation as in untreated galactosaemia, hereditary fructose intolerance, haemolytic disorders of glycosylation as in untreated galactosaemia, hereditary failure [18]. Elevated liver transaminases are frequently seen during intercurrent infection, but may be normal when well.

Lysosomal enzymes are frequently elevated in serum, but low in leukocytes, probably because of insufficient uptake [77]. The measurement of plasma aspartylglucosaminidase has been proven to be an useful additional marker for CDG-I [78]. Compared to normal controls, CDG-Ia fibroblasts contain an increased amount of total glyco-sphingolipids (GSLs) and slower degradation of GSLs, which suggest that the cell metabolic machinery may be able to partially re-equilibrate protein hypoglycosylation with increased biosynthesis of glycosphingolipids [79].

In cerebrospinal fluid hypoglycosylated isoforms of beta-trace protein, a brain derived glycoprotein was shown, confirming the presence of hypoglycosylation in the central nervous system [80]. As there is an increased morbidity in young CDG-Ia patients suffering from severe infections [81], it was thought, that the glycosylation defect might have an effect on immunoglobulin levels of patients, however that has not been confirmed [82]. Examination of membranous glycoconjugates of lymphocytes showed distinct deviations of surface-expressed lactosamiglycan structures. It was speculated, that diminished expression of CD22 ligands may have implications for the maturation process of B lymphocytes [83]. Poor vaccine response has been reported in two CDG-Ia patients [84].

10.2. PMM enzyme activity in fibroblasts and leukocytes

PMM is a cytosolic enzyme and converts Mannose 6-phosphate to Mannose 1-Phosphate in the presence of its cofactor mannose 1,6 biphosphatase or glucose 1,6 biphosphatase, phosphorylating the catalytic side of PMM. Mannose 1-phosphate is the precursor of guanosin diphosphomannose (GDP-mannose) [99]. This nucleotide sugar subsequently donates mannose that is to be attached to the dolichol-pyrophosphate at the cytosolic membrane of the endoplasmatic reticulum (ER). Two N-acetylgalactosamines (GlcNAc2) and five mannoses (Man5) are then added to the lipid-linked oligosaccharide (LLO) precursor which is then flipped to the luminal side of the ER, finally to be assembled to Dol-pyrophosphate-GlcNAc2-Man9-Glc3. This branched oligosaccharide structure is then linked to the asparagine residue of the polypeptide to be further processed in the Golgi apparatus.

PMM deficiency responsible for CDG-Ia was established in 1995. Low PMM activity can be detected in fibroblasts, leucocytes, amniocytes and/ or liver tissue of patients as described by van Schaftingen et al. [2]. It results in a depletion of the mannose-1-P and hence GDP-mannose pool [100,101]. Fibroblasts however do not accumulate mannose-6-phosphate and it has been suggested, that phosphomannose isomerase, the enzyme acting just upstream of PMM maintains an equilibrium between mannose-6-P and fructose-6-P [100].

To confirm the diagnosis the measurement of PMM activity in leucocytes is preferable, as enzyme levels in fibroblasts of genetically confirmed CDG-Ia patients, overlap with control values [102]. However the PMM leucocyte activity of those with mild PMM2 mutations may still overlap with carrier activities [103].

There are two isoenzymes of PMM – PMM1 and PMM2 – that share 66% sequence homology. Although both isoenzymes catalyse the same reaction, PMM2 is much more substrate-specific [104] and its tissue distribution is different [105]. The role of PMM1 still needs to be elucidated.

10.3. Mutational analysis

The identification of the gene responsible for CDG-Ia was complicated by the presence of the similarity of two genes, PMM2 and a pseudogene, so called PMM1. It is now known that mutations in PMM2 are responsible for CDG1a. The incidence for CDG-Ia has been reported as 1: 20 000 [106,107]. CDG-Ia is certainly still under-diagnosed [108]. The PMM2 gene, is located on chromosome 16p13, and has 8 exons, a reading frame of 738 base pairs encoding for a protein of 246
CDG-Ia and no changes of the hypoglycosylation of glycoproteins.

Mannose supplementation has been proven to be beneficial [120, 121]. However, neither oral nor intravenous supplementation is usually used, once an IEF type I pattern has been proven not to be due to PMM or PMI deficiency [114, 115].

11. Prenatal diagnosis

Clayton et al. reported the failure confirming the diagnosis of CDG by isoelectric focusing pattern in a newborn (later CDG-Ia was confirmed) [92], but Edwards et al., obtained cord blood from a CDG-Ia foetus with non-immune hydrops and abnormalities of serum transferrin isoelectric focusing (IEF) were seen as early as 27 weeks’ gestation [118]. Because of these conflicting results, prenatal diagnosis should be performed by mutational analysis with linkage analysis using flanking polymorphic markers that will also detect contamination of the sample. Enzyme analysis of PMM in amniotic fluid or chorionic villus cells are usually used in tandem as prenatal test [108].

Schollen et al. reported a higher recurrence risk in families with CDG-Ia (closer to 1 in 3) which needs to be considered in the genetic counselling of CDG-Ia families [119].

12. Treatment

Mannose is taken up into cells by a mannose-specific transporter and adding mannose to CDG-Ia patients fibroblasts corrected deficient mannose incorporation [120, 121]. However, neither oral nor intravenous mannose supplementation has been proven to be beneficial in CDG-Ia and no changes of the hypoglycosylation of glycoproteins could be shown [122, 123]. Synthesis of a family of mannose-1-phosphate prodrugs which are promising membrane-permanent derivates of mannose-1-phosphate [124] is in progress.

The management issues for CDG-Ia patients can be numerous and include failure to thrive, requiring tube feeding. Motor and speech delay should be helped with combined health therapy, including physio-, speech and language and occupational therapy. Recurrent stroke-like episodes can successfully be prevented with low dose aspirin. The use of anticoagulants however needs to be carefully considered and individually tailored to the risk profile of each patient. Coagulation abnormalities in CDG-Ia can result in thrombosis or bleeding, so acetylsalicylic acid prophylaxis may have an increased risk for CDG-Ia patients and should be avoided in patients who already have had any bleeding complications [32, 76]. Arnoux et al. recently published a study on the risk assessment of vascular events in CDG-Ia patients and identified risk factors for vascular events looking specifically on level of factor VIII and IX [76].

Osteopenia may require treatment with biphosphonates [125]. Some CDG-Ia children will need thyroxin supplementation for hypothyroidism due to low TBG levels. Commonly, female CDG-Ia patients will need hormonal replacement therapy (HRT). The type of HRT needs to be carefully chosen because of the increased risk of thrombembolic complications in CDG-Ia, due to ATIII, protein C and/or S deficiency.

Very recently, a possible role of the use of antisense morpholino oligonucleotides (AMO) in CDG patients with splicing mutations in the Pmm2 gene has been discussed. Using targeted AMO blocking the access of the spliceosome machinery resulted in correctly spliced mRNA (Vega A, communication at SSIEM, 2008).

13. Mouse model

Complete absence of PMM, as in the Pmm knock-out mouse model and the F141H double knock-out leads to very early embryonic death [126]. Compound heterozygote F119L/F141H mouse embryos only developed to day 9.5. Mating the heterozygous Pmm2-deficient mice with wild type mice revealed maternal transmission of the Pmm2 null allele being severely impaired [61, 126]. The homozygous F119L/F119L knock-out mouse however is viable and shows a broad spectrum of phenotypes (early embryonic death to normal phenotype) (Schneider et al., communication SSIEM 2008).

14. Discussion

Since the last review on CDG-Ia in this journal had been published nearly ten years ago [127], we have realised, that the clinical spectrum of CDG-Ia is much broader. This is primarily as a result of extended screening. The differential diagnosis of congenital disorders of glycosylation should be considered in any child presenting with unexplained symptoms. In particular the presence of features such as inverted nipples, abnormal subcutaneous fat distribution and cerebellar atrophy should trigger enzymatic or molecular genetic tests for PMM deficiency. As CDG-Ia can present with involvement of any organ system at any age and with variable degree of severity and is the most commonest CDG subtype, PMM deficiency should be ruled out in any positive CDG-I screening test by enzyme and/or mutational analysis.

There is still the need to explain the effect of hypoglycosylation resulting in such a plethora of symptoms seen in CDG-Ia. The ongoing mouse models are of utmost importance in helping to unravel the pathogenesis of CDG-Ia. With increased understanding of the impact of glycosylation on stability, targeting and clearance of bioactive molecules hopefully new ideas of effective treatment will be developed.

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References


