DOI: 10.1002/jimd.12024

WILEY JIMD SSIEM

REVIEW

International clinical guidelines for the management of phosphomannomutase 2-congenital disorders of glycosylation: Diagnosis, treatment and follow up

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Abstract

Phosphomannomutase 2 (PMM2-CDG) is the most common congenital disorder of N-glycosylation and is caused by a deficient PMM2 activity. The clinical presentation and the onset of PMM2-CDG vary among affected individuals ranging from a severe antenatal presentation with multisystem involvement to mild adulthood presentation limited to minor neurological involvement. Management of affected patients requires a multidisciplinary approach. In this article, a systematic review of

the literature on PMM2-CDG was conducted by a group of international experts in different aspects of CDG. Our managment guidelines were initiated based on the available evidence-based data and experts' opinions. This guideline mainly addresses the clinical evaluation of each system/organ involved in PMM2-CDG, and the recommended management approach. It is the first systematic review of current practices in PMM2-CDG and the first guidelines aiming at establishing a practical approach to the recognition, diagnosis and management of PMM2-CDG patients.

1 | INTRODUCTION

Phosphomannomutase 2 (PMM2)-congenital disorders of glycosylation (CDG) (previously named CDG-Ia) (OMIM 212065) is a disorder of protein *N*-glycosylation characterized by deficiency/dysfunction of phosphomannomutase 2. It is characterized by a broad spectrum of clinical presentations, ranging from severe neonatal to mild adulthood presentation. Almost all systems/organs can be involved in PMM2-CDG.

2 | PREVALENCE

PMM2-CDG is an autosomal recessive panethnic disorder with more than 900 patients with a diagnosis confirmed either by enzyme assay and/or molecular testing. The estimated incidence is 1:20 000.[1,2]

3 | HISTORY

In 1980, Jaeken et al described the first two patients with a CDG-Ia phenotype. Serum transferrin isoelectrofocusing was proposed as a screening tool for CDG by Jaeken et al.[3] Phosphomannomutase 2 deficiency was linked to the so-called carbohydrate-deficient glycoprotein syndrome by Van Schaftingen and Jaeken.[4] *PMM2* (OMIM 601785) was cloned and mutations identified by Matthijs et al.[5] In 2009, the CDG nomenclature was changed for all CDG into the official gene symbol (not in italics) followed by CDG.[6]

4 | BIOCHEMISTRY

PMM2 catalyzes the second step of the mannose pathway namely the conversion of mannose-6-phosphate to mannose-1-phosphate, which is a precursor of Guanosine diphosphate mannose (GDP-Man) and dolichol-P-mannose (Dol-Man). These two mannose compounds are the donors of mannose used in the endoplasmic reticulum (ER) for the dolichol-pyrophosphate oligosaccharide precursor assembly.

5 | PATHOGENESIS

Deficiency of GDP-Man and Dol-P-Man causes hypoglycosylation of numerous glycoproteins, including serum glycoproteins (lysosomal enzymes, and transport proteins) and membrane glycoproteins. This results in multi-organ involvement with predominant neurological involvement. The pathophysiology and the variability of disease severity and course are not well understood.

6 | METHODOLOGY

The initiative to establish guidelines for the diagnosis and treatment of PMM2-CDG was taken at the *International Scientific CDG Symposium* held in July 2017 in Leuven, Belgium. As for most rare disorders, existing studies and reports are often non-systematic, observational studies, case series or case reports, providing generally low quality evidence. However, combining the available evidence with the experts' opinions helped in establishing these guidelines.

A systematic literature review on PMM2-CDG from the time of the princeps description until December 2017 was carried out mainly using PubMed database searches with the following terms: carbohydrate-deficient glycoprotein syndrome OR congenital disorder of glycosylation, type Ia OR PMM2 OR PMM2-CDG OR phosphomannomutase 2 deficiency OR Jaeken syndrome. Evidence levels were classified in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) methodology (http://www.sign.ac.uk) (Supporting Information, Table S1).

7 | RESULTS

The guidelines were designed by a multidisciplinary panel of international experts in different clinical and research specialties. A literature review of the systems involved in PMM2-CDG was conducted using the PubMed searches and

papers collected in a shared folder in Dropbox which was created by the research team and included more than150 peer-reviewed papers. The teamwork was divided into a clinical and a diagnostic group. The data were collected and summarized based on the major system/organ involvement and the statements were written based on the frequency of each sign/-symptom. The following systems were reviewed: antenatal presentations, dysmorphology, neurology, ophthalmology, cardiology, gastroenterology, hepatology, nephrology, hematology, endocrinology, immune system, audiology, skeletal features, lipid metabolism and adult presentations.

Summary of the phenotypes and the proposed recommendations: ordered by system involvement (Table 1 and Tables S2, S3).

TABLE 1 Suggested surveillance for PMM2-CDG patients

Systems	At diagnosis, if not previously obtained	At follow up 1-2 years interval and as needed	As needed depends on the symptoms
Neurology			
Developmental and cognitive assessment	✓	✓	✓
Electroencephalogram			✓
Brain MRI	✓		✓
Audiology	✓		✓
Endocrine			
Height	✓	✓	
Calcium, magnesium and phosphate	✓	✓	
Gonadotropins	✓	✓	✓
Glucose	✓		
Insulin and other labs in case of hypoglycemia[a]	✓		✓
Thyroid function	✓	✓	✓
Cardiology			
Echocardiogram	✓		✓
Electrocardiogram	✓		✓
Holter			✓
Cardiac MRI			✓
Gastroenterology			
Growth and anthropometric parameters	✓	✓	
Swallowing evaluation			✓
Transaminases	✓	✓	✓
Hematology			
Complete blood counts and differential	✓	✓	✓
Coagulation factors	✓	✓	✓
Renal			
Creatinine	✓	✓	✓
Protein	✓		✓
Immunology			✓
Ophthalmology			
Exam	✓	✓	✓
Electroretinogram			✓
Skeletal	✓		✓
Psychiatric evaluation			✓

Abbreviations: PMM2-CDG, phosphomannomutase 2-congenital disorders of glycosylation; MRI, magnetic resonance imaging.
[a]See the full paper for the suggested labs.

8 | SYSTEMS SUMMARIES AND STATEMENTS

8.1 | Antenatal involvement

Non-immune hydrops fetalis (NIHF) is the most common antenatal presentation of PMM2-CDG, reported in 12 patients. Other associated findings, include hydropic placenta and polyhydramnios. Mirror syndrome-fetal hydrops with consecutive oedema and rapid weight gain in the pregnant mother of the affected fetus- was reported in two patients.[7] Other findings antenatal include hypertrophic cardiomyopathy,[8–10] cerebral and cerebellar abnormalities particularly ventriculomegaly[10,11] and cerebellar hypoplasia/atrophy.[12,13] Skeletal deformities have been detected antenatally in a few patients (limb-shortening, and prominent lumbar lordosis).[10,11] All patients presenting with the antenatal/neonatal hydrops fetalis died between 29 gestational weeks and 3 months of life.

8.2 | Statements

8.2.1 | Presentation (Statement #1: grade of recommendation C)

PMM2-CDG can present prenatally as hydrops fetalis, polyhydramnios, hydropic placenta, mirror syndrome, cerebral ventriculomegaly, cerebellar atrophy (CA), and/or skeletal deformities.

8.2.2 | Differential diagnosis (Statement #2: grade of recommendation C)

A broad metabolic screening is necessary to rule out other causes of non-immune hydrops fetalis.

8.2.3 | Diagnosis and follow-up (Statements #3, 4: grade of recommendation D)

Statement #3:

Detailed imaging studies should include antenatal ultrasound, fetal Doppler and fetal echocardiography, looking for any suggestive presentations of PMM2-CDG including hydrops fetalis, ventriculomegaly, CA, hydropic placenta, polyhydramnios or skeletal deformities mainly limb shortening.

Statement #4:

Autopsy should be recommended in all cases of fetal or neonatal death from NIHF, and amniotic fluid and/or fetal cells should be stored for future testing. PMM enzyme assay and molecular analysis of the PMM2 gene should be considered in the diagnostic panels for NIHF.

8.2.4 | Treatment (Statement #5: grade of recommendation D)

There is no specific treatment strategy for hydrops fetalis in PMM2-CDG, but it is a medical emergency and needs a multidisciplinary management approach including a maternal-fetal medicine specialist, a neonatologist and a metabolic specialist.

8.3 | Congenital malformations

Congenital malformations in PMM2-CDG are common. Inverted nipples were seen in half of the reported patients (25%-100% depending on the case series). Inverted nipples can disappear over time, and can sometimes be unilateral.[14,15] Abnormal fat distribution has been reported in about half of the patients (25%-91%). This can also spontaneously regress over time.[16] The reported frequency of dysmorphic features varies from 29% to 65%, and mainly includes a prominent forehead, large ears and ear lobules, thin upper lip, prominent jaw, and long and slender fingers and toes. A prominent jaw develops over time, but there can be retrognathia in infancy.[17] Almond-shaped eyes have also been frequently described.[18] Cryptorchidism which is relatively frequent in normal neonates has often been reported in boys.[16] Other features include peau d'orange, dysplastic ears, low-set ears, long philtrum, high-arched palate, long face, narrow palpebral fissures, epicanthal folds, prominent nose, and anteverted nares. A coarse face was described in older adults in their 60s.[12,19] Conotruncal heart defects were described in only a few patients and thus might be a coincidental finding (see dedicated section).

8.4 | Statements

8.4.1 | Presentation (Statement #1: grade of recommendation C)

PMM2-CDG can present with facial dysmorphic features (prominent forehead, long face, epicanthal folds, almond-shaped eyes, short nose, anteverted nares, long philtrum, thin upper lip, high-arched palate, large and protruding ears), microcephaly/macrocephaly, abnormal fat pads, inverted nipples, cryptorchidism in boys, and, rarely, cardiac structural anomalies.

8.4.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Supragluteal fat pads can also be seen in Wiedemann-Rautenstrauch syndrome (neonatal progeria), although the other dysmorphic features are different. Many other inborn errors of metabolism have occasionally been associated with inverted nipples such as Turner syndrome, Smith-Lemli-Opitz syndrome, Weaver syndrome and Robinow syndrome.

Of note, inverted nipples (unilateral and bilateral) are found in approximately 3% of the general population, so their occasional presence in these other disorders could be coincidental. Almond-shaped eyes are seen in Prader-Willi syndrome, which is often accompanied by hypotonia and feeding difficulties during infancy.

8.4.3 | Diagnosis and follow-up (Statement #3: grade of recommendation C)

The following should be done at the time of the diagnosis: assessment by a clinical geneticist, echocardiogram and ophthalmologic evaluation.

Follow-up investigations should be performed depending on the results of the initial evaluation, or on clinical concern.

8.4.4 | Treatment (Statement #4: grade of recommendation D)

There is no disorder-specific management for congenital malformations in PMM2-CDG patients. Conotruncal heart defects and cryptorchidism are treated standardly. The inverted nipples and abnormal fat distribution do not need any treatment, and in fact, can disappear spontaneously.

8.5 | Neurological involvement

PMM2-CDG can present as an isolated neurological syndrome or a neurologic-multivisceral form; the latter occurs earlier in life and is associated with a more severe presentation. Developmental disability (DD) in PMM2-CDG is an almost constant finding. It has been reported in 96% of 518 clinically described patients and ranged between mild to severe. The severity was not specified in 416 patients. Achievements of specific milestones were not clearly delineated in the literature. In 20 patients, a normal development was reported, and in 5 of these patients, the clinical status was described in detail including the academic achievement.[20–22]

The level of intellectual disability (ID) (including search term "mental retardation") was reported in 179 patients. The intelligence level was normal in 10%, borderline in 2%; disability was mild in 27%, moderate in 28%, severe in 30% and profound in 3%.[12,22–27] Lack of intelligence assessment in many patients was due to the severity of the clinical presentation with multi-organ involvement and early death. The intelligence quotient (IQ) has been reported in only 17% mainly in individuals with normal intelligence, borderline or mild ID. Among 18 individuals with normal IQ the range was 80 to 93 (median 87).[18,20,28,29]

CA is another constant finding in PMM2-CDG; it has been reported in 95.4%. Presentation of CA is usually in the neonatal period or during the first years. In some instances, CA was detected prenatally[12,13] or in the first 4 to 14 postnatal days.[30,31] A few patients had initially a normal cerebellar magnetic resonance imaging (MRI) at first investigation between 2 days and 6 years of age.[20,28,32–34] Global CA with enlarged hemispheric and vermian fissures, particularly of the anterior lobe of the vermis, are the most common presentations. Olivopontocerebellar atrophy is less frequently reported. CA follows a progressive course with volumetric loss particularly at earlier ages.[35] CA has been measured by bi-dimensional measures and volumetric analyses in case-control studies[18,35,36]. Roving eye movements, tonic upward deviation and convergent eye movements are the earliest signs of cerebellar dysfunction detectable in the neonatal period. Hypotonia, clumsy and ataxic movements become increasingly apparent over the first year. The most common cerebellar symptom in PMM2-CDG patients is ataxia, reported in 96.4%. Independent walking is attained in a minority of patients. Cerebellar ataxia is not progressive in PMM2-CDG. However, motor disability may worsen with time. CA was not reported in some patients with normal intelligence.[18,20,22]

Hypotonia is another common symptom in PMM2-CDG, reported in 92%. It can develop beyond the neonatal period, or even at later age (6-38 years). In many studies there is a lack of information on whether the hypotonia was central, or peripheral as a presentation of neuropathy.

Peripheral neuropathy is reported in about half of the patients (53%). It is generally observed after the end of the first decade (range 7-42 years; in most cases over13 years). However, only some cases are documented by nerve conduction velocity (NCV); most patients are described as having no deep tendon reflex and/or muscle wasting and a few with loss of sensation.

Seizures were documented in only 68 patients; 10 showed neonatal seizures. The most reported types were generalized tonic-clonic and partial seizures, and most patients responded well to single anti-epileptic drugs.

Movement disorders, apart from ataxia, have been reported in only few patients, including dystonic dyskinetic hand movements and cervical dystonia.[37–39]

Stroke-like episodes (SLE) have been described in 36 patients (see dedicated section).

8.6 | Statements

8.6.1 | Presentation (Statement #1: grade of recommendation C)

PMM2-CDG can present as either a neurological syndrome or as a neurologic-multivisceral phenotype. The main neurological

manifestations are global DD, cerebellar ataxia, hypotonia, dysarthria, peripheral neuropathy, seizures, and SLEs.

8.6.2 | Differential diagnosis (Statement #2: grade of recommendation D)

The most common differential diagnostic consideration are mitochondrial disorders and disorders of phospholipid synthesis.

8.6.3 | Diagnosis and follow-up (Statement #3: grade of recommendation C)

The following investigations should be done at the time of the diagnosis: neurological and psychological assessment, Electroencephalography (EEG), neuroimaging and nerve conductive study. Cerebellar biometry or volumetric measures should be performed. The ataxia can be evaluated by clinical scales such as International Cooperative Ataxia Rating Scale (ICARS).[18]

8.6.4 | Treatment: (Statement #4: grade of recommendation D)

There is no specific treatment for the neurological manifestations of PMM2-CDG and the management is per standard protocols for each manifestation.

8.7 | Stroke-like episodes

SLE are a potential complication of PMM2-CDG, reported in at least 36 patients.[12,40–50] They can present before the age of 2 years with no episodes in adulthood.[26] The age of presentation for 28 patients was detailed: 89.3% were younger than 10 years at the first episode, 68% have suffered one or two SLE episodes. Some underwent more than two episodes. The cause of the SLE has not yet been identified. However, different SLE triggers have been described, in particular febrile illnesses (n = 12) and head trauma (n = 8). Alcohol ingestion and invasive cerebral studies, that is, angiography have each been reported once. No clear trigger has been identified in 47% of the patients.

The most reported symptoms are: somnolence, stupor and/or irritability (n = 13), mono or hemiparesis (n = 10), seizures (n = 8), and other (n = 3; dysphasia, cortical blindness, headache, vomiting). Hyperthermia or fever is reported in all the patients for whom the body temperature is reported (from 37.4°C to 38.9°C) with or without an infectious context.

Full recovery was reported to be achieved from 1 hour to 6 months post SLE, and complete recovery was achieved by all the patients. EEG data were detailed in 13 patients with EEG abnormalities in 69%. The main reported finding was an abnormal background in all the patients and focal abnormalities in some patients. Neuroimaging studies (cranial MRI), described in 19 patients, showed in the majority CA. In five MRI studies (5/19 patients) a hemispheric edema combined with a focal abnormality was found.[42,45,48,49]

Acute treatment was reported only in 28%. The most frequently reported drugs used are the antiepileptic drugs, both for the acute phase and the prophylactic phase.

Benzodiazepines were used during the acute phase in at least eight SLE patients, phenytoin in five patients, midazolam and lorazepam in continuous infusion each in four patients, levetiracetam in three patients, and valproic acid, carbamazepine, oxcarbazepine and topiramate in single patients each.

8.8 | Statements

8.8.1 | Presentation (Statement #1: grade of recommendation C)

SLE are among the acute neurological complications in PMM2-CDG patients. They could be underdiagnosed as they require a high index of suspicion. Vascular events such as migraine can clinically mimic SLE and are also more prevalent in PMM2-CDG patients due to coagulation abnormalities.

The main SLE symptoms are irritability, stupor, mono- or hemiparesis, epileptic seizures and sometimes vomiting and other focal deficits.

8.8.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Broad metabolic screening is necessary to rule out disorders of small molecules and energy metabolism.

8.8.3 | Diagnosis (Statement #3: grade of recommendation C)

In order to rule out other acute events deserving special management, neurophysiological studies (EEG), neuroimaging (MRI) and hemostatic studies are recommended.

8.8.4 | Acute management (Statement #4: grade of recommendation D)

There is no specific treatment for the SLE in PMM2-CDG patients. Antiepileptic drugs are the most widely used and reports described an improvement in seizures and focal deficits. Benzodiazepines (midazolam, lorazepam) are recommended. The use of antiaggregants or anticoagulants during the acute phase of SLE should be considered in every single situation.

8.8.5 | Long term therapies (Statement #5: grade of recommendation D)

There is no evidence for the safe continuous use of antiaggregants to prevent SLE except in recurrent SLE (unpublished observations about acetylsalicylic acid). Review of the literature does not support nor refute a vascular origin of SLE. Most common antiepileptic drugs such as levetiracetam, valproic acid, carbamazepine, and oxcarbazapine have been used. However, there is no evidence for efficacy in preventing new SLE.

8.9 | Ophthalmological presentation

The ophthalmological manifestations have been documented in 535 PMM2-CDG patients. Strabismus was the commonest reported ophthalmological finding (84%). The type of strabismus was specified (esotropic) only in half of them. Strabismus is frequently present since birth. Later infantile presentation has been reported.[20,29] Pigmentary retinopathies were reported in 22% of patients. Although it is usually associated with the adolescence/adulthood form, three individuals with the early infantile presentation have been reported.[40,51] Other less common retinal anomalies included retinal hypopigmentation (n = 2), retinopathy without pigmentary alterations (n = 1) tapetoretinal degeneration (n = 1). Abnormal electroretinography (ERG) was reported in 10%. In two independent studies,[52,53] patients were found to have more severely affected rod driven-responses, while cone responses were only slightly reduced.[52,53] Nystagmus was seen in 9.5%. The frequency of oculomotor apraxia and abnormal eye movements is 4% and 3%, respectively. Myopia was reported in 8.7%. Less frequent refractive errors have been described including astigmatism, hyperopia and amblyopia. Six percent of the patients exhibited either reduced visual acuity or visual impairment. Legal blindness was reported in only one patient. Abnormal visual evoked potentials (VEP) have been reported in 11 patients. Spontaneously corrected visual inattention has been reported.[54] Cortical blindness has been rarely described and was transient in two patients.[40] Other less common reported ophthalmological manifestations included night blindness, narrow retinal vessels, macula hypoplasia or aplasia, optic nerve involvement, optic disc pallor, ptosis, enophthalmos, iris coloboma and cataract.[55]

8.10 | Statements

8.10.1 | Presentation (Statement #1: grade of recommendation C)

The main ophthalmological manifestations in PMM2-CDG are strabismus, pigmentary retinopathy (due to progressive photoreceptor degeneration), nystagmus, myopia and reduced visual acuity.

8.10.2 | Differential diagnosis (Statement #2: grade of recommendation C)

A broad metabolic screening is necessary to rule out disorders of energy metabolism and complex molecules, and attenuated forms of organic acidemias.

8.10.3 | Diagnosis and Follow up: (Statement # 3: grade of recommendation D)

Since ocular anomalies are frequent in PMM2-CDG and can involve the structural components as well as the ocular mobility, initial and annual ophthalmology evaluation for PMM2-CDG patients is recommended, particularly to assess the progression of the retinopathy.

8.10.4 | Treatment: (Statement #4: grade of recommendation D)

There is no disorder-specific management for the ophthalmological manifestations in PMM2-CDG patients. Ophthalmologist's intervention (as strabismus treatment or correction of myopia) in early life is important to preserve vision through glasses, patching or surgery.

8.11 | Cardiological presentation

Cardiac involvement in PMM2-CDG has been reported in 141 PMM2-CDG patients, with a frequency of 21%.[31] It is always part of the multivisceral presentation of PMM2-CDG. Early presentation of the cardiac manifestations was reported in 45% of the patients.

The most common cardiac manifestations are pericardial effusions/pericarditis, different forms of cardiomyopathy, mostly hypertrophic cardiomyopathy with or without obstruction, cardiac failure and/or cardiac tamponade. Structural heart defects have been reported, particularly conotruncal malformations.[18,27,56–60]

Less common cardiovascular manifestations include systemic hypertension, pulmonary hypertension, arrhythmia, myocardial ischemia and pericardial fibrosis. Sudden cardiac arrest and collapse including cardiac rupture have been reported.[61,62] Pericardial effusions and cardiomyopathy can worsen, stabilize and improve.[16,62–66]

Management of the cardiac manifestations includes medical, surgical, and supportive measures particularly with regard to hydration and nutrition. Improvement of pericardial effusion with steroids and salicylic acid has been reported.[67] Acute left ventricular outflow tract obstruction

from non-obstructive hypertrophic cardiomyopathy was reported due to dehydration.[68]

Mortality due to cardiac involvement was estimated to be 34%, but, this could be an underestimate due to insufficient data on outcome.

8.12 | Statements

8.12.1 | Presentation (Statement #1: grade of recommendation C)

Cardiac involvement can be part of the multisystem presentation in PMM2-CDG. The age of onset is usually from antenatal to the first year. Most common cardiac features are pericardial effusion/pericarditis, cardiomyopathies particularly hypertrophic cardiomyopathy with or without obstruction, cardiac failure and/or cardiac tamponade. Conotruncal malformations are the most significant structural heart defects.

8.12.2 | Differential diagnosis (Statement #2: grade of recommendation C)

A broad metabolic screening is necessary to rule out disorders of energy metabolism, complex molecules, and attenuated forms of organic acidemias.

8.12.3 | Diagnosis and follow-up (Statement #3: grade of recommendation D)

A referral to a cardiologist is recommended for cardiac assessment. Baseline investigations should be done at the time of diagnosis and include chest X-ray, echocardiogram and electrocardiogram (ECG).

Regular cardiac follow-up should be done annually or more frequently as deemed necessary by the cardiologist or as indicated clinically. Antenatal cardiac assessment should be considered for the foetus at risk in case of a positive family history. Other cardiac investigations, for example, pericardial biopsy for suspected pericardial fibrosis should be considered in consultation with the cardiologist.

8.12.4 | Treatment (Statement #4: grade of recommendation D)

Treatment of the cardiac manifestations should be guided by the cardiologists. Hydration, nutrition and albumin transfusions are important supportive measures, and conotruncal heart defects of course need surgical correction.

8.13 | Gastroenterological presentation

Digestive symptoms have been described in 212 patients. Failure to thrive in the first year of life is the most common feature, reported in 66.5%. It is mostly associated with other extra-neurological symptoms[16,21,23,31,51,57,62,65,69–78]. Feeding difficulties are frequent in PMM2-CDG (45%). They are probably mainly secondary to oral muscle dysfunction from the hypotonia. Several patients required feeding assistance via nasogastric tube feeding or gastrostomy feeding especially in the first years in association with severe enteropathy and/or cardiac complications. In a series of 96 patients, half of the patients who required enteral nutrition had cardiac involvement.[31]

Diarrhea was reported in only 27% of the patients. Data about the duration and the type of the diarrhea were missing in most reports. Malabsorption and enteropathy were diagnosed in a number of patients. Hypoalbuminemia was reported at least in 58% of patients with severe diarrhea.

Vomiting was reported in 19% of the patients. The causes were not well studied.

The reported electronmicroscopic findings of the intestine mucosa in affected patients with chronic diarrhea were non-specific. Four out of seven children had short villi, increased inflammatory cells in the stroma, dilatation of smooth ER and abnormal inclusions containing lipids that did not respond to elimination of food containing proteins. Moderate inflammation of the chorion (lamina propria) was reported in two patients, intra-enterocyte fat accumulation in two patients, and partial villous atrophy with lymphangiectasia in one patient. The histology of intestinal biopsies in two patients was normal.[65] Growth and gastrointestinal symptoms improved spontaneously with age.

8.14 | Statements

8.14.1 | Presentation (Statement #1: grade of recommendation C)

The main digestive presentations in PMM2-CDG are failure to thrive secondary to feeding difficulties, that is, vomiting; diarrhea secondary to malabsorption or protein losing enteropathy.

8.14.2 | Differential diagnosis (Statement #2: grade of recommendation D)

A broad metabolic screening is necessary to rule out disorders of energy metabolism, small molecules, and protein/-gluten intolerance disorders.

8.14.3 | Diagnosis and follow up (Statement #3: grade of recommendation D)

The following parameters/investigations should be measured/performed at the time of the diagnosis: anthropometric parameters, body mass index (BMI), blood albumin, prealbumin, and electrolytes.

Follow-up investigations should include annual surveillance of these parameters.

8.14.4 | Treatment (Statement #4: grade of recommendation D)

There is no disorder-specific management for digestive dysfunction in PMM2-CDG patients. Nutritional support is required in all the affected patients.

Special instructions include:

- Maximal caloric intake with any type of formula (no special food required for PMM2-CDG patients)
- Feeding assistance by nasogastric tube or gastrostomy tube
- Anti-gastroesophageal reflux measures including thickening of feeds, maintenance of an upright position after eating, and antacids
- Evaluation by a gastroenterologist and nutritionist especially in the first year of life
- Continued speech therapy and oral motor therapy in the patients with feeding difficulties

8.15 | Liver involvement

The description of the liver involvement in PMM2-CDG was mostly vague. In the severe infantile type, liver failure was often present in the setting of multi-organ failure often associated with pericardial effusions. Postmortem histologic examination can show cholestasis with prominent bile canaliculi, periportal fibrosis, portoportal bridging fibrosis or cirrhosis and steatosis.[7,8,13,30,68,79–82]

In the later presentation of the multivisceral type, hepatomegaly is the most frequent clinical finding. This has been associated with elevated serum transaminases (particularly of ALAT) in 12.5% to 100%[16,26,40,83] more often than in the neurological form.[31] Usually, the transaminases become more elevated during viral infections and seem to decrease with age normalizing often in the second decade. Liver biopsies have rarely been performed. They mostly show liver steatosis[51,57,84] and lysosomal inclusions in the hepatocytes.[85] This liver presentation does not seem to be progressive. Liver ultrasound often demonstrates steatosis.[56,69,86]

Coagulopathy asks for special attention in CDG (see dedicated section) but is also considered as a marker of liver function. Cholestasis and liver failure (International Normalised Ratio (INR) > 2) only occur in the severe infantile type.[26,31,40,69,76,83,87]

Generally, in the severe infantile type, liver failure contributes to demise, most often in the setting of multi-organ failure. In the less severe multivisceral type, liver disease manifests mainly as liver steatosis with or without hepatomegaly and elevated serum transaminases.

8.16 | Statements

8.16.1 | Presentation (Statement #1: grade of recommendation C)

Liver involvement in PMM2-CDG presents as either severe neonatal liver failure associated with multi-organ failure in the setting of the severe neonatal multivisceral type of PMM2-CDG, or (usually mild) hepatomegaly with mildly increased serum transaminases and liver steatosis that often improves with age.

8.16.2 | Differential diagnosis (Statement #2: grade of recommendation C)

The list of differential diagnoses for neonatal liver failure, cholestasis or increased serum transaminases is long and age-dependent, and outside the scope of these guidelines. Elevated transaminases can be the main presentation of PMM2-CDG. Serum transferrin isoelectric focusing (IEF) in "cryptogenic hepatitis" can lead to the diagnosis of PMM2-CDG. PMM2-CDG should therefore be looked for in unexplained hepatitis.

8.16.3 | Diagnosis and follow-up (Statement #3: grade of recommendation D)

Liver tests (transaminases and coagulation) should be followed yearly until normalization occurs. Liver ultrasound at the time of diagnosis and every 3 to 5 years thereafter seems justified. In patients with chronic increase of transaminases, the development of liver fibrosis or cirrhosis can be monitored with non-invasive elastography techniques. The identification of evolution to cirrhosis is important, given the occurrence of potentially life-threatening complications (variceal bleeding, hepatocellular carcinoma, ascites) associated with cirrhosis.

8.16.4 | Treatment (Statement #4: grade of recommendation C)

There is no disorder-specific management for liver disease in PMM2-CDG. Elevated transaminases usually normalize before puberty.

8.17 | Renal involvement

Renal involvement in PMM2-CDG has been reported in 56 patients. In the severe infantile multisystem type there is major renal involvement in about 85%. Presentation in the late-infantile and childhood type has also been also reported. Multicystic kidneys are the most common presentation followed by nephromegaly. Hydronephrosis was less reported. The most reported functional abnormality was tubulopathy, mainly proteinuria, followed by aminoaciduria. Nephrotic range proteinuria has been described in six patients[11,31,88–90] including the diffuse mesangial sclerotic type in one patient.[90] Abnormal renal ultrasound, including increased echogenicity, increased or decreased corticomedullary differentiation has also been reported.[91]

8.18 | Statements

8.18.1 | Presentations (Statement #1: grade of recommendation C)

PMM2-CDG can present with congenital renal anomalies including bilateral multicystic kidneys, nephromegaly, hydronephrosis and/or tubulopathy. Proteinuria can be an isolated feature in PMM2-CDG. Nephrotic range proteinuria is a rare presentation of PMM2-CDG.

8.18.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Screening for other disorders including metabolic tubulopathy, that is, energy metabolism and complex molecules. Genetic syndromes with multiscystic kidneys and nephrotic syndrome should be also considered.

8.18.3 | Diagnosis and Follow up (Statement #3: grade of recommendation C)

The following investigations should be done at the time of diagnosis: blood pressure measurement, urine analysis for proteins and amino acids, serum creatinine and renal ultrasound (looking for microcysts, nephromegaly, hyperechogenicity, abnormal corticomedullary differentiation).

Follow-up investigations should include annual surveillance with blood pressure measurement, urine analysis/ dipstick, and serum creatinine/urea.

8.18.4 | Treatment: (Statement #4: grade of recommendation D)

There is no disorder-specific management for renal dysfunction in PMM2-CDG patients.

8.19 | Hematological involvement

Coagulation abnormalities were described in 344 PMM2-CDG patients. Both procoagulant and anticoagulant factors are affected. Antithrombin deficiency was the most reported abnormality followed closely by factor XI (FXI) and protein C (PC) deficiencies respectively. Protein S (PS) and FIX can also be decreased. Low factor II (FII), factor V (FV), factor VII (FVII) or factor X (FX) were reported in a few patients as well as prolonged prothrombin time and increased D-dimer levels.

PMM2-CDG is largely underdiagnosed and some cases may have a mild phenotype with only coagulation abnormalities such as antithrombin deficiency.[92] These coagulation abnormalities disturb the hemostatic equilibrium, which may induce hemorrhagic or thrombotic events. A thrombotic event was reported in 12.5% of patients, both venous and arterial. Four cases of cerebral thrombosis were described. Tissue damage such as due to surgery or catheterization was identified as a risk factor for the occurrence of thrombotic events.[93] In four PMM2-CDG patients, disseminated intravascular coagulation was described, always occurring during thrombosis or a SLE.

Data on antithrombotic treatment in PMM2-CDG patients are limited. There is one report of inefficient low molecular weight heparin treatment (LMWH) in congenital antithrombin deficiency.[94] Rivaroxaban (factor Xa inhibitor) has been successfully used as an alternative prophylaxis in PMM2-CDG patients.[95]

Of note, fluctuations of coagulation abnormalities have been noted with age,[96] and with during fever, probably due to thermolability of PMM2.[31,97]

Other hematological abnormalities like thrombocytopenia and neutropenia have rarely been reported. Thrombocytopenia has been described in only seven patients.[26] Interestingly, three of them presented with severe congenital thrombocytopenia in the context of hydrops fetalis without evidence of bacterial or viral infection.[73] In PMM2-CDG patients, platelet reactivity against all agonists was normal but there was a spontaneous hyperreactivity. This causes platelet hyperaggregability explaining the thrombotic tendency in these patients.[98] Complete bone marrow failure was noted in only two patients (personal communication) (for neutropenia see immunology section).

8.20 | Statements

8.20.1 | Presentations (Statement #1: grade of recommendation C)

The main coagulation disorders observed in PMM2-CDG are antithrombin and FXI deficiencies which can be associated to PC, PS and FIX deficiencies and prolonged prothrombin time. Because of these coagulation abnormalities

affecting both procoagulant and anticoagulant factors, patients exposed to thrombotic or hemorrhagic risk. Because of the platelet hyperaggregability, the risk of thrombosis is higher than the risk of bleeding.

8.20.2 | Differential diagnosis (Statement #2: grade of recommendation C)

The differential diagnosis includes congenital coagulopathy syndromes and liver failure or disseminated intravascular coagulopathy.

8.20.3 | Diagnosis and follow up (Statement #3: grade of recommendation D)

At diagnosis, a complete blood count and hemostasis study should be performed, including prothrombin time, fibrinogen, FVIII, FIX, FXI, antithrombin, PC and PS. If prothrombin time is prolonged, FII, FV, FVII, and FX should be measured.

Coagulation studies should be conducted once a year and before any surgery, invasive procedure or environmental stress like fever, in combination with liver function tests. In these situations, hemostasis studies should include prothrombin time, fibrinogen, factor IX, factor XI, antithrombin, protein C and protein S.

8.20.4 | Treatment (Statement #4: grade of recommendation D)

The following proposals should take into account the coagulation profile and the history of bleeding and/or thrombosis of the patient.

8.21 | Thrombotic event

In the absence of specific guidelines for PMM2-CDG patients, we suggest to follow the guidelines of the American College of Chest Physicians for curative and prophylactic use of antithrombotic therapy.[99,100] Low molecular weight heparin should be used by individualized dose. Use of antithrombin concentrate in antithrombin deficiency can be discussed if dose adjustment of heparin is difficult. Rivaroxaban can be used as an alternative prophylaxis in LMWH-nonresponsive patients.

8.22 | Management of coagulopathy during surgery

According to the levels of clotting factors and inhibitors and the hemorrhagic risk of the procedure, we propose the prophylactic use of fresh frozen plasma or prothrombin complex concentrate (PCC). However, the use of PCC containing protein C and protein S should be considered according to PC and PS levels. Factor XI concentrate or recombinant FVIIa (rFVIIa) infusion is not recommended owing to the high risk of unbalancing the hemostasis.[101]

8.23 | Endocrinological symptoms

The endocrine system is one of the major systems affected in PMM2-CDG. Four major domains are affected: growth, thyroid function, sexual development and blood glucose levels.

Data regarding height were available for 53 patients; 49% presented with short stature. After a normal anthropometry at birth, postnatal growth decline is common in PMM2-CDG children. A prospective study of the prepubertal growth in 25 patients revealed a notable decline in length (standard deviation score (SDS) 0-2.4) during the first 7 months of life. Failure to thrive is a common feature of PMM2-CDG and is associated with growth failure (in 96% of the patients with short stature).[71] PMM2-CDG patients have lower serum levels of IGF-1, IGFBP3 and acid-labile subunit (ALS) despite normal or increased levels of growth hormone.[51,102] IGF-1 itself is not glycosylated. However, in serum, over 90% of IGF-1 forms a protein complex formed by glycoproteins IGFBP3 and ALS.[103] Only one report regarding the use of recombinant human IGF-1 (rhIGF-1) therapy in a PMM2-CDG patient with an excellent growth response.[75]

Thyroid function tests are frequently ordered in PMM2-CDG, reported in 255 patients. TSH was the most requested biochemical test. In 16%, TSH was above the normal range, in which 29% of those were detected in the newborn screening test while in the remaining, elevated TSH was noticed after the neonatal period.[9,10,15,18,21,29,43,56,69,77,84,88,102,104–106]

Partial deficiency of thyroxine-binding globulin (TBG) is present in approximately 75% of CDG patients probably due to increased TBG hypoglycosylation which reduces its half-life by 15%. In general, TBG deficiency does not appear to affect thyroid function.[107]

FT4 is the most reliable marker for thyroid function and indicator for treatment to avoid over-treatment based only on a high TSH.[105] Among 255 PMM2-CDG patients, 13% were labeled as hypothyroidism. Levothyroxine therapy was begun in all but was discontinued after few months in some patients presenting with transient hypothyroidism. Hypothyroidism related symptoms including low body temperature, low energy, constipation, and lymphedema have rarely been reported.[77]

Hypoglycemia has been reported in 24 patients.[7–11,18,21,37,40,56,62,74,76,84,108,109] Patients presented mostly with poor feeding, lethargy or seizures. It was the main presentation in three patients.[21,108] All of the hypoglycemia attacks occurred during the infantile period. There

was no documented difference in the timing of the presentation between hyperinsulinemic vs normoinsulinemic hypoglycemia. Hyperinsulinemia was determined to be the cause in 40% of the affected patients. The cause was not precisely reported for the rest of patients, that is, no insulin, cortisol, growth hormone or ketone levels were available.[10,11,21,40,56,74,84,108] Pancreatic biopsy (available for one patient) revealed normal histology.[108] The hyperinsulinemic hypoglycemia successfully responded to oral diazoxide.[10,20,54,70,78,99] Subtotal pancreatectomy was required in only one patient with hyperinsulinemia who responded well to diazoxide but developed severe hyponatremia as a side effect.[99] The outcome of the hypoglycemia in the other 14 patients was not available. Literature review did not reveal hyperglycemia in PMM2-CDG.

Gonadal function has been described in 29 adult females. They presented either with delayed, incomplete or absent puberty, amenorrhea and hypergonadotropic hypogonadism[26,65,102,107,110] regardless of neurological or visceral symptoms. Three females have been described with normal puberty and normal menstruation[31,111,112]. Additionally, one female patient has been described with normal puberty and irregular, scarce menstruations[41] and one patient with lack of secondary sexual development and two episodes of vaginal spotting within 4 years post menarche.[47] The pathogenesis of premature ovarian failure in PMM2-CDG is not fully understood. Hypoglycosylation of gonadotropins, gonadotropin receptors or sex hormones may result in hypergonadotropic hypogonadism.[102] At least 27 females were treated with estrogens to induce puberty[30,31,56,107,113] and although there is theoretically a risk for thrombosis, no reports were found in the literature. Pubertal abnormalities in males are less reported. Puberty and testosterone levels are mostly reported normal. Small testicular volumes with or without hypogonadism have been described.[47,79,102] Other abnormalties include increased Follicle-stimulating hormone (FSH)[29,56,102], and cryptorchidism.[30,84,105,109,110,114]

8.24 | Statements

8.24.1 | Presentation (Statement #1: grade of recommendation C)

PMM2-CDG can present with short stature but have usually an appropriate length at birth,

High TSH and low TBG levels with euthyroidism are common findings in PMM2-CDG while hypothyroidism is rare.

PMM2-CDG can show hypoglycemia, that can be a presenting sign.

The main pubertal abnormalities in PMM2-CDG are premature ovarian failure with hypergonadotropic hypogonadism in females, and hypogonadism with or without small testicular volume and cryptorchidism in males.

8.24.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Disorders such as glycogen storage disease, galactosemia, mitochondrial disorders and autoimmune endocrinopathy should be considered.

8.24.3 | Diagnosis and follow up (Statement #3: grade of recommendation D)

The length/height of PMM2-CDG patients should be regularly monitored. At the time of diagnosis IGF-1, IGFBP3 should be measured. If growth failure installs later, these investigations should be repeated. PMM2-CDG patients have mostly normal serum growth hormone levels and show growth hormone resistance on IGF-1 stimulation.

Serum FT4, TBG and TSH should be measured at the time of diagnosis and at follow-up.

The following investigations should be done in any PMM2-CDG patient presenting with hypoglycemia: plasma insulin, cortisol, growth hormone, lactic acid, ammonia, beta-hydroxybutyrate, free fatty acids and urinary ketones. Transferrin IEF as a screening test should be considered in any neonate/infant with persistent hypoglycemia of undetermined cause.

Gonadal function should be assessed in males and females at the age of puberty, and the following parameters should be measured: Tanner stage, growth curve, bone age, FSH, luteinizing hormone (LH), estradiol in females and testosterone/Sex hormone binding globulin (SHBG) in males.

8.24.4 | Treatment (Statement #4: grade of recommendation D)

There is no disorder-specific management for the endocrine abnormalities in PMM2-CDG patients.

The diagnosis of hypothyroidism and L-thyroxine supplementation should be reserved for those patients with concomitant elevated TSH and low free thyroxine especially in the presence of clinical symptoms.

The management of hypoglycemia should include continuous tube feeding, iv glucose infusion at a rate 8 to 10 mg/kg/min and inclusion of complex carbohydrates in the diet standard treatments for hyperinsulinemic hypoglycemia. Management with oral diazoxide as a first choice of therapy is recommended in case of hyperinsulinemic hypoglycemia.

Hormone replacement therapy should be started at a normal age of pubertal induction, and to reduce the risk of venous thrombosis, treatment is preferentially natural estrogen by the dermal route.[115]

8.25 | Infections and immunological abnormalities

Infections and or immunological abnormalities were reported in 88 PMM2-CDG patients. Recurrent infections are a common manifestation in early life and childhood and become less frequent and less severe in adolescence and adulthood. Forty percent were reported with recurrent and/or organ-specific infections (respiratory and gastrointestinal tracts). In most of the reported patients, there was at least single episode of severe infection, which was lethal in few patients. Fifty-three percent of the patients who suffered from infections were below 7 years of age. Antibiotic and immunoglobulin infusions were the most frequently suggested treatment with, in general, a good response.

Nine patients showed different types of leukopenia: progressive lymphopenia,[116] persistent lymphopenia[73] and neutropenia.[26] Low T cell levels have been rarely reported.[117] Leukocytosis was reported in a few patients including increased Natural killer (NK) cell levels,[117] increased lymphocyte counts,[118,119] and increased monocyte levels.[73] Reduced neutrophil chemotaxis was reported in one paper.[118]

Furthermore, a set of 12 PMM2-CDG patients with varying ages and disease severity, showed a decrease in the CD16 marker in neutrophils of children as well as a generalized decrease in CD14 epitope in monocytes of both children and adults.[120]

Hypogammaglobulinemia has been described with decreased IgA and IgG levels being the most common finding followed by low IgM levels.[57,69,118]

Cytokine levels were reported in only one patient, who showed very high levels (Interleukins (IL-2), IL-4, IL-6, IL-8, IL-10, gamma interferons (IFNγ), Tumor necrosis factor (TNFα), IL-1β and Granulocyte-macrophage colony-stimulating factor (GM-CSF)) in pericardial and ascites fluids while presenting normal serum levels except for elevated IL-6, IL-8 and IL-10.[76]

Episodes of fever without apparent cause were reported in 22% of the patients[12,42,44,69,118,121]. In two patients, fever was also associated with pericarditis and vasculitis.[40,75] Half of the patients reported responded normally to vaccination.[117] Age-appropriate vaccination is recommended.[76]

8.26 | Statements

8.26.1 | Presentation (Statement #1: grade of recommendation C)

PMM2-CDG may present with infections, immunodeficiency, lack of response to vaccination, and hypogammaglobulinemia. Infection sometimes can progress to septic shock and more frequent in younger children. Infections have also been reported as a cause of death in a few young PMM2-CDG patients.

8.26.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Other disorders including immunodeficiency syndromes, Glycogen storage disease (GSD) type Ib, lysinuric protein intolerance, purine and pyrimidine disorders should be evaluated.

8.26.3 | Diagnosis and follow-up (Statement #3: grade of recommendation D)

The following investigations should be done at the time of the diagnosis of PMM2-CDG, and in case of recurrent infections: leukocyte count (including neutrophil, lymphocyte and NK cell count), and immunoglobulin count (including IgA, IgG, and IgM counts). These investigations should be repeated periodically, especially during infancy, and/or in case of suspected or confirmed infection. Antibody titers should always be tested after vaccination. Monitoring of PMM2-CDG patients after infection is necessary to prevent complications and eventual sepsis, especially in early life and childhood.

8.26.4 | Treatment (Statement #4: grade of recommendation D)

Infections in PMM2-CDG patients must be managed according to good standards of care, with appropriate antibiotic administration, and patients should be followed closely until infection remission. Intravenous administration of immunoglobulins may be considered if infection is not responsive to antibiotic therapy. Patients should be vaccinated, unless medical history advises against it with the understanding that adverse reactions and non-response are possible.

8.27 | Skeletal involvement

Skeletal involvement in PMM2-CDG is common but often overshadowed by other organ involvement. The skeletal manifestations of PMM2-CDG have only been reported as part of a multisystem phenotype. Kyphoscoliosis was reported in 53% (in series of over 10 patients ranging from 32%[12] to 71%[26]). This finding is more common in adult patients but can start during childhood.[12] Low bone mineral density (BMD), in the range of osteopenia or even osteoporosis, was seen in 60%. In one series, it was seen in all seven patients older than 15 years of age.[26] This finding can also start as early as in childhood but becomes more frequent after adolescence and has been associated with significant

fractures.[113] One large series reported fractures under minimal trauma in 26%.[16] Thoracic deformities in the form of pectus carinatum or excavatum were seen in 84%. Various types of foot deformities have been reported, including talipes equinovarus, talipes equinus, pes varus, pes valgus/everted feet, and pes planus. Atlantoaxial subluxation leading to symptomatic spinal cord compression and laminectomy was described.[34,122] Changes reminiscent of dysostosis multiplex in the axial skeleton have been reported, including a dorsolumbar kyphosis with a slight hook-like dysplasia of L1, wide ribs, broad clavicles, thickened ischia and pubis,[103] and anterior beaking of the vertebral bodies.[10,11] Changes reminiscent of a type II collagenopathy have been reported,[11] including hypomineralization of the pubic rami, metaphyseal expansion of the long bones, and delayed epiphyseal ossification. Other skeletal changes reported in more than one patient include shortening of long bones,[10,11,15] 13 pairs of ribs,[10,11] and flared iliac wings.[10,63]

8.28 | Statements

8.28.1 | Presentation (Statement #1: grade of recommendation C)

PMM2-CDG can present with skeletal involvement, most notably osteoporosis, scoliosis-kyphosis, dysostosis multiplex-like changes, and a type II collagenopathy phenotype.

8.28.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Screening for lysosomal storage disease, type II collagenopathy skeletal phenotype should be considered.

8.28.3 | Diagnosis and follow up (Statement #3: grade of recommendation C)

The following investigations should be done at the time of the diagnosis: cervical spine X-rays first in neutral position, followed by flexion/extension to assess for atlantoaxial instability.

Follow-up investigations should include annual clinical assessment of scoliosis (X-rays obtained when needed) and BMD by age-appropriate dual-energy X-ray absorption (DXA) scan every 3 to 5 years starting in adolescence. In patients with severe spinal and thoracic deformities, pulmonary function should be tested (concern for restrictive lung disease).

8.28.4 | Treatment (Statement #4: grade of recommendation D)

- There is no disorder-specific management for skeletal abnormalities in PMM2-CDG patients.
- Atlantoaxial instability/cord compression is treated with standard measures, including cervical spine stabilization or surgical stabilization in patients with symptoms of spinal cord compression.
- Scoliosis is also treated by standard care, with regular monitoring, braces or surgery depending on severity.
- Standard treatment of pectus is recommended, which can include external bracing for pectus carinatum or surgery for severe pectus excavatum leading to cardiopulmonary morbidity.
- Low BMD (Z-score ≤ -2.0): encourage mobility in a safe environment especially with the ataxic patient. Recognize and treat micronutrient deficiencies, such as vitamin D deficiency. Recognize and treat hypergonadotropic hypogonadism to maximize BMD. Standardized WHO Fracture risk assessment tool (FRAX) guidelines for the use of bisphosphonates for PMM2-CDG patients with recurrent fractures.

8.29 | Lipid abnormalities

Hypocholesterolemia is a classic feature of PMM2-CDG[24,37,69,89,123]. More specifically, affected patients can have decreased concentrations of total cholesterol, low-density lipoprotein (LDL-cholesterol), and apolipoprotein B.[124] Hypotriglyceridemia has also been described.[89]

8.30 | Statements

8.30.1 | Presentation (Statement #1: grade of recommendation C)

PMM2-CDG can present with low concentrations of total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides.

8.30.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Screening for other disorders including abetalipoproteinemia, familial hypobetalipoproteinemias type 1 and 2, chylomicron retention disease, and Smith-Lemli-Opitz syndrome should be considered.

8.30.3 | Diagnosis and follow up (Statement #3: grade of recommendation C)

A fasting lipid panel is recommended at the time of the diagnosis (caution with hypoglycemic infants).

No recommended follow-up recommendation can be established, as although it might be an important diagnostic clue, it's unlikely that the particular lipid pattern would lead to an increased cardiovascular risk.

8.30.4 | Treatment (Statement #4: grade of recommendation D)

There is no disorder-specific management required for lipid abnormalities in PMM2-CDG patients, as it is unlikely to be associated with an increased cardiovascular risk.

8.31 | Hearing loss

The exact frequency of sensorineural hearing loss in PMM2-CDG is still unknown. A recent paper reported that its frequency might not be increased over that of the general population, the latter varying from 3.2% to 13%.[125] A literature review of papers that reported sensorineural hearing loss revealed this finding in 21% of patients In particular, there are four cohorts of nine or more patients reporting sensorineural hearing loss as a finding, and the reported frequency in those series ranged from 8%[12] to 33%.[16] Whether or not patients with PMM2-CDG are at an increased risk of sensorineural hearing loss, hearing assessment should be offered to children with speech-language delay, or based on parental concerns.[126]

8.31.1 | Presentation (Statement #1: grade of recommendation C)

Patients can present with sensorineural hearing loss, although it is still controversial if this finding is associated with the disease or is incidental.

8.31.2 | Differential diagnosis (Statement #2: grade of recommendation D)

Although sensorineural hearing loss is not a classic feature of PMM2-CDG, its finding should not dissuade the clinician from considering this diagnosis.

8.31.3 | Diagnosis and follow up: (Statement #3: grade of recommendation C)

The following investigations should be done at the time of the diagnosis: audiology evaluation.

Follow-up investigations should be performed depending on the results of the initial evaluation, or on clinical concern.

8.31.4 | Treatment: (Statement #4: grade of recommendation D)

There is no disorder-specific management for sensorineural hearing loss in PMM2-CDG patients. Standard of care should be provided, including therapeutic options such as hearing aids.

8.32 | Adult presentations

Total number of reported adult PMM2-CDG patients is 93 (the oldest is 66 years old). The most common reported neurological presentations in adults were the following: stable ataxia (95%), cognitive delay (87%) ranging between mild to severe cognitive delay, peripheral neuropathy (50%), seizures (27%), dysarthria (20%), and SLE (18%).

The seizure disorder, if present, was stable and responsive to regular antiepileptic management in all of the reported adult patients. None of the patients had SLEs beyond adolescence.

The most common endocrinological abnormalities were short stature, and delayed secondary sexual development including ovarian failure and hypogonadism in both males and females. No major thyroid abnormalities were reported except for three patients reported with hypothyroidism, low thyroid binding globulin, and thyroid nodules respectively.

The most common hematological abnormalities were decreased coagulation factors; F IX, F XI and F XII, antithrombin, PC, and PS. Deep vein thrombosis (DVT) was reported in a few patients and bleeding in only two patients. No clinical description of bleeding is reported. However, bleeding associated with surgery and trauma has been reported in affected children.

Bone abnormalities were common in adult patients (74%) including osteoporosis (24%), osteopenia (13%) and kyphoscoliosis (62%).

The main ophthalmological abnormalities in adults were strabismus, non-specified retinopathy, retinitis pigmentosa, myopia and nystagmus.

Psychological abnormalities have rarely been reported in adult patients, aggressiveness was reported in six patients, apathy in two patients and depression in one patient.[12,26]

The functionality of adult PMM2-CDG patients was not well documented, but it has been reported that affected adults require variable levels of support in functional life skills due to the progression of the neuropathy and the orthopedic issues. Three patients were reported to live independently, two have mild neurological involvement[113] and one asymptomatic homozygous individual with normal cognition was diagnosed incidentally after carrier testing of affected offspring.[22]

8.33 | Statements

8.33.1 | Presentations (Statement #1: grade of recommendation C)

Adult patients with PMM2-CDG present mainly with stable neurological manifestations including cerebellar ataxia, peripheral neuropathy, strabismus, retinopathy and retinitis pigmentosa associated with endocrinopathies and/or kyphoscoliosis.

8.33.2 | Differential diagnosis (Statement #2: grade of recommendation C)

Other disorders with multisystems involvement including energy disorders, cerebrotendineous xanthomatosis and complex molecule disorders should be evaluated.

8.33.3 | Diagnosis and follow-up (Statements #3, 4: grade of recommendation D, D)

Statement #3 Diagnosis

Enzyme assay and/or molecular testing should be considered in any adult with suspected PMM2-CDG diagnosis. (Caveat: serum transferrin glycosylation analysis can be mildly abnormal or near normal in adult patients[127].

Statement #4 Follow up

The following surveillance labs should be considered in adults diagnosed with PMM2-CDG: yearly thyroid function, liver function, coagulation factors including FIX, FXI, PC, PS, and antithrombin quantification. Serum concentration of gonadotropins in adolescent and adult women should be monitored to identify hypogonadotropic hypogonadism. Yearly ophthalmology follow-up for the retinitis pigmentosa and myopia, and bone density testing should be done to assess for osteopenia/osteoporosis every 3-5 years.

8.33.4 | Treatment (Statement #5: grade of recommendation D)

Treatment of adults with PMM2-CDG requires care from a multidisciplinary team including a metabolic specialist, ophthalmologist, endocrinologist, orthopedist, hematologist, physical therapist and occupational therapist.

Specific considerations in treatment and follow up of adults with PMM2-CDG:

- Management of increased coagulopathy risk for adults with PMM2-CDG undergoing surgery: Adults with PMM2-CDG are prone to develop DVT; hematology consultation prior to surgery with close monitoring of the coagulation factors, pre-surgical anticoagulant prophylaxis and early treatment of DVT is warranted. DVT prevention with low molecular weight heparins should be considered, especially in case of prolonged immobilization or orthopedic surgery.
- Treatment of the osteopenia and osteoporosis sequelae, that is, fractures: calcium and vitamin D supplementation and consideration of treatment with bisphosphonate in case of vertebral compression fractures or recurrent low-impact fractures.
- Orthopedic management for the scoliosis: supportive management or surgical corrective intervention for severe scoliosis
- Physical therapy: therapy program directed to improve strength, range of motion, and function.
- Clinical hypothyroidism with biochemical hypothyroidism: correction of the thyroid hormone deficiency.
- Support of independent living: education and training throughout the school years in functional life skills and self-care to prepare the young adults for independence.
- Hypogonadism and delayed sexual development in women: hormonal replacement therapy (HRT) can be initiated cautiously to decrease risk of osteoporosis, keeping in consideration the thromboembolic risk with some of HRT.

8.34 | Diagnostic tools, treatment and follow up

8.34.1 | Biochemical diagnosis

IEF of serum transferrin was first introduced in 1984[3] and remains the frontline test for the identification of a patient presenting a deficiency in N-glycosylation. The main advantage of using transferrin as a biomarker for CDG is its high abundance in blood, allowing fast, detailed and sensitive detection of N-glycosylation in small sample volumes. Similarly, High Performance Liquid Chromatography (HPLC) or by capillary electrophoresis (CE) are also techniques that allow separation of transferrin isoforms on the basis of the charge state determined by the number of terminal sialic acid residues. Transferrin carries two identical complex N-glycans harbouring each two terminal sialic acid residues. Because those are negatively charged, the isoelectric point of transferrin is determined by its glycosylation status. In addition, although tetrasialotransferrin represents the major glycoform is healthy controls, other glycoforms can be distinguished due to variable branching of the sugar trees. Hypoglycosylation or altered processing of the glycan chains will both result in a loss of negative charges of the transferrin. PMM2-CDG is characterized by a type 1 transferrin IEF pattern, with a decrease of tetrasialotransferrin and an increase of di- and mostly also of asialotransferrin.

Surprisingly, only scarce detailed information is available for transferrin analysis in literature, and results were only reported in 155 patients. A type 1 transferrin pattern was reported in 46% of the patients (n = 72), and a global increase in both a- and disialotransferrin, together with a decrease in tetrasialotransferrin was reported in 34% (n = 55). In 29 patients, the different transferrin glycoforms were quantified by HPLC. Analysis of serum transferrin by CE has been reported.[20] In most patients (70%, n = 108) was IEF performed, and in the remaining 16 patients no information is provided regarding the method used.

Besides IEF, N-glycan profiles of serum transferrin and total serum proteins can also be analyzed by mass

spectrometry (MS) in body fluids and cell lysates. The growing contribution of MS in the diagnosis of CDG is outlined in a recent review by Sturiale et al[128] and Lefeber et al.[129] Furthermore, the analysis of intact glycoprotein analysis of purified transferrin by MS has now been added to routine diagnosis,[130] and very recently to therapy monitoring of CDG.[131] Hypoglycosylation of serum transferrin has been reported in 28 PMM2-CDG patients, by using either Electrospray ionization (ESI-MS),[132,133] Liquid chromatography-tandem mass spectrometry (LC-MS-MS) (Zhang et al 2016),[155] or matrix-assisted laser desorption/ionization time-of-flight-Mass spectrometry (MALDI-TOF-MS).[12,86] Also purified transferrin or isolated transferrin glycans can be used for the analysis.[132]

Statement #1 (grade of recommendation: C)

Serum transferrin is a sensitive but non-specific biomarker for PMM2-CDG. The typical tf IEF pattern in PMM2-CDG is type 1 (decrease of tetrasialotransferrin and increase of di- and asialotransferrin.[134]

8.34.2 | The sensitivity of the biochemical tests

The presence of transferrin polymorphisms can however complicate the diagnostic interpretation of abnormal profiles, by impacting its isoelectric point and generating isoforms that can co-migrate with abnormally glycosylated transferrin isoforms.[135] In case of an abnormal CDG pattern it is suggestive to incubate the serum samples with neuraminidase prior to the analysis. Removal of sialic acid residues will unmask rare transferrin variants. Analysis of parental transferrin can also rule out the presence of hereditary variants.[136] Noteworthy, PMM2-CDG newborns and infants might present a normal profile that later on becomes abnormal. Conversely, the transferrin pattern sometimes normalizes with age, without improvement of the symptoms, as reported in one patient.[43]

Statement #1 (grade of recommendation: D)

In case of an abnormal serum sialotransferrin pattern the presence of a transferrin polymorphism has to be excluded, either by pre-incubation of the sample with neuraminidase or by analysis of parental samples.

8.34.3 | Pre-analytical requirements for the biochemical testing

The recommended blood sample handling for isolation and purification of serum transferrin is as follows. Serum or heparin plasma should be stored at −20°C. Extra care should be taken when isolating the serum fraction to avoid contamination by neuraminidase producing-bacteria.[137] Preferably, the serum sample should not be taken in an acutely ill patient, a patient presenting fever or infections, or a malnourished patient. If an abnormal profile is obtained, we recommend repeating the test on an independent sample and in an experienced lab.

Statement #1 (grade of recommendation: D)

Serum or heparin plasma should be stored at −20°C and contamination by neuraminidase producing-microorganisms avoided. An abnormal profile should be retested on an independent sample in an experienced lab.

8.34.4 | False positive results of the biochemical tests (other causes of a positive Carbohydrate deficient transferrin (CDT%) test)

Secondary glycosylation defects can also lead to abnormal Tf IEF results. In patients with untreated galactosemia or fructosemia, accumulating intermediates inhibit N-glycosylation, thereby causing an abnormal Tf IEF pattern. Chronic alcoholism (>70 g per day), liver disease, severe infections, and chronic inflammatory diseases can also lead to an abnormal pattern.

8.34.5 | Confirmatory enzymatic and molecular testing

Conventionally, the follow-up after obtaining a type 1 pattern consists of enzymatic analysis in fibroblasts or leukocytes to look for PMM2-CDG and Phosphomannose isomerase (PMI-CDG). Preferably the measurements should be performed on freshly isolated leukocytes rather than on fibroblasts, since the latter might present a high residual PMM activity.[83] The cells should be lysed by sonication right before analysis, and both enzymes spectrophotometrically assayed at 37°C by the reduction of Nicotinamide adenine dinucleotide phosphate (NADP) to NADPH, according to the procedure described by Van Schaftingen and Jaeken.[4] Abnormal PMM enzymatic activity is reported in 198 PMM2-CDG patients. In 53% of the reported cases (n = 55), enzymatic activity was performed on skin fibroblasts, and on white blood cells (lymphocytes or leukocytes) in 33 patients (32%). Enzymatic analysis was performed in both cell types in12 patients. In addition, decreased PMM activity in amniocytes was also reported in three patients, in the context of prenatal diagnosis[13] (Kjaergaard et al 1998).

When intermediate PMM activities are found, mutations should next be performed. Sanger sequencing of the eight exons and flanking intronic sequences of the *PMM2* gene (NCBI reference sequence NM_000303.2) allows to identify mutations in >99% of patients with an enzymatically confirmed PMM deficiency. Deep intronic mutations and deletions would however be missed using this approach.[123] The standard reference sequence indicating reported variants (ENSG00000140650) and a reference for exon numbering (ENST00000268261) can be found at www.ensembl.org.

Mutation analysis of *PMM2* has been reported in 475 patients, with mutations mostly identified by direct Sanger sequencing. In addition, three patients have been molecularly diagnosed by whole exome sequencing,[39,138] one by autozygocyty mapping,[139] and four by gene panel targeted sequencing.[29,140]

Statement #1 (grade of recommendation: B-C).

PMM2-CDG should be confirmed by measurement of phosphomannomutase activity in fibroblasts or leukocytes and/or by mutation analysis of the *PMM2* gene.

8.34.6 | Genotype-phenotype correlations

PMM2 is the 246 amino acids product of the *PMM2* gene, localized to chromosome 16p13. Mutations have been described throughout the gene. Some 117 mutations have been reported to date, including 91 missense mutations, 5 nonsense mutations, 8 frameshift mutations, 11 splicing defects, and 1 complete loss of exon 8 due to a Alu retrotransposition-mediated deletion of 28 kb.[123] The p.R141H mutation (50 alleles) was the most frequent mutation, reported in 60% of the patients. No patient homozygous for this mutation has been reported, because this severe mutation is lethal in the homozygous state.[141,142] A higher frequency than average (approximately 1/72) of the R141H allele is however observed in the Dutch and Danish populations[2] and has been attributed to a survival advantage in heterozygotes in whom the mutation may confer resistance to hepatitis B and C viruses.[143] (Tables S4 and S5).

Four patients[144–146] were reported homozygous for the p.F119L mutation (genotype prevalence 0.8%), three patients[120,147,148] for the p.P113L mutation (genotype prevalence 0.6%), and one patient (genotype prevalence 0.2%) for either the p.C241S,[1] the p.T237M[148] or the p.T237R[36] mutation. Despite being the second most frequent mutation for *PMM2* with a prevalence of 10.3%, the variant p.V231M has only been reported so far as compound heterozygote.

Based on the he crystal structure of the isozyme of PMM2, for example, PMM1, it is possible to extrapolate on how specific frequent mutations could impact PMM2 protein function and stability. For instance, the arginine residues at positions p.R141 and p.R123 are hence assumed to be involved in binding either the phosphate or the C2 hydroxyl group of the substrate.[149] On the other hand, the p.F119L mutation might disrupt the hydrophobic core of PMM2 enzymes, which is assumed to mediate its homodimeric interaction.[149] No direct genotype/phenotype correlation can strictly be established for PMM2 deficiency, although it is strongly speculated that milder phenotypes are associated to mutations affecting the folding and/or stability of the PMM2 homodimer. Moreover, no specific mutation appears to be associated with a more severe clinical phenotype. Surprisingly, the prevalence of the frequent variant p.F119L is extremely low in phenotypes with predominant neurological symptoms (2.6%), whilst its general prevalence for PMM2-CDG is higher than 20%. Finally, it is very likely that the highly variable phenotype of PMM2-CDG, as in other monogenic diseases, is probably determined not only by the PMM2 mutant alleles but also by the other genes modulating the effect on the final functional enzyme activity.[150]

Statement #1 (grade of recommendation: C)

Over 117 disease causing genetic variants in PMM2 gene are known with no clear genotype/phenotype correlations. R141H mutation is the most frequent mutation reported only in compound heterozygous states.

8.34.7 | Common laboratory findings

The plasma concentrations of glycoproteins are often decreased in PMM2-CDG patients, such as haptoglobin, ceruloplasmin, TBG,[34,63,69,79,81,113,121] haptoglobulin,[121] alpha-1 anti-trypsin[151,152] (Sarar et al 2009) several clotting and anticlotting factors, including factor XI (decreased in 193/197 investigated patients), antithrombin (decreased in 207/210 investigated patients), protein C (decreased in 191/194 investigated patients) and protein S (decreased in 158/162 investigated patients). Other coagulation factors can be decreased as well, such as factor IX (decreased in 18/32 patients), factor II (decreased in 10/13 investigated patients), factor X,[24] and factor XII.[50,153] In addition, PMM2-CDG patients often present increased and discordant levels of ALT (elevated in 63/108 investigated patients) and AST (elevated in 70/86 investigated patients), as well as low cholesterol as reported in 10 patients[69,79,89,121,123] (Kjaergaard et al 1999; Vabres et al 1998).

Statement #1 (grade of recommendation: D)

Plasma concentrations of cholesterol, haptoglobin, alpha-1-antitrypsin, factors II, V, IX, X, and XI, antithrombin, protein C, and protein S are usually decreased in PMM2-CDG patients. Levels of these compounds may fluctuate during follow-up.

8.35 | Prenatal testing

Prenatal diagnosis is possible by enzymatic analysis of amniocytes[13]; this should be combined with mutation analysis of the PMM2 gene. Foetal transferrin IEF however leads to false results.[142] Prenatal diagnosis using short-tandem-repeat-polymorphisms (STRP) of the *PMM2* gene has been reported.[144] Using a combination of linkage and mutation analyses, they have been able to provide prenatal diagnostic information for 15 PMM2-CDG families. Five of the analyses indicated an affected foetus, seven were carriers and three tested as non-carriers.[144] Besides, decreased PMM

activity in amniocytes was also reported in three patients in the context of prenatal diagnosis.[13,154]

Statement #1 (grade of recommendation: D)

Molecular analysis is the preferred technique for the first-trimester prenatal diagnosis if the mutations in both parents are known. Alternatively, enzyme analysis can be performed in cultured amniocytes but not in chorionic villi. Preimplantation genetic testing is feasible.

ACKNOWLEDGMENT

We would like to thank the Metabolic ERN (MetabERN) for their support to our study.

CONFLICTS OF INTEREST

Honzik Tomas and Cechova Anna were supported by General University Hospital in Prague, Czech Republic (RVO-VFN 64165), and the Ministry of Health of the Czech Republic (MZ CR AZV 16-31932A). All other authors have no conflicts of interest to declare.

REFERENCES

1. Matthijs G, Schollen E, Bjursell C, et al. Mutations in PMM2 that cause congenital disorders of glycosylation, type Ia (CDG-Ia). *Hum Mutat*. 2000;16(5):386-394.
2. Schollen E, Kjaergaard S, Legius E, Schwartz M, Matthijs G. Lack of Hardy-Weinberg equilibrium for the most prevalent PMM2 mutation in CDG-Ia (congenital disorders of glycosylation type Ia). *Eur J Hum Genet*. 2000;8(5):367-371.
3. Jaeken J, van Eijk HG, van der Heul C, Corbeel L, Eeckels R, Eggermont E. Sialic acid-deficient serum and cerebrospinal fluid transferrin in a newly recognized genetic syndrome. *Clin Chim Acta*. 1984;144(2-3):245-247.
4. Van Schaftingen E, Jaeken J. Phosphomannomutase deficiency is a cause of carbohydrate-deficient glycoprotein syndrome type I. *FEBS Lett*. 1995;377(3):318-320.
5. Matthijs G, Schollen E, Pardon E, et al. Mutations in PMM2, a phosphomannomutase gene on chromosome 16p13, in carbohydrate-deficient glycoprotein type I syndrome (Jaeken syndrome). *Nat Genet*. 1997;16(1):88-92. Erratum in: Nat Genet 1997 Jul;16(3):316.
6. Jaeken J, Hennet T, Matthijs G, Freeze HH. CDG nomenclature: time for a change! *Biochim Biophys Acta*. 2009;1792(9):825-826.
7. Wurm D, Hänsgen A, Kim YJ, Lindinger A, Baghai A, Gortner L. Early fatal course in siblings with CDG-Ia (caused by two novel mutations in the PMM2 gene): clinical, molecular and autopsy findings. *Eur J Pediatr*. 2007;166(4):377-378.
8. Aronica E, van Kempen AA, van der Heide M, et al. Congenital disorder of glycosylation type Ia: a clinicopathological report of a newborn infant with cerebellar pathology. *Acta Neuropathol*. 2005;109(4):433-442.
9. Gehrmann J, Sohlbach K, Linnebank M, et al. Cardiomyopathy in congenital disorders of glycosylation. *Cardiol Young*. 2003;13(4):345-351.
10. Malhotra A, Pateman A, Chalmers R, Coman D, Menahem S. Prenatal cardiac ultrasound finding in congenital disorder of glycosylation type 1a. *Fetal Diagn Ther*. 2009;25(1):54-57.
11. Coman D, Irving M, Kannu P, Jaeken J, Savarirayan R. The skeletal manifestations of the congenital disorders of glycosylation. *Clin Genet*. 2008;73(6):507-515.
12. Barone R, Carrozzi M, Parini R, et al. A nationwide survey of PMM2-CDG in Italy: high frequency of a mild neurological variant associated with the L32R mutation. *J Neurol*. 2015;262(1):154-164.
13. Edwards M, McKenzie F, O'callaghan S, et al. Prenatal diagnosis of congenital disorder of glycosylation type Ia (CDG-Ia) by cordocentesis and transferrin isoelectric focusing of serum of a 27-week fetus with non-immune hydrops. *Prenat Diagn*. 2006;26(10):985-988.
14. Léticée N, Bessières-Grattagliano B, Dupré T, et al. Should PMM2-deficiency (CDG Ia) be searched in every case of unexplained hydrops fetalis? *Mol Genet Metab*. 2010;101(2-3):253-257.
15. van de Kamp JM, Lefeber DJ, Ruijter GJ, et al. Congenital disorder of glycosylation type Ia presenting with hydrops fetalis. *J Med Genet*. 2007;44(4):277-280.
16. Kjaergaard S, Schwartz M, Skovby F. Congenital disorder of glycosylation type Ia (CDG-Ia): phenotypic spectrum of the R141H/F119L genotype. *Arch Dis Child*. 2001;85(3):236-239.
17. Al-Maawali AA, Miller E, Schulze A, Yoon G, Blaser SI. Subcutaneous fat pads on body MRI-an early sign of congenital disorder of glycosylation PMM2-CDG (CDG1a). *Pediatr Radiol*. 2014;44(2):222-225.
18. Serrano M, de Diego V, Muchart J, et al. Phosphomannomutase deficiency (PMM2-CDG): ataxia and cerebellar assessment. *Orphanet J Rare Dis*. 2015;10:138.
19. Bortot B, Cosentini D, Faletra F, et al. PMM2-CDG: phenotype and genotype in four affected family members. *Gene*. 2013;531(2):506-509.
20. Giurgea I, Michel A, Le Merrer M, Seta N, de Lonlay P. Underdiagnosis of mild congenital disorders of glycosylation type Ia. *Pediatr Neurol*. 2005;32(2):121-123.
21. Shanti B, Silink M, Bhattacharya K, et al. Congenital disorder of glycosylation type Ia: heterogeneity in the clinical presentation from multivisceral failure to hyperinsulinaemic hypoglycaemia as leading symptoms in three infants with phosphomannomutase deficiency. *J Inherit Metab Dis*. 2009;32(suppl 1):S241-S251.
22. Vuillaumier-Barrot S, Isidor B, Dupré T, Le Bizec C, David A, Seta N. Expanding the Spectrum of PMM2-CDG Phenotype. *JIMD Rep*. 2012;5:123-125.
23. Barone R, Sturiale L, Fiumara A, Uziel G, Garozzo D, Jaeken J. Borderline mental development in a congenital disorder of glycosylation (CDG) type Ia patient with multisystemic involvement (intermediate phenotype). *J Inherit Metab Dis*. 2007;30(1):107.
24. Briones P, Vilaseca MA, Schollen E, et al. Biochemical and molecular studies in 26 Spanish patients with congenital disorder of glycosylation type Ia. *J Inherit Metab Dis*. 2002;25(8):635-646.
25. Casado M, O'Callaghan MM, Montero R, et al. Mild clinical and biochemical phenotype in two patients with PMM2-CDG (congenital disorder of glycosylation Ia). *Cerebellum*. 2012;11(2):557-563.

26. Monin ML, Mignot C, De Lonlay P, et al. 29 French adult patients with PMM2-congenital disorder of glycosylation: outcome of the classical pediatric phenotype and depiction of a late-onset phenotype. *Orphanet J Rare Dis*. 2014;9:207.
27. Vermeer S, Kremer HP, Leijten QH, et al. Cerebellar ataxia and congenital disorder of glycosylation Ia (CDG-Ia) with normal routine CDG screening. *J Neurol*. 2007;254(10):1356-1358.
28. Pancho C, Garcia-Cazorla A, Varea V, et al. Congenital disorder of glycosylation type Ia revealed by hypertransaminasemia and failure to thrive in a young boy with normal neurodevelopment. *J Pediatr Gastroenterol Nutr*. 2005;40(2):230-232.
29. Vals MA, Morava E, Teeäär K, et al. Three families with mild PMM2-CDG and normal cognitive development. *Am J Med Genet A*. 2017;173(6):1620-1624.
30. García Silva MT, de Castro J, Stibler H, et al. Prenatal hypertrophic cardiomyopathy and pericardial effusion in carbohydrate-deficient glycoprotein syndrome. *J Inherit Metab Dis*. 1996;19 (2):257-259.
31. Schiff M, Roda C, Monin ML, et al. Clinical, laboratory and molecular findings and long-term follow-up data in 96 French patients with PMM2-CDG (phosphomannomutase 2-congenital disorder of glycosylation) and review of the literature. *J Med Genet*. 2017;54(12):843-851.
32. Coman D, Klingberg S, Morris D, McGill J, Mercer H. Congenital disorder of glycosylation type Ia in a 6-year-old girl with a mild intellectual phenotype: two novel PMM2 mutations. *J Inherit Metab Dis*. 2005;28(6):1189-1190.
33. Drouin-Garraud V, Belgrand M, Grünewald S, et al. Neurological presentation of a congenital disorder of glycosylation CDG-Ia: implications for diagnosis and genetic counseling. *Am J Med Genet*. 2001;101(1):46-49.
34. Schade van Westrum SM, Nederkoorn PJ, Schuurman PR, Vulsma T, Duran M, Poll-The BT. Skeletal dysplasia and myelopathy in congenital disorder of glycosylation type IA. *J Pediatr*. 2006;148(1):115-117.
35. de Diego V, Martínez-Monseny AF, Muchart J, et al. Longitudinal volumetric and 2D assessment of cerebellar atrophy in a large cohort of children with phosphomannomutase deficiency (PMM2-CDG). *J Inherit Metab Dis*. 2017;40(5):709-713.
36. Serrano NL, De Diego V, Cuadras D, et al. A quantitative assessment of the evolution of cerebellar syndrome in children with phosphomannomutase-deficiency (PMM2-CDG). *Orphanet J Rare Dis*. 2017;12(1):155.
37. Antoun H, Villeneuve N, Gelot A, Panisset S, Adamsbaum C. Cerebellar atrophy: an important feature of carbohydrate deficient glycoprotein syndrome type 1. *Pediatr Radiol*. 1999;29(3):194-198.
38. Neumann LM, von Moers A, Kunze J, Blankenstein O, Marquardt T. Congenital disorder of glycosylation type 1a in a macrosomic 16-month-old boy with an atypical phenotype and homozygosity of the N216I mutation. *Eur J Pediatr*. 2003;162 (10):710-713.
39. Rossi M, Medina Escobar A, Ameghino L, Merello M. Expanding the phenotype of phosphomannomutase-2 gene congenital disorder of glycosylation: Cervical dystonia. *J Neurol Sci*. 2017; 378:52-54.
40. Arnoux JB, Boddaert N, Valayannopoulos V, et al. Risk assessment of acute vascular events in congenital disorder of glycosylation type Ia. *Mol Genet Metab*. 2008;93(4):444-449.
41. Artigas J, Cardo E, Pineda M, Nosas R, Jaeken J. Phosphomannomutase deficiency and normal pubertal development. *J Inherit Metab Dis*. 1998;21(1):78-79.
42. Dinopoulos A, Mohamed I, Jones B, Rao S, Franz D, de Grauw T. Radiologic and neurophysiologic aspects of stroke-like episodes in children with congenital disorder of glycosylation type Ia. *Pediatrics*. 2007;119(3):e768-e772.
43. Hahn SH, Minnich SJ, O'Brien JF. Stabilization of hypoglycosylation in a patient with congenital disorder of glycosylation type Ia. *J Inherit Metab Dis*. 2006;29(1):235-237.
44. Ishikawa N, Tajima G, Ono H, Kobayashi M. Different neuroradiological findings during two stroke-like episodes in a patient with a congenital disorder of glycosylation type Ia. *Brain and Development*. 2009;31(3):240-243.
45. Izquierdo-Serra M, Martínez-Monseny AF, López L, et al. Stroke-like episodes and cerebellar syndrome in phosphomannomutase deficiency (PMM2-CDG): evidence for hypoglycosylation-driven channelopathy. *Int J Mol Sci*. 2018;19(2):619.
46. Kondo I, Mizugishi K, Yoneda Y, et al. Missense mutations in phosphomannomutase 2 gene in two Japanese families with carbohydrate-deficient glycoprotein syndrome type 1. *Clin Genet*. 1999;55(1):50-54.
47. Krasnewich D, O'Brien K, Sparks S. Clinical features in adults with congenital disorders of glycosylation type Ia (CDG-Ia). *Am J Med Genet C Semin Med Genet*. 2007;145C(3):302-306.
48. Pearl PL, Krasnewich D. Neurologic course of congenital disorders of glycosylation. *J Child Neurol*. 2001;16(6):409-413.
49. van Baalen A, Stephani U, Rohr A. Increased brain lactate during stroke-like episode in a patient with congenital disorder of glycosylation type Ia. *Brain and Development*. 2009;31(2):183.
50. van Ommen CH, Peters M, Barth PG, Vreken P, Wanders RJ, Jaeken J. Carbohydrate-deficient glycoprotein syndrome type 1a: a variant phenotype with borderline cognitive dysfunction, cerebellar hypoplasia, and coagulation disturbances. *J Pediatr*. 2000; 136(3):400-403.
51. Pérez-Dueñas B, García-Cazorla A, Pineda M, et al. Long-term evolution of eight Spanish patients with CDG type Ia: typical and atypical manifestations. *Eur J Paediatr Neurol*. 2009;13(5): 444-451.
52. Jensen H, Kjaergaard S, Klie F, Moller HU. Ophthalmic manifestations of congenital disorder of glycosylation type 1a. *Ophthalmic Genet*. 2003;24(2):81-88.
53. Messenger WB, Yang P, Pennesi ME. Ophthalmic findings in an infant with phosphomannomutase deficiency. *Doc Ophthalmol*. 2014;128(2):149-153.
54. Wang BZ, Siriwardana P, Taranath D. Macular hypoplasia in congenital disorder of glycosylation type ia. *Case Rep Ophthalmol*. 2012;3(1):142-144.
55. Morava E, Wosik HN, Sykut-Cegielska J, et al. Ophthalmological abnormalities in children with congenital disorders of glycosylation type I. *Br J Ophthalmol*. 2009;93(3):350-354.
56. Al Teneiji A, Bruun TU, Sidky S, et al. Phenotypic and genotypic spectrum of congenital disorders of glycosylation type I and type II. *Mol Genet Metab*. 2017;120(3):235-242.
57. Damen G, de Klerk H, Huijmans J, den Hollander J, Sinaasappel M. Gastrointestinal and other clinical manifestations in 17 children with congenital disorders of glycosylation type Ia, Ib, and Ic. *J Pediatr Gastroenterol Nutr*. 2004;38(3):282-287.

58. Romano S, Bajolle F, Valayannopoulos V, et al. Conotruncal heart defects in three patients with congenital disorder of glycosylation type Ia (CDG Ia). *J Med Genet*. 2009;46(4):287-288.
59. Coman D, Bostock D, Hunter M, et al. Prenatal cardiac ultrasound finding in congenital disorder of glycosylation type 1a. *Fetal Diagn Ther*. 2009;25(1):54-57.
60. Footitt EJ, Karimova A, Burch M, et al. Cardiomyopathy in the congenital disorders of glycosylation (CDG): a case of late presentation and literature review. *J Inherit Metab Dis*. 2009;32 (suppl 1):S313-S319.
61. Kusa J, Pyrkosz A, Skiba A, Szkutnik M. Cardiac manifestations of carbohydrate-deficient glycoprotein syndrome. *Pediatr Cardiol*. 2003;24(5):493-494.
62. Rudaks LI, Andersen C, Khong TY, Kelly A, Fietz M, Barnett CP. Hypertrophic cardiomyopathy with cardiac rupture and tamponade caused by congenital disorder of glycosylation type Ia. *Pediatr Cardiol*. 2012;33(5):827-830.
63. Clayton PT, Winchester BG, Keir G. Hypertrophic obstructive cardiomyopathy in a neonate with the carbohydrate-deficient glycoprotein syndrome. *J Inherit Metab Dis*. 1992;15(6):857-856.
64. Işıkay S, Başpınar O, Yılmaz K. A case of congenital disorder of glycosylation Ia presented with recurrent pericardial effusion. *Iran J Pediatr*. 2014;24(5):652-654.
65. Kristiansson B, Borulf S, Conradi N, Erlanson-Albertsson C, Ryd W, Stibler H. Intestinal, pancreatic and hepatic involvement in carbohydrate-deficient glycoprotein syndrome type I. *J Pediatr Gastroenterol Nutr*. 1998;27(1):23-29.
66. Resende C, Carvalho C, Alegria A, et al. Congenital disorders of glycosylation with neonatal presentation. *BMJ Case Rep*. 2014;2014.
67. Feldman BJ, Rosenthal D. Carbohydrate-deficient glycoprotein syndrome-associated pericardial effusion treated with corticosteroids and salicylic acid. *Pediatr Cardiol*. 2002;23(4):469-471.
68. Marquardt T, Hülskamp G, Gehrmann J, Debus V, Harms E, Kehl HG. Severe transient myocardial ischaemia caused by hypertrophic cardiomyopathy in a patient with congenital disorder of glycosylation type Ia. *Eur J Pediatr*. 2002;161(10): 524-527.
69. de Lonlay P, Seta N, Barrot S, et al. A broad spectrum of clinical presentations in congenital disorders of glycosylation I: a series of 26 cases. *J Med Genet*. 2001;38(1):14-19.
70. Eyskens F, Ceuterick C, Martin JJ, Janssens G, Jaeken J. Carbohydrate-deficient glycoprotein syndrome with previously unreported features. *Acta Paediatr*. 1994;83(8):892-896.
71. Kjaergaard S, Müller J, Skovby F. Prepubertal growth in congenital disorder of glycosylation type Ia (CDG-Ia). *Arch Dis Child*. 2002;87(4):324-327.
72. McKenzie FA, Fietz M, Fletcher J, Smith RL, Wright IM, Jaeken J. A previously undescribed form of congenital disorder of glycosylation with variable presentation in siblings: early fetal loss with hydrops fetalis, and infant death with hypoproteinemia. *Am J Med Genet A*. 2007;143A(17):2029-2034.
73. Noelle V, Knuepfer M, Pulzer F, et al. Unusual presentation of congenital disorder of glycosylation type 1a: congenital persistent thrombocytopenia, hypertrophic cardiomyopathy and hydrops-like aspect due to marked peripheral oedema. *Eur J Pediatr*. 2005;164(4):223-226.
74. Westphal V, Peterson S, Patterson M, et al. Functional significance of PMM2 mutations in mildly affected patients with congenital disorders of glycosylation Ia. *Genet Med*. 2001;3(6): 393-398.
75. Miller BS, Duffy MM, Addo OY, Sarafoglou K. rhIGF-1 therapy for growth failure and IGF-1 deficiency in congenital disorder of glycosylation Ia (PMM2 deficiency). *J Investig Med High Impact Case Rep*. 2013;1(3):2324709613503316.
76. Truin G, Guillard M, Lefeber DJ, et al. Pericardial and abdominal fluid accumulation in congenital disorder of glycosylation type Ia. *Mol Genet Metab*. 2008;94(4):481-484.
77. Verstegen RH, Theodore M, van de Klerk H, Morava E. Lymphatic edema in congenital disorders of glycosylation. *JIMD Rep*. 2012;4:113-116.
78. Ren C, Fang F, Huang Y, Cheng H, Dai L. Clinical and genetic analysis for two children with congenital disturbance of glycosylation with PMM2 gene mutations. *Zhonghua Er Ke Za Zhi*. 2015;53(12):938-942.
79. Schoffer KL, O'Sullivan JD, McGill J. Congenital disorder of glycosylation type Ia presenting as early-onset cerebellar ataxia in an adult. *Mov Disord*. 2006;21(6):869-872.
80. Grünewald S. The clinical spectrum of phosphomannomutase 2 deficiency (CDG-Ia). *Biochim Biophys Acta*. 2009;1792(9): 827-834.
81. Ong BB, Gole GA, Robertson T, McGill J, de Lore D, Crawford M. Retinal hemorrhages associated with meningitis in a child with a congenital disorder of glycosylation. *Forensic Sci Med Pathol*. 2009;5(4):307-312.
82. Marques-da-Silva D, Dos Reis Ferreira V, Monticelli M, et al. Liver involvement in congenital disorders of glycosylation (CDG). A systematic review of the literature. *J Inherit Metab Dis*. 2017;40(2):195-207.
83. Grünewald S, Schollen E, Van Schaftingen E, Jaeken J, Matthijs G. High residual activity of PMM2 in patients' fibroblasts: possible pitfall in the diagnosis of CDG-Ia (phosphomannomutase deficiency). *Am J Hum Genet*. 2001;68(2):347-354.
84. Enns GM, Steiner RD, Buist N, et al. Clinical and molecular features of congenital disorder of glycosylation in patients with type 1 sialotransferrin pattern and diverse ethnic origins. *J Pediatr*. 2002;141(5):695-700.
85. Grünewald S, Matthijs G, Jaeken J. Congenital disorders of glycosylation: a review. *Pediatr Res*. 2002;52(5):618-624.
86. Barone R, Sturiale L, Sofia V, et al. Clinical phenotype correlates to glycoprotein phenotype in a sib pair with CDG-Ia. *Am J Med Genet A*. 2008;146A(16):2103-2108.
87. Veneselli E, Biancheri R, Di Rocco M, Tortorelli S. Neurophysiological findings in a case of carbohydrate-deficient glycoprotein (CDG) syndrome type I with phosphomannomutase deficiency. *Eur J Paediatr Neurol*. 1998;2(5):239-244.
88. Hutchesson AC, Gray RG, Spencer DA, Keir G. Carbohydrate deficient glycoprotein syndrome; multiple abnormalities and diagnostic delay. *Arch Dis Child*. 1995;72(5):445-446.
89. Jamroz E, Adamek D, Paprocka J, Adamowicz M, Marszał E, Wevers RA. CDG type Ia and congenital cytomegalovirus infection: two coexisting conditions. *J Child Neurol*. 2009;24(1):13-18. https://doi.org/10.1177/0883073808321041.
90. van der Knaap MS, Wevers RA, Monnens L, Jakobs C, Jaeken J, van Wijk JA. Congenital nephrotic syndrome: a novel phenotype of type I carbohydrate-deficient glycoprotein syndrome. *J Inherit Metab Dis*. 1996;19(6):787-791.

91. Altassan R, Witters P, Saifudeen Z, et al. Renal involvement in PMM2-CDG, a mini-review. *Mol Genet Metab*. 2018;123(3):292-296.
92. de la Morena-Barrio ME, Sevivas TS, Martinez-Martinez I, et al. Congenital disorder of glycosylation (PMM2-CDG) in a patient with antithrombin deficiency and severe thrombophilia. *J Thromb Haemost*. 2012;10(12):2625-2627.
93. Linssen M, Mohamed M, Wevers RA, Lefeber DJ, Morava E. Thrombotic complications in patients with PMM2-CDG. *Mol Genet Metab*. 2013;109(1):107-111. https://doi.org/10.1016/j.ymgme.2013.02.006.
94. Tomkowski WZ, Dybowska M, Kuca P, Gralec R, Burakowski J. The inefficacy of enoxaparin prophylaxis in a patient with congenital antithrombin deficiency. *Clin Appl Thromb Hemost*. 2009;15(2):241. https://doi.org/10.1177/1076029607308861.
95. Lefrère B, Stepanian A, Itzhar-Baïkian N, et al. Deep venous thrombosis treated by rivaroxaban in a young patient with type Ia carbohydrate-deficient glycoprotein (CDG) syndrome. *Ann Biol Clin (Paris)*. 2018;76(2):217-223.
96. Ono H, Sakura N, Yamashita K, Yuasa I, Ohno K. Novel nonsense mutation (R194X) in the PMM2 gene in a Japanese patient with congenital disorder of glycosylation type Ia. *Brain Dev*. 2003;25(7):525-528. Erratum in: Brain Dev. 2004 Aug;26(5):347.
97. Le Bizec C, Vuillaumier-Barrot S, Barnier A, Dupré T, Durand G, Seta N. A new insight into PMM2 mutations in the French population. *Hum Mutat*. 2005;25(5):504-505.
98. Van Geet C, Jaeken J, Freson K, et al. Congenital disorders of glycosylation type Ia and IIa are associated with different primary haemostatic complications. *J Inherit Metab Dis*. 2001;24(4):477-492.
99. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352.
100. Monagle P. Diagnosis and management of deep venous thrombosis and pulmonary embolism in neonates and children. *Semin Thromb Hemost*. 2012;38(7):683-690.
101. Meaudre E, Meyrieux V, Suprano I, Camboulives J, Paut O. Anesthesia considerations in carbohydrate-deficient glycoprotein syndrome type I. *Paediatr Anaesth*. 2005;15(10):905-906.
102. de Zegher F, Jaeken J. Endocrinology of the carbohydrate-deficient glycoprotein syndrome type 1 from birth through adolescence. *Pediatr Res*. 1995;37(4 pt 1):395-401.
103. Miller BS, Khosravi MJ, Patterson MC, Conover CA. IGF system in children with congenital disorders of glycosylation. *Clin Endocrinol*. 2009;70(6):892-897.
104. Funke S, Gardeitchik T, Kouwenberg D, et al. Perinatal and early infantile symptoms in congenital disorders of glycosylation. *Am J Med Genet A*. 2013;161A(3):578-584.
105. Mohamed M, Theodore M, Claahsen-van der Grinten H, et al. Thyroid function in PMM2-CDG: diagnostic approach and proposed management. *Mol Genet Metab*. 2012;105(4):681-683.
106. Schade van Westrum SM, Nederkoorn PJ, Schuurman PR, Vulsma T, Duran M, Poll-The BT. Skeletal dysplasia and myelopathy in congenital disorder of glycosylation type IA. *J Pediatr*. 2006;148(1):115-117.
107. Jaeken J, Stibler H, Hagberg B. The carbohydrate-deficient glycoprotein syndrome. A new inherited multisystemic disease with severe nervous system involvement. *Acta Paediatr Scand Suppl*. 1991;375:1-71.
108. Böhles H, Sewell AA, Gebhardt B, Reinecke-Lüthge A, Klöppel G, Marquardt T. Hyperinsulinaemic hypoglycaemia--leading symptom in a patient with congenital disorder of glycosylation Ia (phosphomannomutase deficiency). *J Inherit Metab Dis*. 2001;24(8):858-862.
109. Fiumara A, Barone R, Del Campo G, Striano P, Jaeken J. Electroclinical features of early-onset epileptic encephalopathies in congenital disorders of glycosylation (CDGs). *JIMD Rep*. 2016;27:93-99.
110. Barone R, Fiumara A, Jaeken J. Congenital disorders of glycosylation with emphasis on cerebellar involvement. *Semin Neurol*. 2014;34(3):357-366. https://doi.org/10.1055/s-0034-1387197.
111. Pineda M, Pavia C, Vilaseca MA, et al. Normal pubertal development in a female with carbohydrate deficient glycoprotein syndrome. *Arch Dis Child*. 1996;74(3):242-243.
112. Pérez-Dueñas B, García-Cazorla A, Pineda M, et al. Long-term evolution of eight Spanish patients with CDG type Ia: typical and atypical manifestations. *Eur J Paediatr Neurol*. 2009;13(5):444-451.
113. Coman D, McGill J, MacDonald R, et al. Congenital disorder of glycosylation type 1a: three siblings with a mild neurological phenotype. *J Clin Neurosci*. 2007;14(7):668-672.
114. Garel C, Baumann C, Besnard M, Ogier H, Jaeken J, Hassan M. Carbohydrate-deficient glycoprotein syndrome type I: a new cause of dysostosis multiplex. *Skelet Radiol*. 1998;27(1):43-45.
115. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod*. 2016;31(5):926-937.
116. Brum JM, Rizzo IM, Mello WD, Speck-Martins CE. Congenital disorder of glycosylation type Ia: a non-progressive encephalopathy associated with multisystemic involvement. *Arq Neuropsiquiatr*. 2008;66(3A):545-548.
117. García-López R, de la Morena-Barrio ME, Alsina L, et al. Natural killer cell receptors and cytotoxic activity in phosphomannomutase 2 deficiency (PMM2-CDG). *PLoS One*. 2016;11(7):e0158863.
118. Blank C, Smith LA, Hammer DA, et al. Recurrent infections and immunological dysfunction in congenital disorder of glycosylation Ia (CDG Ia). *J Inherit Metab Dis*. 2006;29(4):592.
119. Dyer JA, Winters CJ, Chamlin SL. Cutaneous findings in congenital disorders of glycosylation: the hanging fat sign. *Pediatr Dermatol*. 2005;22(5):457-460.
120. de la Morena-Barrio ME, Di Michele M, Lozano ML, et al. Proteomic analysis of platelet N-glycoproteins in PMM2-CDG patients. *Thromb Res*. 2014;133(3):412-417.
121. Pavone L, Fiumara A, Barone R, et al. Olivopontocerebellar atrophy leading to recognition of carbohydrate-deficient glycoprotein syndrome type I. *J Neurol*. 1996;243(10):700-705.
122. Mehlman CT, Nematbakhsh AR, Crawford AH, Berlin RE. Spinal deformity associated with carbohydrate-deficient glycoprotein syndrome (Jaeken's syndrome): a report of three cases. *Spine (Phila Pa 1976)*. 2003;28(7):E132-E135.
123. Schollen E, Keldermans L, Foulquier F, et al. Characterization of two unusual truncating PMM2 mutations in two CDG-Ia patients. *Mol Genet Metab*. 2007;90(4):408-413.
124. van den Boogert MAW, Rader DJ, Holleboom AG. New insights into the role of glycosylation in lipoprotein metabolism. *Curr Opin Lipidol*. 2017;28(6):502-506.
125. Kasapkara ÇS, Barış Z, Kılıç M, et al. PMM2-CDG and sensorineural hearing loss. *J Inherit Metab Dis*. 2017;40(5):629-630.
126. Harlor AD Jr, Bower C, Committee on Practice and Ambulatory Medicine; Section on Otolaryngology-Head and Neck Surgery. Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics*. 2009;124(4):1252-1263.

127. Wolthuis DF, Janssen MC, Cassiman D, Lefeber DJ, Morava E. Defining the phenotype and diagnostic considerations in adults with congenital disorders of N-linked glycosylation. *Expert Rev Mol Diagn*. 2014;14(2):217-224.
128. Sturiale L, Barone R, Garozzo D. The impact of mass spectrometry in the diagnosis of congenital disorders of glycosylation. *J Inherit Metab Dis*. 2011;34(4):891-899.
129. Lefeber DJ, Morava E, Jaeken J. How to find and diagnose a CDG due to defective N-glycosylation. *J Inherit Metab Dis*. 2011;34(4):849-852.
130. Lacey JM, Bergen HR, Magera MJ, Naylor S, O'Brien JF. Rapid determination of transferrin isoforms by immunoaffinity liquid chromatography and electrospray mass spectrometry. *Clin Chem*. 2001;47(3):513-518.
131. Tegtmeyer LC, Rust S, van Scherpenzeel M, et al. Multiple phenotypes in phosphoglucomutase 1 deficiency. *N Engl J Med*. 2014;370(6):533.
132. Chu KL, Chien YH, Tsai CE, Freeze HH, Eklund E, Hwu WL. Carbohydrate deficient glycoprotein syndrome type Ia. *J Formos Med Assoc*. 2004;103(9):721-723.
133. Coorg R, Lotze TE. Child neurology: a case of PMM2-CDG (CDG 1a) presenting with unusual eye movements. *Neurology*. 2012;79(15):e131-e133.
134. Jaeken J, Artigas J, Barone R, et al. Phosphomannomutase deficiency is the main cause of carbohydrate-deficient glycoprotein syndrome with type I isoelectrofocusing pattern of serum sialotransferrins. *J Inherit Metab Dis*. 1997;20(3):447-449.
135. Zühlsdorf A, Park JH, Wada Y, et al. Transferrin variants: pitfalls in the diagnostics of congenital disorders of glycosylation. *Clin Biochem*. 2015 Jan;48(1-2):11-13. https://doi.org/10.1016/j.clinbiochem.2014.09.022.
136. Denecke J. Biomarkers and diagnosis of congenital disorders of glycosylation. *Expert Opin Med Diagn*. 2009;3(4):395-409.
137. Gornik O, Lauc G. Glycosylation of serum proteins in inflammatory diseases. *Dis Markers*. 2008;25(4-5):267-278.
138. Choi R, Woo HI, Choe BH, et al. Application of whole exome sequencing to a rare inherited metabolic disease with neurological and gastrointestinal manifestations: a congenital disorder of glycosylation mimicking glycogen storage disease. *Clin Chim Acta*. 2015;444:50-53.
139. Cabezas OR, Flanagan SE, Stanescu H, et al. Polycystic kidney disease with hyperinsulinemic hypoglycemia caused by a promoter mutation in phosphomannomutase 2. *J Am Soc Nephrol*. 2017;28(8):2529-2539.
140. Bastaki F, Bizzari S, Hamici S, et al. Single-center experience of N-linked congenital disorders of glycosylation with a summary of molecularly characterized cases in Arabs. *Ann Hum Genet*. 2018;82(1):35-47.
141. Vals MA, Pajusalu S, Kals M, Mägi R, Õunap K. The prevalence of PMM2-CDG in estonia based on population carrier frequencies and diagnosed patients. *JIMD Rep*. 2018;39:13-17.
142. Matthijs G, Schollen E, Cassiman J-J, Cormier-Daire V, Jaeken J, van Schaftingen E. Prenatal diagnosis in CDG1 families: beware of heterogeneity. *Eur J Hum Genet*. 1998;6(2):99-104.
143. Freeze HH, Westphal V. Balancing N-linked glycosylation to avoid disease. *Biochimie*. 2001 Aug;83(8):791-799.
144. Bjursell C, Wahlström J, Berg K, et al. Detailed mapping of the phosphomannomutase 2 (PMM2) gene and mutation detection enable improved analysis for Scandinavian CDG type I families. *Eur J Hum Genet*. 1998;6(6):603-611.
145. Bjursell C, Erlandson A, Nordling M, et al. PMM2 mutation spectrum, including 10 novel mutations, in a large CDG type 1A family material with a focus on Scandinavian families. *Hum Mutat*. 2000;16(5):395-400.
146. Erlandson A, Bjursell C, Stibler H, Kristiansson B, Wahlström J, Martinsson T. Scandinavian CDG-Ia patients: genotype/phenotype correlation and geographic origin of founder mutations. *Hum Genet*. 2001;108(5):359-367.
147. Matthijs G, Schollen E, Heykants L, Grünewald S. Phosphomannomutase deficiency: the molecular basis of the classical Jaeken syndrome (CDGS type Ia). *Mol Genet Metab*. 1999;68(2):220-226.
148. Vega AI, Pérez-Cerdá C, Abia D, et al. Expression analysis revealing destabilizing mutations in phosphomannomutase 2 deficiency (PMM2-CDG): expression analysis of PMM2-CDG mutations. *J Inherit Metab Dis*. 2011;34(4):929-939.
149. Silvaggi NR, Zhang C, Lu Z, Dai J, Dunaway-Mariano D, Allen KN. The X-ray crystal structures of human alpha-phosphomannomutase 1 reveal the structural basis of congenital disorder of glycosylation type 1a. *J Biol Chem*. 2006;281(21):14918-14926.
150. Dipple KM, McCabe ER. Modifier genes convert "simple" Mendelian disorders to complex traits. *Mol Genet Metab*. 2000;71(1-2):43-50.
151. Dupré T, Barnier A, de Lonlay P, et al. Defect in N-glycosylation of proteins is tissue-dependent in congenital disorders of glycosylation Ia. *Glycobiology*. 2000;10(12):1277-1281.
152. Hertz-Pannier L, Déchaux M, Sinico M, et al. Congenital disorders of glycosylation type I: a rare but new cause of hyperechoic kidneys in infants and children due to early microcystic changes. *Pediatr Radiol*. 2006;36(2):108-114.
153. Stefanits H, Konstantopoulou V, Kuess M, Milenkovic I, Matula C. Initial diagnosis of the congenital disorder of glycosylation PMM2-CDG (CDG1a) in a 4-year-old girl after neurosurgical intervention for cerebral hemorrhage. *J Neurosurg Pediatr*. 2014;14(5):546-549.
154. Nogueira C, Quelhas D, Vilarinho L. Prenatal diagnosis for CDG Ia based on post-mortem molecular study of Guthrie card. *Mol Genet Metab*. 2006;87(4):379.
155. Zhang W, James PM, Ng BG, et al. A Novel N-Tetrasaccharide in Patients with Congenital Disorders of Glycosylation, Including Asparagine-Linked Glycosylation Protein 1, Phosphomannomutase 2, and Mannose Phosphate Isomerase Deficiencies. *Clin Chem*. 2016;62(1):208-217.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Altassan R, Péanne R, Jaeken J, et al. International clinical guidelines for the management of phosphomannomutase 2-congenital disorders of glycosylation: Diagnosis, treatment and follow up. *J Inherit Metab Dis*. 2019;42:5–28. https://doi.org/10.1002/jimd.12024