



Published in final edited form as:

J Inherit Metab Dis. 2021 January ; 44(1): 148–163. doi:10.1002/jimd.12286.

International consensus guidelines for phosphoglucomutase 1 deficiency (PGM1-CDG): Diagnosis, follow-up, and management

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AUTHOR CONTRIBUTIONS

Ruqaiyah Altassan designed the work, collected the literature in a shred folder for the teams, coordinated the clinical section team, contributed in the preparation of the adult and management chapters, drafted the clinical chapters and the relative tables in the manuscript, unified the text, and finalized the manuscript. Silvia Radenkovic contributed in literature collection, coordinated the diagnostic section team, contributed in the preparation of the management chapter, drafted the diagnostic chapter and the relative tables and figures in the manuscript, Andrew C. Edmondson contributed in the preparation of the adult and management chapters, revised and edited the manuscript. Rita Barone, Agata Fiumara, and Malgorzata Seroczynska prepared the neurological chapter including the literature review, statements grading and revision. Jaak Jaeken prepared the endocrine chapter with Paula Videira including the literature review, grading and revision and edited the manuscript. Sandra Brasil, Vanessa Ferreira, Rita Francisco, Carlota Pascoal, and Paula Videira prepared the endocrine and respiratory chapters including the literature review, statements grading and revision. Anna Cechova, Tomas Honzik, and Nicol Voermans prepared the muscular chapter including the literature review, statements grading and revision. David Coman, Jolanta Sykut-Cegielska, and Mercedes Serrano prepared the ophthalmological chapter including the literature review, statements grading and revision. Sarah Donoghue, Joy Lee, Christina Lam, and Donna Krasnewich prepared the cardiology chapter including the literature review, statements grading and revision. Kristina Falkenstein, Hudson Freeze, Dirk Lefeber, Dulce Quelhas, Kimiyo M. Raymond, Christian Thiel, and Frederic Tort prepared the diagnostic chapter including the literature review, statements grading, and revision. Carlos Ferreira prepared the congenital malformation chapter with Eva Morava including the literature review, statements grading and revision. Stephanie Grunewald prepared the hematology chapter with Paula Videira and gastroenterology chapter with Mari-Anne Vals including the literature review, statements grading and revision. Daisy Rymen and Peter Witters prepared the liver chapter including the literature review, statements grading and revision. Eva Morava supervised all the steps of the article preparation, approved the statements grading, revised and edited the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

SUPPORTING INFORMATION

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

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Abstract

Phosphoglucomutase 1 (PGM1) deficiency is a rare genetic disorder that affects glycogen metabolism, glycolysis, and protein glycosylation. Previously known as GSD XIV, it was recently reclassified as a congenital disorder of glycosylation, PGM1-CDG. PGM1-CDG usually manifests as a multisystem disease. Most patients present as infants with cleft palate, liver function abnormalities and hypoglycemia, but some patients present in adulthood with isolated muscle involvement. Some patients develop life-threatening cardiomyopathy. Unlike most other CDG, PGM1-CDG has an effective treatment option, D-galactose, which has been shown to improve many of the patients' symptoms. Therefore, early diagnosis and initiation of treatment for PGM1-CDG patients are crucial decisions. In this article, our group of international experts suggests diagnostic, follow-up, and management guidelines for PGM1-CDG. These guidelines are based on the best available evidence-based data and experts' opinions aiming to provide a practical resource

for health care providers to facilitate successful diagnosis and optimal management of PGM1-CDG patients.

Keywords

congenital disorder of glycosylation; D-galactose; management guidelines; PGM1-CDG; phosphoglucomutase 1 deficiency

1 | GENERAL BACKGROUND

PGM1-CDG (OMIM 614921), previously known as congenital disorder of glycosylation (CDG), type It (CDG-It) and glycogen storage disorder GSD XIV, is a rare autosomal recessive disorder caused by PGM1 (phosphoglucomutase 1) enzyme deficiency. This disorder was initially reported in two patients with diverse clinical presentations. In 1963, Thomson et al reported a child who presented with a cardiac conduction defect and skeletal myopathy.¹ In contrast, in 1988 Sugie et al reported PGM1 deficiency in an infant with recurrent vomiting, failure to thrive and hepatopathy.²

PGM1 deficiency is caused by biallelic pathogenic variants in *PGM1*, which encodes PGM1, the predominant isoform of the PGM family. In most cell types, it contributes approximately 90% of total PGM activity and is expressed ubiquitously in different tissues. In contrast, PGM1 is absent in red blood cells, where PGM2 is the predominant isoform.³

PGM1 catalyzes the interconversion of glucose 1-phosphate and glucose 6-phosphate,¹ and is involved in several crucial metabolic pathways, including: glycolysis, glycogenolysis, glycogenesis and N-linked glycosylation.³ This disorder was first categorized as a GSD⁵ and only later as a CDG.⁶

PGM1-CDG presents as two major phenotypes: a primary myopathic one and a multisystem one. The latter involves congenital malformations (cleft palate, bifid uvula, cardiac valve anomalies, anal atresia, and vertebral anomalies), variable endocrine and hematological abnormalities, cardiac, muscle, and hepatic involvement.⁷ The prevalence of PGM1-CDG is unknown. Fifty-seven molecularly confirmed PGM1-CDG patients have been reported from different ethnicities.

PGM1-CDG is one of the few CDG types with an effective treatment in the form of D-galactose.³ This monosaccharide can restore glycosylation in PGM1-CDG patients by replenishing the depleted pools of UDP-glucose and UDP-galactose necessary for N-glycosylation and can improve several symptoms.⁸ Early diagnosis and treatment with D-galactose is thus essential for these patients. To facilitate the diagnosis and management of PGM1-CDG, we offer detailed guidelines specifically focusing on the affected organ systems, diagnostic tools and treatment with D-galactose.

2 | METHODOLOGY

An international group of experts in CDG reviewed the evidence base and developed management guidelines. A PubMed database search was performed from the date of the first

clinical description until December 2019 using the following terms: carbohydrate-deficient glycoprotein syndrome *OR* congenital disorder of glycosylation type It *OR* PGM1-CDG *OR* phosphoglucomutase 1 deficiency. Congenital malformations, as well as neurological, ophthalmologic, cardiac, endocrine, hematological, immunological, gastrointestinal, hepatic, and musculoskeletal systems were reviewed. Next, a consensus regarding diagnosis, treatment, and management was developed in each area. For the most part, the evidence and resulting recommendations are considered experts' opinions because additional levels of evidence were not available in the literature. Evidence levels were classified in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) methodology (<http://www.sign.ac.uk>) (Table S1).

3 | RESULTS

Thirty-five articles were found through PubMed database search: 13 case reports, 9 case series, 7 diagnostic papers and 6 reviews. A review of the 57 molecularly confirmed PGM1-CDG patients, common phenotype, molecular data, and suggested surveillance are summarized in Figure 1 and Table 1

3.1 | Systems summaries and statements

3.1.1 | Congenital malformations—Of 57 patients with PGM1-CDG reported to date, cleft palate was the most commonly reported anomaly (n = 28), followed by bifid uvula (n = 25) and Pierre-Robin sequence (n = 15). The term “first branchial arch syndrome”⁹ was also used to describe the findings of a patient later reported as having Pierre-Robin sequence.¹⁰

In the largest cohort published to date, the presence of either bifid uvula, cleft palate, or Pierre-Robin sequence was identified in 23/27 patients.¹⁰ Other findings occasionally reported include prominent forehead, small face and depressed nasal bridge,¹¹ hypertelorism, short neck, retrognathia, smooth philtrum and low set ears,¹² dysmorphic ears, preauricular tissue,¹³ undescended testes,¹⁴ foreshortened esophagus,¹⁵ anal atresia, and a missing lumbar vertebra.¹⁰

Presentation (statement #1: grade of recommendation C): PGM1-CDG can present with facial dysmorphic features, including micrognathia or retrognathia, bifid uvula, cleft hard palate, or full Pierre-Robin sequence. The combined frequency of these findings is 85%.

Diagnosis and follow-up: (statement #2: grade of recommendation D): Assessment by a clinical geneticist (evaluating for dysmorphic features) should be done at the time of the diagnosis. If bifid uvula or cleft hard palate is found, evaluation by a craniofacial specialist is warranted. If Pierre-Robin sequence is present, evaluation by an otolaryngologist is warranted, as surgery may be required to ensure airway patency. Ideally, management should take place at a multidisciplinary craniofacial clinic, with access to specialists in otolaryngology, oral and maxillofacial surgery, plastic surgery, speech-language pathology, and dentistry.

Treatment: (statement# 3: grade of recommendation D): There is no disorder-specific management for congenital malformations in PGM1-CDG patients. Standard care for cleft

palate and Pierre-Robin sequence should be pursued, such as surgical repair, feeding intervention, and speech therapy.

3.1.2 | Neurological involvement—Neurological involvement is not a frequent presentation of PGM1-CDG. Normal neurodevelopment was reported in 17 PGM1-CDG patients. Motor delay was described in four patients.^{8,14,16,17} Cognitive impairments were noted in 14 patients, intellectual disability in 8, learning disabilities in 11 and speech delay in 2.^{3,10,14,16,17} IQ was reported only in one patient with a global IQ of 78 at 6 years and 66 at 10 years, suggesting cognitive regression.¹⁶ In three patients, learning difficulties were attributed as probably secondary to recurrent hypoglycemic episodes.¹⁸ Epileptic seizures have been reported in three patients with developmental delay, with an abnormal EEG detected in one patient.^{8,10,17} No perinatal injuries or other plausible causes were reported for these patients. Brain MRI was normal in five patients and a thin pituitary was reported in one patient.¹⁷ Other rare neurological phenotypes included left hemiplegia due to carotid thrombosis in one patient,¹² and sensorineural deafness in another patient.¹⁴

Presentation (statement #1: grade of recommendation C): Cognition, motor development, speech, and hearing can be affected in multisystem PGM1-CDG. Seizures can be primary or secondary to hypoglycemia.

Diagnosis and follow-up (statement# 2: grade of recommendation D): Neurological assessment should be done at the time of the diagnosis with particular attention to patients who had suffered hypoglycemia attacks. EEG and brain MRI should be considered if clinically indicated. Follow-up should include early stimulation programs for the infants and toddlers, and psychometric tests and adaptations of educational programs when needed.

Treatment (statement# 3: grade of recommendation D): No specific treatment is available for the psychomotor delay and/or learning disabilities in PGM1-CDG besides early physical and speech therapy. Although the relationship between hypoglycemia and CNS involvement is not clear, diet or treatments to prevent CNS damage secondary to hypoglycemia are suggested.

3.1.3 | Ophthalmologic involvement—Ophthalmologic involvement is only reported with the multisystemic presentation of PGM1-CDG. It has been reported in five patients. The most commonly reported ophthalmologic abnormalities were unspecified abnormal eye movements (n = 2)^{8,10} and strabismus (n = 2).¹⁰ Less common findings were nasolacrimal duct obstruction and epiphoria (n = 1).¹¹ These features may be underestimated due to scarce data available with respect to ophthalmologic examination, management, and outcome.

Presentation (statement #1: grade of recommendation C): PGM1-CDG can present with eye abnormalities, including: strabismus, abnormal eye movements, nasolacrimal duct obstruction, and/or epiphoria.

Diagnosis and follow-up (statement #2: grade of recommendation D): Ophthalmologic assessment is recommended standard of care of PGM1-CDG.

Management (statement #3: grade of recommendation D): Ophthalmologic abnormalities appear to be rare and should be treated individually, including surgery, if necessary. Standard supportive treatment (eg, glasses or orthoptic therapy) is recommended for the strabismus.

3.1.4 | Endocrine involvement—Endocrine and growth problems are common in PGM1-CDG and were reported in 39 patients. Hypoglycemia was the main endocrine presentation, reported in 38 patients. Hypoglycemia was primarily due to hyperinsulinism in young patients.^{8,10,12,17} Ketotic hypoglycemic episodes secondary to starvation and/or febrile events have also been reported^{8,18} which suggests complexity underlying the origins of hypoglycemia at different ages.¹⁹ Hypoglycemic episodes can spontaneously resolve later in life.¹⁸ Oral administration of uncooked corn starch before bedtime was successful in preventing hypoglycemia in one patient,²⁰ while the administration of hydrocortisone (12 mg/m²/day) reduced hypoglycemic events in another patient.¹⁸ Combination of D-galactose, frequent feedings, complex carbohydrate diet in treating hyperinsulinemic hypoglycemia along with and diazoxide has been suggested by experts.¹⁹ Hypogonadotropic hypogonadism was reported in three patients^{3,12}; two of them presented with delayed puberty and decreased serum follicle-stimulating hormone (FSH). In both patients, D-galactose supplementation (0.5–1.0 g/kg/day) resolved both features.³ Adrenal function deterioration was reported in three patients.¹⁸ High levels of serum thyroid-stimulating hormone (TSH) were reported in three patients and decreased levels of thyroxin-binding globulin (TBG) in six.^{10,11,16} Moreover, seven patients presented with hypocortisolism and five of them had increased adrenocorticotropic hormone levels.^{11,12,17,18} Decreased levels of growth hormone or IGF1 was reported in 12 patients^{9,1–14,17,18,21} and 9 patients showed decreased serum insulin-like growth factor-binding protein 3 (IGFBP-3)^{10,21} Growth hormone therapy has been described in only 3 patients.^{12,14,22} Furthermore, Nolting et al¹⁴ reported a patient whose growth rate did not improve upon treatment with D-galactose alone or in combination with uridine.

Presentations (statement #1: grade of recommendation C): PGM1-CDG frequently presents with endocrine and growth problems, particularly, hyperinsulinemic, and also with ketotic hypoglycemia, hypogonadotropic hypogonadism, hypocortisolism, and delayed puberty.

Diagnosis and follow-up: (statement# 2: grade of recommendation D): The growth of PGM1-CDG patients, as well as the serum levels of IGF-1, IGFBP3, TGB, TSH, free T4, ACTH, cortisol, and glucose, should be assessed at the time of diagnosis and regularly monitored.

The following investigations should be included in critical sampling of any PGM1-CDG patient presenting with hypoglycemia: plasma insulin, cortisol, growth hormone, lactic acid, ammonia, beta-hydroxybutyrate, free fatty acids and urine ketones. TIEF as a screening test should be considered in any neonate/infant with persistent hypoglycemia of undetermined cause.

Treatment: (statement#3: grade of recommendation D): There is no disorder-specific management for endocrine dysfunction in PGM1-CDG patients, although endocrine dysfunction may improve with D-galactose supplementation. Hypoglycemia can be managed with frequent feedings and complex carbohydrates.

The management of acute hypoglycemia should include intravenous bolus of 10% dextrose followed by a continuous glucose infusion at rate of 4 to 6 mg/kg/min for full-term infants, and 8 to 10 mg/kg/min for premature infants. D-Galactose should be considered in PGM1-CDG hypoglycemia management (refer to D-galactose therapy section). Continuous tube feeding should be considered in young infants to maintain the normoglycemia. The oral administration of uncooked corn starch before bedtime can be initiated over the age of 6 months. Modified cornstarch (Glycosade) can be used in children over 3 years. Oral diazoxide therapy should be considered for hyperinsulinemic hypoglycemia.

Therapy with L-thyroxine is indicated for clinical hypothyroidism treatment. Cortisol supplements are recommended to treat hypocortisolism. Growth impairment can be managed with growth hormone therapy, although not all patients respond to this treatment.

3.1.5 | Cardiac involvement—Twenty-four PGM1-CDG patients had cardiac manifestations as part of the multisystem involvement.

The main cardiac abnormality was cardiomyopathy (CM) with dilated CM being the most common type (n = 12).^{3,6,10,12,14,18,21,23} CM resulted in cardiac arrest in eight patients, and heart failure in nine patients. There is unpublished data about one patient who initially had restrictive cardiomyopathy, which evolved into combined dilated restrictive cardiomyopathy with predominant restrictive findings (personal communication, J. L.).

Electrocardiogram (ECG) abnormalities including long QT interval, ST wave elevation, T wave inversion, sinus tachycardia, and minor incomplete intraventricular conduction disturbance were observed in five patients. Other echocardiogram abnormalities include mild left ventricular enlargement (n = 3), septal defects (n = 2), and valvular heart defects (n = 2). The documented age of onset for cardiac findings was variable; onset has been observed within the first 5 years (n = 5), between 5 to 10 years (n = 2) and after 10 years (n = 6). The oldest age of onset was 49 years. There was limited information on the evolution of the cardiac manifestations with time but one patient reported to have a normal cardiac function at 19 months of age, developed cardiomyopathy on follow-up. Death secondary to cardiac complication was reported in six patients.^{3,6,12,18} Sudden cardiac death in 12 and 13-year-old siblings diagnosed with PGM1-CDG was recently reported.²¹

Presentation (statement #1: grade of recommendation C): Cardiac involvement occurs frequently in PGM1-CDG with variable age of presentation and onset. The most common cardiac feature is cardiomyopathy, specifically dilated CM. Conduction and structural heart abnormalities are less common.

Diagnosis and follow-up (statement #2: grade of recommendation D): Cardiac assessment and baseline investigations should be done at the time of diagnosis and include

creatine kinase MM (CK-MM), chest X-ray, echocardiogram and electrocardiogram (ECG). Further cardiac evaluation, that is, Holter monitor, cardiac MRI and exercise testing, should be done if clinically indicated. Annual cardiac screening is recommended, especially in childhood and adolescence. Continued cardiology screening in affected adults should be considered.

Treatment (statement #3: grade of recommendation D): There is no specific treatment for cardiac involvement in PGM1-CDG. Treatment of cardiac manifestations is based on current clinical practice and guidelines.

3.1.6 | Respiratory symptoms—Overt respiratory symptoms are rare manifestations of PGM1-CDG, reported in eight patients and all are sequelae of congenital facial malformations, underlying heart disease, or exercise intolerance.^{3,6,13,18,23,24}

Upper airway obstruction (requiring a tracheostomy and placement of a tracheal tube) occurred in the neonatal period in one patient with Pierre Robin sequence.¹⁸ Two adult PGM1-CDG patients experienced breathing difficulties during physical exercise. In one patient, physical training led to considerable improvement, whereas galactose administration was reported to ameliorate the clinical status of the other patient.^{13,23} Both patients showed mild to moderate cardiac involvement.

Presentations (statement #1: grade of recommendation C): PGM1-CDG seldom presents with overt respiratory symptoms. Breathing difficulties tend to occur when there are underlying congenital malformations (eg, Pierre Robin sequence), severe cardiac dysfunction, or during intense physical exercise. Hence, respiratory involvement seems to be secondary to other clinical features.

Diagnosis and follow-up: (statement# 2: grade of recommendation D): The following investigations should be done at the time of the diagnosis: pulse oximetry, and more extensive exams upon clinical suspicion. In the presence of congenital facial malformation, one should be wary of breathing difficulties. Surgical procedures such as tracheostomy and surgical correction of the malformations may be necessary.

Treatment: (statement# 3: grade of recommendation D): There is no specific treatment for respiratory symptoms in PGM1-CDG. Treatment of these manifestations is based on current clinical practice and guidelines. Early surgical correction of midline malformations is recommended.

3.1.7 | Gastrointestinal involvement—Hard and/or soft cleft palate (with or without bifid uvula) and/or without Pierre Robin sequence, were the most frequently presented congenital anomalies of the gastrointestinal tract (GI) (refer to congenital malformation section). Feeding difficulties were reported in only 5 patients; one patient with dysphagia did not have cleft palate.²³ One patient had an imperforate anus.¹² One obese patient had cholelithiasis.¹⁶

Presentation (statement #1: grade of recommendation D): Gastrointestinal symptoms are not characteristic of PGM1-CDG patients while bifid uvula/cleft palate are frequent in the multisystem form.

Diagnosis and follow-up (statement #2: grade of recommendation D): The diagnosis of cleft palate and Pierre Robin sequence is clinical. An ultrasound scan of the abdomen is advised to exclude other possible congenital anomalies of the GI tract. Referrals to an oral and maxillofacial surgeon, nutritionist and speech therapist are recommended for the patients with cleft palate.

Treatment (statement #3: grade of recommendation D): Treatment of the cleft palate should be guided by oral and maxillofacial surgeons based on current practice and expertise. Patients with cleft palate should be followed for feeding difficulties and possible need for feeding assistance.

3.1.8 | Liver involvement—Liver involvement has not been described in patients with the muscular form.^{5,23} On the other hand, all patients with the multisystem form presented with intermittent or chronically elevated serum transaminases.^{3,6,8,9,11–18,20,22,24–26} A positive effect of D-galactose treatment was observed, with an improvement of serum aspartate aminotransferase (AST) values and a normalization of alanine aminotransferase (ALT) values.^{8,26} Hepatomegaly was only described in three patients.^{8,11,16} Liver biopsy, performed in five patients, showed steatosis, cholestasis and/or slight fibrosis.³ Cirrhosis has not been reported. Glycogen accumulation, defined by increased PAS-positive staining, was observed in two out of five liver biopsies.³ There is insufficient data about the evolution of liver involvement in PGM1-CDG. Episodes of acute hepatic failure were described in five patients, however, without details concerning the circumstances or the extent of presentation.¹⁰ The occurrence of acute liver failure did not correlate with the overall severity of the phenotype.¹⁰

Presentation (statement #1: grade of recommendation C): Elevated serum transaminases are the most common biochemical finding of liver involvement in PGM1-CDG. In addition, steatosis, cholestasis, fibrosis, and episodes of acute hepatic failure may occur.

Diagnosis and Follow-up (statement #2: grade of recommendation D): Transaminases are the best markers to follow the disease progression and to use as treatment and compliance indicators. Screening tests for PGM1-CDG and other CDG subtypes should be considered in the instance of unexplained liver disease. Liver tests and biochemical markers of the liver's synthetic capacity should be monitored yearly. Liver ultrasound should be performed at the time of diagnosis. Noninvasive elastography can be used to monitor the development of liver fibrosis.

Treatment (statement #3: grade of recommendation D): D-Galactose treatment positively influences the transaminase levels in PGM1-CDG. Hepatotoxic medication should be avoided.

3.1.9 | Hematological/vascular involvement—Twenty-nine reported PGM1-CDG patients presented with hematological/vascular anomalies. The coagulation anomalies included both procoagulant and anticoagulant factors. The most common abnormality was antithrombin III deficiency, reported in 14 patients, while prolonged aPTT and elevated PT were found in 5 and 2 patients, respectively. Low factor XI was reported in six patients and low factor VII, IX, X, and XIII in two patients. Additionally, reduced levels of protein S and C were described in three patients.

Isolated or recurrent thrombotic events were reported in 5% of the patients. A cerebrovascular accident was the cause of death in an 8-year-old patient who had left carotid artery thrombosis after an episode of transient hemiplegia at the age of 4.^{6,12} In another patient, recurrent thrombosis developed after resuscitation from a cardiac arrest.³

Specific treatment for coagulation issues in PGM1-CDG patients was not reported. However, supplementation with D-galactose was found to improve antithrombin III levels in five patients.^{8,26}

Presentations (statement #1: grade of recommendation C): The main coagulation abnormality observed in PGM1-CDG is antithrombin III deficiency. PGM1-CDG can also be associated with factor VII, IX, X, XI, and XIII deficiency, reduced protein C and S as well as increased PT and prolonged aPTT. Since procoagulant and anticoagulant factors can be affected, patients are susceptible to thrombotic and hemorrhagic events.

Diagnosis and follow-up: (statement #2: grade of recommendation D): At diagnosis, a complete blood count and hemostasis study should be performed, including PT and aPTT, antithrombin III, factors VII, IX, X, and XIII, as well as protein C and S. Coagulation assessment should be done at least yearly, and before surgery.

Treatment: (statement #3: grade of recommendation D): There is no standard disease-specific treatment for coagulation anomalies in PGM1-CDG. Management procedures should be done according to standard protocols considering the clinical status and history of the patient. D-Galactose treatment improves antithrombin III levels in some patients.

3.1.10 | Muscular involvement—Muscular involvement is a predominant feature of PGM1-CDG and can be similar to that of other muscle glycogenosis with exercise intolerance, fatigability, muscle weakness, and attacks of rhabdomyolysis.⁵ Muscular manifestation can be the only symptom of the disease as described in four patients.^{3,5,15,24} The primary muscular form can be related to specific *PGM1* mutations.^{10,27} The degree of muscular involvement can be an important predictor of disease severity with more significant myopathy reported in severe phenotypes.^{8,10,28}

Exercise intolerance was reported in 20 patients.^{2,3,5,6,8,10,12,16,23,26,29} A second wind phenomenon, patient's better tolerance for aerobic exercise such as walking and cycling after approximately 10 minutes of rest, was explicitly reported as absent in some patients^{3,5,15} and present in the patients reported by Wong et al.¹⁰ Cramps provoked by exercise were observed in one patient.⁵

Muscle weakness was reported in 18 patients, with very limited information on the pattern of muscle weakness. Only three patients were reported to have more weakness in the pelvic girdle and/or legs than in the upper extremities.^{5,14,24} In one report, muscle weakness was proximal.²³

Hypotonia was mentioned in only three patients.^{2,12,16} Episodes of generalized hypotonia and hyporeflexia during episodes of metabolic decompensation were described in one patient.²

Myopathic gait and muscle wasting was described in only two patients who had predominant muscle symptomatology.^{1,24} Abnormal toe gait from the age of 2.5 years was the major complaint of the first patient who also had muscular wasting but no exercise intolerance or muscular pain.¹ The second one presented with life-long muscle weakness, fatigability, and slow myopathic gait. Muscle wasting was not mentioned.²⁴

Attacks of rhabdomyolysis were studied in 43 patients and occurred in 25% of patients (11/43). Patients suffered most often from moderate attacks with levels of creatine kinase (CK) from 10 000 to 50 000 IU/l.^{3,26} Severe rhabdomyolysis with renal failure was not described in any patient. The age of rhabdomyolysis was seldom mentioned; it occurred from infancy to adulthood. In one patient the first and only attack happened at 52 years of age.²³

Chronic CK elevation was present in 13 patients and in almost half of them without any history of rhabdomyolysis. The maximum CK levels in those patients were 1.5 to 13-fold the upper normal limit (ie, 300–2600 IU/L). Serum myoglobin was reported only in 4 patients^{10,16,24,26,30} with normal levels. Other laboratory markers of muscle damage were not mentioned.

Muscular involvement is part of the Tulane PGM1-CDG Rating Scale (TPCRS).¹⁰ The exact muscular subscore was mentioned in only 12 patients, but it can be partially derived from the information in the articles in 46 patients. Moderate degree of myopathy (ie, 2 TPCRS points) with generalized weakness, rhabdomyolysis, and/or exercise-related pain was stated in 11 patients. Mild involvement with localized muscle weakness, and/or exercise intolerance (ie, 1 TPCRS point) was present in 14 patients. Normal muscle tone was reported in 21 patients. None of the patients was wheelchairdependent or had respiratory compromise due to the myopathy.

Clinical neurophysiological studies (electromyography [EMG], nerve conduction studies [NCS]) were reported only in five patients. The EMG in two patients showed a myopathic pattern.^{5,24} In another patient, EMG showed the myopathic pattern only during voluntary contraction consisting of polyphasic low-voltage potentials of short duration (quadriceps, gastrocnemii).¹ Normal nerve conduction studies and EMG were stated in two patients.^{10,12}

Muscle biopsy was performed in 12 patients; 10 biopsies were abnormal, showing myopathic changes (increase of internal nuclei or fiber size variation) and/or accumulation of fat or glycogen.^{1–3,5,6,19,24} The fat accumulation, indicative for glycogen storage disease, was reported in 6 of these 10 patients. In two patients, the biopsy was normal.^{9,10}

Twenty patients were treated with oral D-galactose in variable doses (0.5–2.5 g/kg/day). The duration varied between 4.5 and 16.5 months. Six patients reported a positive effect on exercise intolerance and fatigability, and in one the effect was not clear. The number of rhabdomyolysis episodes did not decrease in any of the questioned 14 patients. CK elevation decreased after initiation of D-galactose.^{8,10}

Presentation (statement #1: grade of recommendation C): Muscular involvement is one of the predominant features of PGM1-CDG. The main skeletal muscle manifestations are exercise intolerance, fatigability, muscle weakness and attack(s) of rhabdomyolysis. The disease can progress to significant generalized myopathy in about half of the patients with skeletal muscle involvement.

Diagnosis and follow-up (statement# 2: grade of recommendation D): Initial and annual neurological evaluation measurement is recommended. According to the disease progression, neurophysiological studies should be performed. Muscle biopsy investigation is not required to diagnose PGM1-CDG and the invasiveness of this procedure limits its indication to research purposes. Because of the risk of marked myoglobinuria, serum creatine kinase and myoglobin level determination are warranted during any acute intercurrent infections and each time when the patient complains about sudden episodes of myoglobinuria, muscle pain, swelling and /or weakness.

Treatment: (statement#3: grade of recommendation D): Dietary D-galactose supplementation should be considered in all patients since a positive effect on exercise intolerance, fatigability and reduction of creatine kinase elevation has been observed. In case of rhabdomyolysis, treatment should be focused at prevention of kidney failure and electrolytes abnormalities.

3.1.11 | Malignant hyperthermia susceptibility—There is limited information in the literature about surgeries and anesthetic agents used in PGM1-CDG patients. The most common reported surgery is cleft palate repair. Malignant hyperthermia was reported in only 2 patients of 22 operated PGM1-CDG patients (one of whom had a history of exercise intolerance), and rhabdomyolysis was reported in both patients.^{3,30} Detailed anesthetic information, including anesthetic agents used for surgery, was only reported in one patient.³⁰ Halothane was the anesthetic agent used for cleft palate repair and it was associated with malignant hyperthermia. The diagnosis was based on the clinical grading scale previously reported by Larach et al.³¹ Propofol and remifentanyl were reported to cause minor rise in CK in the same patient.³⁰ Pseudocholinesterase activity, when measured, was reported to be low and this was associated with risk of prolonged recovery from anesthetic agents in children.^{3,31}

Presentation (statement #1: grade of recommendation D): Malignant hyperthermia was reported in PGM1-CDG in association with the use of halothane.

Diagnosis and follow-up (statement #2: grade of recommendation D): Malignant hyperthermia may be a risk, particularly in PGM1-CDG patients with skeletal myopathy and rhabdomyolysis. Pre-anesthetic evaluation is strongly recommended for PGM1-CDG

patients undergoing surgery. Pseudocholinesterase activity can be measured in patients with PGM1-CDG.

Treatment (statement #2: grade of recommendations D): Caution should be exercised with the use of anesthetic agents, particularly depolarizing muscle relaxants and volatile anesthetic agents in patients with PGM1-CDG.

3.1.12 | Adult presentation—There are 15 adult PGM1-CDG patients described in the medical literature, including one patient who was initially described as a 13 year-old and subsequently as a 32-year old adult.^{9,22} PGM1-CDG patients can live into adulthood but frequently present to medical care in infancy with classic multisystem presentations of PGM1-CDG, including congenital anomalies, hypoglycemia, hepatopathy, and cardiomyopathy. Some adult patients had mild presentations that delayed diagnosis, including recurrent exercise-induced myopathy with and without rhabdomyolysis, muscular fatigue, and short stature. Severe symptoms can persist into adulthood, including hypoglycemia, cardiomyopathy, and hepatopathy.

Presentation (statement #1: grade of recommendation D): Adult PGM1-CDG patients may first present in adulthood with recurrent myopathy or rhabdomyolysis.

Diagnosis and follow up (statement #2: grade of recommendation D): Adult patients presenting with recurrent myopathy or rhabdomyolysis should be evaluated for PGM1-CDG. Adult PGM1-CDG patients should continue to have ongoing health screening at least annually.

Treatment: (statement #3: grade of recommendation D): Treatment of adult presentation is based on the standard of care of adults.

3.2 | Diagnostic tools

3.2.1 | Biochemical diagnosis

Transferrin and N-glycan analysis: Serum transferrin (Tf) analysis by isoelectric focusing (TIEF), capillary electrophoresis (CE), high-performance liquid chromatography (HPLC), or by liquid chromatography coupled with mass spectrometry (LC/MS) has been used in diagnostic testing of different CDG subtypes (Table S2).

All the above-mentioned methods are based on monitoring glycosylation changes of serum Tf. This protein is abundant in serum and has two N-linked glycans attached to the Tf protein. The most abundant Tf species in healthy controls is Tf with two complete glycans and corresponds with tetrasialotransferrin as the major band when using IEF. CDG-I profiles are characterized by transferrin missing one or both oligosaccharide chains (on IEF corresponding to asialotransferrin and disialotransferrin). CDG-II profiles are characterized by transferrin with truncated oligosaccharide chains (on IEF corresponding with elevation of one or more bands of asialoto trisialotransferrin).

The majority of reported PGM1-CDG patients exhibited a mixed type 1/2 pattern by TIEF analysis, the most commonly used screening technique for the currently known PGM1-CDG

patients. By HPLC and CE analysis, mostly a dominant type 1 pattern is observed, while critical inspection shows additional intermediate peaks that likely represent the truncated transferrin glycoforms. The type-1/2 pattern is a phenomenon so far seen only in PGM1-CDG and during acute illness episodes in patients with ARCN1 mutation.³²

This profile suggests that this disorder affects both ER (CDG-I) and Golgi apparatus (GA) (CDG-II)-associated glycosylation. This has partially been explained by the depletion of UDP-glucose and UDP-galactose in PGM1-CDG patients. These sugar nucleotides are essential glycan building blocks for glycosylation processes involved in ER (type 1) and GA (type 2), respectively.⁸

The most commonly used method in the diagnosis of CDG is TIEF; it has been performed in more than 81% of the reported PGM1-CDG patients.^{3,6,9,10–16,18,20,26,33} TIEF is a fast and easily applicable laboratory technique in clinical settings, as well as application of HPLC and CE. However, these methods lack the possible detection of specific glycan structures, which is especially helpful for CDG-II defects and in particular for PGM1-CDG.

Increased sensitivity and specificity is offered by different mass-spectrometry (MS) techniques. Methods for N-glycan analysis in CDG include MALDI-TOF,^{14,34} ESIMS³⁵ and ESI-QTOF.³⁶ In particular, high-resolution mass spectrometry techniques are capable of diagnosing PGM1-CDG,³ based on the combined identification of glycan loss and loss of galactose. The LC/MS pattern of PGM1-CDG is unique and characteristic for the vast majority of confirmed patients. The pathognomonic pattern consists of transferrin missing one entire glycan while the remaining glycans are truncated at the galactose level.³ In few cases, mainly the adult myopathy phenotype, an isolated and mild type 1 profile is observed, similar to that in the animal model (ref 55).³

For CDG in general, glycosylation of transferrin can fluctuate, which is particularly common in the first months of life, most commonly found in PMM2-CDG. Moreover, spontaneous improvement of overall glycosylation, as has been described in adult CDG patients such as PMM2-CDG,³⁷ has never been observed in PGM1-CDG. In addition, the changes in transferrin glycosylation are not limited to CDG and can be seen in other conditions, such as liver dysfunction, endocrine anomalies and infections.^{38–42}

The analysis of other glycosylated proteins, such as apoC-III, is commonly used during CDG diagnosis as a complementary analysis to transferrin analysis.^{43–45} Most PGM1-CDG patients have a normal apoC-III profile^{3,26,33} with only a few exceptions.⁴⁵

Statement #1 (grade of recommendation: B): PGM1-CDG patients exhibit a diagnostic, pathognomonic glycosylation pattern of serum transferrin with partially missing glycans and truncated glycans lacking galactose. This can best be detected via mass spectrometry based methods, while other CDG screening methods (HPLC, CE, IEF) show mixed profiles, ranging from type 1 to type 2 and mostly exhibit mixed type 1 and type 2 profiles.

Therapy monitoring using Tf and N-glycan analysis: MS methods offer the possibility to monitor the patients' response to treatment.^{23,26,33} It is important to note that analysis of intact transferrin should be used.⁴⁶ Mass spectrometry analysis of total plasma N-

glycoproteins by HPLC-CHIP-QTOF LC-MS³³ has also been reported and can provide additional information on the glycan structures in blood of PGM1-CDG patients. However, total plasma N-glycan profiling cannot determine the absence of entire glycans (unoccupied N-glycosylation sites), which is essential for PGM1-CDG. Via analysis of transferrin glycosylation by mass spectrometry, the effect of galactose treatment can be distinguished on the loss of glycans and the presence of truncated glycans separately (Ref 55). Abu Bakar et al³³ specifically defined three glycan indexes which can be extracted from transferrin QTOF spectra and can be used to monitor the treatment response of PGM1-CDG. It was noted that the response of the galactose loss was faster than the loss of glycans. Also, it was noted that some patients showed a better response than others.

Statement #1 (grade of recommendation: C): LC-MS platforms are the recommended methodology for monitoring therapy effectiveness in PGM1-CDG patients.

Enzymatic studies: Most PGM1-CDG patients have severely diminished PGM1 enzymatic activity. Fibroblasts and leukocytes (red blood cells should not be used as PGM1 is absent) are commonly used for enzymatic studies. PGM1 activity can also be measured in muscle tissue.³

The enzymatic activity of PGM1 in reported patients ranges from undetectable to 20% of controls.^{3,5,6,8-10,12,14-16,20,23,25,26,28,47} Unusually, PGM1 activity does not correlate with the severity of the patient's phenotype and the differences in activities of other PGM isoforms have been proposed as one of the possible explanations.^{3,10} It is important to note that, although enzymatic studies are informative, they are not substantial for assessing the severity of the patient's phenotype and predicting the outcome.

Statement#1 (grade of recommendation: C): PGM1 enzymatic assays are frequently used in PGM1-CDG as complementary analysis and most of the patients present with <20% enzymatic activity. Patient fibroblasts or leukocytes can be used for enzymatic studies. However, the final diagnosis is based on molecular testing.

Other biochemical analyses: Galactose-related metabolites (blood galactose-1-phosphate levels) can be measured in order to screen for PGM1 deficiency³ and to monitor the safety of D-galactose therapy (galactitol).²⁶ Interestingly, red blood cell galactose-1-phosphate is paradoxically elevated in untreated PGM1-CDG patients in a mild to moderate degree.³ Therefore, galactosemia screening based on galactose-1-phosphate levels in newborn screening (NBS) can show false positive results in PGM1-CDG patients. This marker could be used in early disease screening and potentially NBS. Patients who are started on galactose therapy should be monitored, as high levels of galactose-1-phosphate could be toxic. The maximum daily Dgalactose limit which is considered to be safe is 50 g⁴⁸ and increased galactitol excretion has only been reported in patients receiving more than 50 g/day.²⁶

In order to understand the pathomechanisms of the disease, an extended analysis of galactose metabolism has been reported.⁸ This approach used a variety of (tracer) MS techniques such as GC-MS and LC-MS, to elucidate the role of galactose in the treatment of

PGM1-CDG. These labor-intensive and costly techniques are highly informative but not used in clinical practice.

Statement#1 (grade of recommendation: C): Galactose-1-phosphate is mildly increased in untreated patients with PGM1-CDG. In order to monitor the safety of Dgalactose therapy, galactose related metabolites (plasma galactose-1-phosphate and galactitol in urine) can be tested.

Sensitivity of biochemical testing: Though the majority of PGM1-CDG patients present with a mixed TIEF pattern, some patients can present with a type 1 or a type 2 pattern.^{9,11,12,14} Therefore, PGM1-CDG should not be excluded solely on the basis of the TIEF results. As described above, more specific MS based methods can be applied for subsequent diagnostics, combined with enzymatic assays and genetic testing.

Statement #1 (grade of recommendation: D): Though the majority of PGM1-CDG patients present with a mixed TIEF pattern, some patients present with a type 1 or a type 2 pattern in which case it is recommended to use MS methods to make a correct diagnosis, followed by genetic testing.

Pre-analytical requirements for biochemical testing: Detailed statements on transferrin analysis sensitivity and the pre-analytical requirements for the biochemical testing are given in the PMM2-CDG clinical guidelines.⁴⁹

False positives: Aberrant glycosylation patterns can also be detected in individuals affected by other genetic disorders with secondary glycosylation defects such as untreated galactosemia⁴⁰ or hereditary fructose intolerance.⁵⁰ Moreover, various conditions affecting the liver (eg, infections, immune disorders) can similarly affect glycosylation, leading to mainly Golgi-related glycan abnormalities (glycan truncation).

Statement #1 (grade of recommendation: C): The presence of other clinical conditions should also be excluded in case of abnormal CDG screening results. However, MS based methods are directly indicative of a PGM1-CDG diagnosis.

3.3 | Molecular diagnosis

3.3.1 | Genetic testing—PGM1-CDG can further be confirmed by standard genetic tests such as Sanger sequencing, whole-exome sequencing (WES) or homozygosity mapping. PGM1-CDG is located on chromosome 1p31.3 and contains 11 exons. So far, 41 different variants in PGM1 have been reported spanning across the whole *PGM1* gene. The most common variant is c.112A>T; p. Asn38Tyr (n = 9) located in the first exon, followed by c.988G>C; p.Gly330Arg (n = 5). The majority of variants are missense (24) or frameshift/nonsense variants (11), with only a few splicing (4) and gross rearrangement type of variants reported (1). The frequency of compound heterozygotes and homozygotes is approximately similar in PGM1-CDG while deletions (n = 2) and inversions (n = 1) are very rare (Table S3).

Statement #1 (grade of recommendation: B): Genetic testing is the standard method to confirm PGM1-CDG diagnosis.

3.3.2 | Genotype-phenotype correlations—As mentioned earlier, PGM1-CDG phenotypes do not correlate with PGM1 enzymatic activities. Furthermore, several *PGM1* variants do not correlate with phenotype severity, clinical outcome or response to D-galactose therapy.

One possible explanation is the existence of different PGM isoforms. For example, PGM2, which is the predominant PGM isoform in red blood cells, may be more active in some patients and therefore able to take over the role of PGM1 to some extent.³ However, PGM1 remains the most important PGM isoform responsible for the interconversion of glucose-6-P into glucose-1-P and the discrepancy in the activities of different isoforms can provide only a partial explanation. Therefore, further studies are needed to understand the lack of the correlation between the genotype and phenotype in PGM1-CDG.

Statement #1 (grade of recommendation: C): No genotype/phenotype correlation has been seen in PGM1-CDG. A partial explanation can come from the existence of different PGM isoforms, but more insight is needed in order to understand these discrepancies.

3.4 | Common laboratory findings

Standard laboratory testing in PGM1-CDG usually reveals low or fluctuating glucose levels as well as elevated serum transaminases. Decreased coagulation factors including antithrombin-III, factor IX, factor XI, and prolonged PT and aPTT are also common. In addition, the majority of PGM1-CDG patients, especially those with exercise intolerance, present with high creatine kinase (CK) levels. Other laboratory findings include altered plasma concentrations of cortisol, ACTH, GH, IGF1, IGFBP3, gonadotropins (LH, FSH) and thyroid hormones.^{3,5,8,9,11,14–18,20,22–24}

Monitoring mentioned laboratory findings is helpful during D-galactose therapy. Coagulation parameters and liver enzymes usually normalize during the first year of the treatment. Similarly, CK levels improve on long term D-galactose therapy while glucose levels tend to fluctuate without additional nutritional intervention, frequent complex carbohydrate treatment or diazoxide therapy.^{8,26} In addition, the overall glycosylation of secretory glycoproteins improves on D-galactose therapy and is easily monitored as well.³³ The improvement of the patients' laboratory findings correlates with their outcome and is highly informative for therapy compliance as well.^{8,26}

Statement #1 (grade of recommendation: B): Low blood sugar levels, elevated transaminases, and decreased antithrombin activity are the most consistently altered biochemical markers in patients with PGM1-CDG. Similarly, changes in other laboratory parameters such as aPTT, factor VIII, factor XI, CK, LH, FSH are frequent. Hence, their levels should be closely monitored, especially during D-galactose therapy. Liver enzymes, thyroid hormones, and coagulation factors normalize on long term D-galactose therapy and

are easily monitored, while blood sugar levels might fluctuate regardless of D-galactose therapy.

3.5 | Prenatal testing, screening and genetic counseling

Although the detection of PGM1 deficiency is possible from dried blood spots using a modified Beutler test,³ currently there is no newborn screening available for PGM1-CDG. Prenatal genetic testing can be done if the parents are known carriers of PGM1-CDG or if there is a family history of PGM1-CDG. TIEF of fetal plasma results are not conclusive and therefore not recommended.⁵¹ Genetic counseling is an important part of PGM1-CDG diagnosis and should be offered to any parents with a child suspected or diagnosed with PGM1-CDG.

Statement #1 (grade of recommendation: B): Molecular analysis of *PGM1* is the gold standard of the diagnosis at any age in any individual with suspected PGM1 deficiency. However, after birth, additional biochemical studies might be needed in case of detection of novel genetic variants.

3.5.1 | D-Galactose therapy—D-Galactose therapy in PGM1-CDG is able to restore glycosylation by replenishing nucleotide sugar pools UDP-glucose and UDP-galactose necessary for ER-linked glycosylation and Golgi-linked glycosylation, respectively.⁸ Regarding clinical treatment, D-galactose supplementation was trialed in more than 20 PGM1-CDG patients who showed marked improvement in most symptoms, including exercise intolerance, fatigability, hypogonadism, delayed puberty, rhabdomyolysis and the frequency of hypoglycemia.^{3,8,13,14,26,52} Long-term follow-up of PGM1-CDG patients receiving D-galactose showed an improvement in laboratory parameters, including transaminase levels, normalization of antithrombin III and FSH levels and reduction in CK levels.^{3,8,13,19,23,26,52} In addition to D-galactose therapy, enrichment of the diet with complex carbohydrates is essential to maintain normal blood glucose levels in most PGM1-CDG patients.⁵³

N-glycosylation changes were monitored by different methods in multiple patients^{3,13,14,23,26,32,36} during galactose therapy and showed sustained improvement in all except one.¹⁴

D-Galactose dose in trials ranged between 0.5 and 3 g/kg/day (maximum dose 50 g /day) and showed no adverse effects in most patients.^{3,8,13,14,26} One patient did not tolerate higher doses of D-galactose and was ultimately prescribed a maximum dose of 0.3 g/kg/day.¹² It is important to note, however, that although D-galactose is able to alleviate multiple symptoms and improve patient outcome, it is not a perfect treatment. Patients are required to consume high amounts of this sugar as well as other complex carbohydrates, and a consult with a dietician is recommended.

Characteristic (statement #1: grade of recommendation: D): Oral D-galactose supplementation is a recommended treatment for PGM1-CDG patients presenting with hypoglycemia, rhabdomyolysis, coagulopathy, and or hepatopathy.

Method of administration (statement #2: grade of recommendation: D): The recommended galactose dose starts at 0.5 to 1 g/kg and could be increased gradually up to 3 g/kg/dose in infants, in a single dose or orally divided in 4 doses daily. The maximum tolerated dose is 50 g/ day.

Monitoring of treatment (statement #3: grade of recommendation: D): Monitoring of transaminases (ALT, AST), anticoagulation factors (ATIII) as well as CK levels is recommended especially at the start of treatment. In addition, N-glycosylation should be monitored for treatment efficacy. Methods such as intact transferrin analysis, or more potent LC/MS methods can be used.

Undesirable effects (statement #4: grade of recommendation: D): Higher doses of galactose treatment might not be tolerated in all patients and therefore should be carefully monitored. Doses higher than 50 g/day should be avoided as galactose can result in the increase of galactose-1-phosphate and galactitol which could be toxic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

P. W. is supported by the Clinical Research Fund, University Hospitals Leuven, Leuven, Belgium. This work is partially funded by the grant titled Frontiers in Congenital Disorders of Glycosylation (1U54NS115198-01) from the National Institute of Neurological Diseases and Stroke (NINDS), the National Center for Advancing Translational Sciences (NCATS), and the Rare Disorders Consortium Research Network (RDCRN) (E. M., K. R., C. F., H. F., C. L., and A. E.)

Funding information

National Institutes of Health, Grant/Award Number: 1U54NS115198-01; Universitaire Ziekenhuizen Leuven, KU Leuven; Rare Disorders Consortium Research Network; National Center for Advancing Translational Sciences

Abbreviations:

ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDG	congenital disorders of glycosylation
CE	capillary electrophoresis
CK	creatine kinase
CM	cardiomyopathy
CNS	central nervous system
EEG	electroencephalogram
EMG	electromyography

ER	endoplasmic reticulum
FSH	follicle-stimulating hormone
GA	golgi apparatus
GSD	glycogen storage disorder
HPLC	high-performance liquid chromatography
IGFBP-3	insulin-like growth factor-binding protein 3
LC/MS	liquid chromatography/mass spectrometry
MRI	magnetic resonance imaging
NCS	nerve conduction studies
PGM1-CDG	phosphoglucomutase 1 deficiency
SIGN	Scottish Intercollegiate Guidelines Network
TBG	thyroxin-binding globulin
Tf	serum transferrin
TIEF	transferrin isoelectric focusing
TPCRS	Tulane PGM1-CDG Rating Scale

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SYNOPSIS

These international consensus guidelines provide a practical, evidence-based resource for health care providers to facilitate successful diagnosis and optimal management of PGM1-CDG patients.

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Most common clinical and laboratory findings in PGM1-CDG

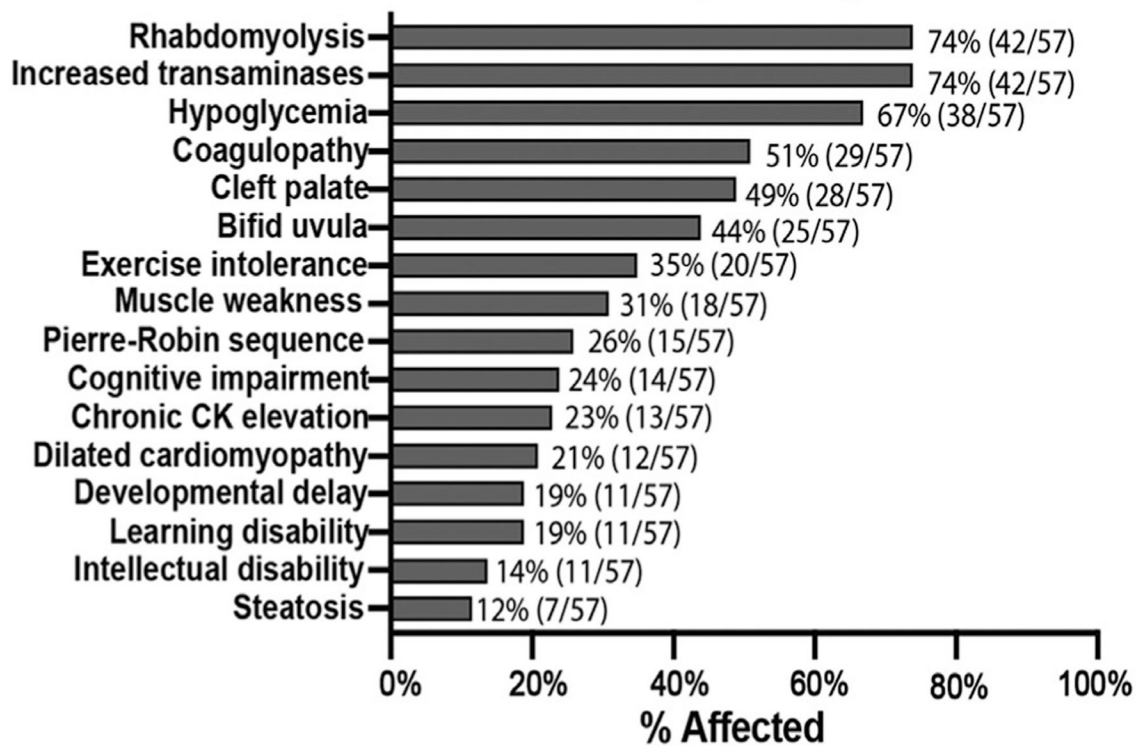


FIGURE 1.
Most common laboratory findings in PGM1-CDG

TABLE 1

Clinical presentation in patients with PGM1 deficiency and suggested surveillance

Phenotype	Suggested surveillance frequency
Congenital malformations	Complete physical examination at the time of diagnosis and referral to necessary services
Neurological	Complete physical examination at the time of diagnosis and yearly developmental assessment, especially in patients who had suffered hypoglycemia attacks. EEG and brain MRI if clinically indicated
Ophthalmological	Eye exam at the time of diagnosis and monitoring if clinically indicated
Endocrine	Strabismus, abnormal eye movements, nasolacrimal duct obstruction, and/or epiphoria Hypothyroidism, hypogonadotropic hypogonadism, delayed puberty, hyperinsulinemia
Cardiac	Assessment of growth at the time of diagnosis and on follow-up. Serum levels of IGF-1, IGFBP3, TIGB, and TSH at the time of diagnosis and regularly monitored. Serum cortisol and ACTH levels at the time of diagnosis; further on if clinically indicated
Muscle	Electrocardiography (ECG) and echocardiography at the time of diagnosis and monitored if clinically indicated. Annual cardiac screening in childhood and adolescence. CK at the time of diagnosis, then if clinically indicated (during acute illnesses); neurophysiological study if clinically indicated
Liver	Transaminases and hepatic function at time of diagnosis and monitored regularly
Hematological	Coagulation profiles at the time of diagnosis and monitored regularly
Metabolic	Glucose level at the time of diagnosis and during illnesses with urine ketones and insulin levels
Other	Caution is advised with anesthesia prior to surgeries