

PGM1-CDG

PGM1-CDG predominantly presents with congenital malformations (including cleft palate and bifid uvula) and muscular-skeletal involvement, associated with heart disease, exercise intolerance and hypoglycemia. It is a complex disease, which affects multiple cellular pathways.



What is PGM1-CDG?

The first reported patient presented only muscular-related signs, and the disorder was called glycogenosis type XIV¹. However, further clinical observation and tests revealed that the patient also suffered from hepatic anomalies and an abnormal transferrin pattern, thus associating this clinical phenotype with CDG². PGM1 (MIM:171900) codes for phosphoglucomutase 1, an enzyme involved in the transfer of phosphate between the 1 and 6 positions of glucose.

What are CDG?

Congenital Disorders of Glycosylation (CDG) are a rapidly growing group of monogenic metabolic diseases, which counts over 130 different types.

When to suspect PGM1-CDG?

PGM1-CDG should be considered in the presence of a cleft palate or bifid uvula in combination with cardiomyopathy, muscle weakness, short stature, endocrine deficiencies, (mostly mild) coagulation anomalies, liver disease and/or recurrent hypoglycaemia. Rhabdomyolysis related to exercise and behaviour issues are also common features which should prompt screening for this CDG type. Antenatally, femur and radius length has been reported to be below average.

Causes

As the wide majority of CDG, PGM1-CDG is an autosomal recessive disorder.

Diagnosis

Biochemically PGM1-CDG is a complex disease, as PGM1 mutations affect both the glycosylation and gluconeogenesis processes. The diagnosis of this condition can be made by the serum transferrin isoelectric focusing assay (which usually shows a mixed type 1/2 pattern) and sugar-metabolite measurement (exhibiting decreased levels of UDP-galactose). The diagnosis is confirmed through molecular testing. Contact us if you wish to connect with a CDG diagnosis laboratory: sindromecdg@gmail.com.

Major signs and symptoms

Muscular & Skeletal

Cleft Palate | Bifid Uvula | Pierre-Robin Sequence | Short Stature | Myopathy | Lordosis | Kyphoscoliosis | Anal Atresia | Rhabdomyolysis | Exercise-Intolerance

Cardiac

Dilated Cardiomyopathy

Neurologic

Microcephaly | Learning Disability

Endocrine

Growth Hormone Deficiency | Hypothyroidism | Adrenocorticotropic Hormone (ACTH) | Deficiency | Decreased Levels of Insulin-Like Growth Factor 1 (IGF-1) | Cortisol Deficiency | Hypogonadotropic Hypogonadism

Hepatic

Increased Serum Transaminases | Hepatopathy | Coagulopathy

Behavioural

Distractibility | Hyperactivity | Inattentiveness

Other Symptoms / Signs

Recurrent Infections (Mainly Otitis Media) | Ketotic Hypoglycemia (Recurrent Episodes) | Episodes of Ravenous Appetite

Prevalence

A total of 35 patients have been diagnosed worldwide (for 14 patients the nationality is not available). (7 Israeli | 1 Czech | 1 Spanish | 1 Colombian | 1 Portuguese).

Clinical Management

Exciting developments regarding PGM1-CDG management and treatment have been taking place, with the most relevant being galactose supplementation. Dietary supplementation of this sugar has shown potential benefit in clinical trials (improved liver function, coagulation, hypogonadotropic hypogonadism, and partial correction of the transferrin glycosylation pattern)³. However, be aware that the underlying mechanism leading to dilated cardiomyopathy may not be (entirely) related to glycosylation defects, thus galactose supplementation may not have any effect on cardiac disease. However, heart medication, such as captopril, metildigoxin, enalapril, and metoprolol has been administered to patients with some positive effect and cardiac transplantation in PGM1-CDG patients has been performed⁴. Also, controlled, regular aerobic training has been found to have a protective effect on the dilated cardiomyopathy, preventing acute damage and improving fitness⁵. Additionally, families have reported that the daily intake of both galactose and starch is a better management strategy for hypoglycemia.

Hypoglycemia has been treated by frequent meals, complex carbohydrates, hydrocortisone or overnight tube feeding² and galactose supplementation has also been described to ameliorate hypoglycaemia episodes. L-thyroxin substitution is administered to normalize thyroid function⁶. A lactose-rich diet has resulted in clinical improvements in some patients⁶.

PGM1-CDG patients may also benefit from physical, occupational and speech therapy.

Prognosis

At birth, phenotypic presentation maybe limited to cleft palate/bifid uvula. However, later on additional clinical signs emerge².

Dilated cardiomyopathy in these patients is usually progressive, and may not respond to galactose supplementation or other therapeutic approaches, requiring heart transplantation. In fact, dilated cardiomyopathy has been identified as a primary or secondary cause of death in PGM1-CDG patients, who suffered premature deaths. In contrast, heart disease has been reported to improve and even resolve with age².

Although hypoglycemia frequently requires continuous treatment in these patients, it is most significant in childhood with hypoglycaemic episodes having been reported to resolve spontaneously with age. Surgical correction of cleft palate has been successfully performed, but, ATTENTION, malignant hyperthermia with severe rhabdomyolysis occurred in two patients after the administration of general anaesthesia².

A validated scale and scoring system has been developed for PGM1-CDG – the Tulane PGM1-CDG Rating Scale (TPCRS), which has associated the presence/absence of certain clinical manifestations with disease severity, namely: congenital malformation, cardiac involvement, endocrine deficiency, myopathy, and growth. Patients were divided into 3 groups according to disease severity: 1) Severe – when patients manifested with congenital defects and dilated cardiomyopathy; 2) Moderate – when patients exhibited congenital anomalies without heart defects; 3) Mild – when patients presented neither congenital abnormalities nor heart involvement. This scale may have a predictive value, thus helping improve disease management, preventing future complications, and assessing therapy effectiveness⁷.



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References

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