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Central nervous involvement is common in PGM1-CDG

Silvia Radenkovic^{1,2,3}, Peter Witters^{4,5}, Eva Morava^{4,6}

1. Metabolomics Expertise Center, Center for Cancer Biology, CCB-VIB, Leuven, Belgium
2. Laboratory of Hepatology, Department of Chronic Diseases, Metabolism and Ageing, KU Leuven, Leuven, Belgium
3. Department of Oncology, KU Leuven, Leuven, Belgium
4. Metabolic Center, Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium
5. Department of Development and Regeneration, KU Leuven, Leuven, Belgium.
6. Center of Individualized Medicine, Department of Clinical Genomics, Mayo Clinic, Rochester, US

Corresponding author: Eva Morava, Center of Individualized Medicine, Department of Clinical Genomics, Mayo Clinic, Rochester, US, Morava-Kozicz.eva@mayo.edu

Abstract

PGM1, the enzyme responsible for the reversible inter-conversion of glucose-1-P and glucose-6-P, is also involved in glycosylation, leading to a wide range of clinical manifestations, such as congenital malformations, hypoglycemia, hormonal dysregulation, myopathy, hepatopathy, and cardiomyopathy. So far, PGM1 deficiency has not been associated with central nervous system involvement or intellectual disability. Seizures and neurologic involvement in PGM1-CDG were thought to be a consequence of hypoglycemia.

We reviewed all reported PGM1 deficient patients for the presence of the central nervous system involvement, their treatment and disease history.

We detected 17 patients out of the 41 reported PGM1-CDG cases with significant neurologic involvement. Several of these patients had no severe hypoglycemic episodes, or were adequately treated for hypoglycemia with no recurrent episodes of low blood sugars, while one patient had no reported hypoglycemic episodes.

We suggest that neurological symptoms are frequent in PGM1-CDG and could present even in the absence of hypoglycemia. The central nervous system should be assessed early on during the diagnostic process to optimize outcome in patients with PGM1-CDG.

Key words: phosphoglucomutase 1, glycosylation, CDG, seizures, hypoglycemia, developmental delay, intellectual disability, central nervous system

Abbreviations:

ACTH: Adrenocorticotrophic hormone

ALG: Asparagine-linked glycosylation homolog

ALT: Alanine transaminase

CDG: Congenital disorders of glycosylation

CNS: Central nervous system

PGM: Phosphoglucomutase

PMM: Phosphomannomutase

Introduction

Congenital disorders of glycosylation (CDG) are a clinically highly variable group of genetic diseases affecting glycosylation. This complex process of glycan synthesis, processing and transfer to the protein happens across all cell types (Jaeken and Péanne, 2017). Treatment of CDGs is complicated and these disorders are managed mainly by nutritional therapies, while only a few of them are effective, such as the treatment of MPI-CDG with oral mannose supplementation (Witters *et al*, 2017). PGM1-CDG, which has recently earned more attention, is another rare example of CDG which is successfully treated by oral D-galactose supplementation (Tegtmeyer *et al*, 2014). PGM1-CDG is caused by the mutations of *PGM1*, coding for the phosphoglucomutase 1 enzyme (Stojkovic *et al*, 2009). PGM1 is the key player in the reversible inter-conversion of glucose-1-P and glucose-6-P (Quick *et al*, 1973). It lies at the crossroads of multiple biochemical pathways such as glycolysis, glycogenolysis, glycogenesis. In addition, PGM1 is involved in glycosylation by providing necessary building blocks for glycosylation reactions, adding another layer of complexity to the disease (Timal *et al*, 2012). This complexity is further reflected in the wide range of clinical manifestations such as congenital malformations (micrognathia, Pierre-Robin sequence, cleft palate or bifid uvula), hypoglycemia, hormonal dysregulation (hypogonadotropic hypogonadism, delayed puberty, short stature), myopathies (weakness, rhabdomyolysis, elevated creatine kinase), hepatopathy and dilated cardiomyopathy (Tegtmeyer *et al*, 2014). So far, most patients have not been reported to present with central nervous system (CNS) involvement or intellectual disability, which has been explained by the compensation of PGM1 enzyme deficiency by the presence of PGM2 and PMM (phosphomannomutase) enzymes in the brain (Tegtmeyer *et al*, 2014). The CNS involvement (seizures and consecutive developmental delay, or intellectual disability) recently reported in a smaller cohort of PGM1-CDG patients, were thought to be a potential consequence of hypoglycemia, without clear supporting evidence (Ondruskova *et al*, 2014; Lowenthal *et al*,

2015; Wong *et al*, 2016; Zeevaert *et al*, 2016; Nolting *et al*, 2017, Ding *et al*, 2018). In our review, we provide a literature overview of all reported PGM1 cases presenting with CNS symptoms, their endocrine features and therapy.

Patients and Methods

Review of literature was performed by identifying PGM1-CDG related articles with reports on patients with neurologic involvement with or without hypoglycaemia. Search databases of Google Scholar, PubMed, Web of Science, Scopus, Science Direct were used.

Following keywords were used: glycogen storage disorder (6662), congenital disorder of glycosylation (1244), phosphoglucomutase 1 (1684), PGM1 (724), PGM1 deficiency (24), PGM1-CDG (14), and comprehensive overview of articles led to the identification of a total of 41 reported PGM1-CDG patients [as of August 2018].

We reviewed the clinical features, disease history, and treatment in 41 patients previously described with PGM1 deficiency. In the patients who had central nervous system involvement, we collected data on the presence of congenital malformations, history of hypoglycemia, the origin of hypoglycemia, and their treatment. We also evaluated their CNS manifestations.

Results

We found 17 cases from the total of 41 reported patients with significant neurologic manifestations (Table 1). All but one of 17 patients with CNS involvement had congenital malformations. All but two had a history of hypoglycemia. Two other patients had spontaneously resolving mild transient hypoglycemia. Not all patients needed dietary intervention, three patients were on cortisol supplementation and none of the patients were on Diazoxide therapy. All patients who were later started on lactose or galactose supplements were already free of hypoglycemic episodes before the onset of treatment.

Ondruskova *et al*, 2014 reported a first PGM1-CDG patient with CNS involvement suffering from learning disability, mild neurological impairment, deteriorating IQ and significant motor skills delay, which was thought to be the consequence of fasting related hypoglycemia. The patient's hypoglycemia resolved by dietary intervention, while neurologic symptoms persisted. In addition, hepatopathy, hyperlipidemia, coagulopathy and CK levels were present even after lactose treatment. Lowenthal *et al*, 2015 reported 7 PGM1-CDG patients from a Bedouin consanguineous family. Six out of 7 patients suffered from hypoglycemia and three of them presented with learning disabilities. The learning disability in three patients was not formally assessed due to the patients' age (2 ½ years, 5, 6 years respectively), but no developmental delay was reported in these patients. All of the reported patients suffering from hypoglycemia presented with altered ACTH and cortisol levels and were treated with hydrocortisone, which did not completely resolve the hypoglycemic episodes. Interestingly, hypoglycemic episodes resolved spontaneously in two patients, still, one of them presented with learning disability. Brain MRI in four of these patients showed no abnormalities. This family case of PGM1-CDG is

particularly interesting due to the fact that all of the patients suffered from the same homozygous mutations, but their symptoms varied, further supporting previously reported lack of relation between patients' phenotype and genotype (Wong *et al*, 2016). The authors have suggested that adrenal insufficiency might be a common, treatable PGM1-CDG feature, and successfully treated their patients. No explanation was found for the occurrence of CNS symptoms in their patient cohort. Zeevaert *et al*, 2016 reported an 8-year-old patient who presented with several asymptomatic hypoglycemic episodes and recurrent paralysis of the arms as well as the left leg and whose MRI, EEG and EMG findings were normal. The patient's morning cortisol levels ranged from low to normal. This patient was also treated with hydrocortisone and complex carbohydrate supplements but neither of these prevented hypoglycemic episodes. Due to the atypical presentation, the patient was finally diagnosed with PGM1-CDG at 8 years of age, after which he was started on the galactose treatment. Unfortunately, the patient died the same year due to the cardiac complications. The authors have not discussed the unusual neurologic symptoms in the reported patient. Furthermore, Wong *et al*, 2016 conducted a study on 27 PGM1-CDG patients (some previously reported by Tegtmeyer *et al*, 2014; Ondruskova *et al*, 2014; Perez *et al*, 2013), which all presented with low glucose levels. In spite of adequate treatment, 8 out of those patients also presented with neurological symptoms such as intellectual disability, speech delay and developmental delay, and one of them also suffered from seizures. The authors didn't comment on untreated/unreported hypoglycemic episodes. Further, Nolting *et al*, 2017 have reported a 10-year-old PGM1-CDG patient with developmental delay, impairment of fine motor skills, weakness of legs and hearing loss. Hypoglycemia was not reported. The patient was started on galactose, which improved patient's symptoms to a certain extent and with the later addition of uridine, which did not result in further improvement. The authors have not discussed the causality behind the CNS symptoms of their patient. Most recently, Ding *et al*, 2018 reported a 4-year-old male and a 7-year-old female PGM1-CDG patients, both of which suffered from recurrent hypoglycemia. Interestingly, the first patient presented with no congenital malformation and no obvious neurologic involvement. However, the brain MRI did reveal a slightly hypoplastic pituitary, while the EEG results appeared normal. On the contrary, the female patient presented with congenital malformation (cleft palate and micrognathia) as well as substantial neurologic involvement (developmental delay, speech delay, mild intellectual impairment, learning disability). The EEG was mildly abnormal while the brain imaging showed no apparent abnormalities. The authors stated uncertainty behind the origin of CNS symptoms in this patient.

In summary more than 40% of the reported patients showed mild to moderate developmental delay and intellectual disability, while the presence and severity of hypoglycemia was variable, and CNS symptoms appeared in many of the successfully treated patients (Supplementary Table 1). Other neurological clinical features included seizures (n=1), recurrent episodes of hemiplegia (n=1), eye movement abnormalities (n=1) and mild hearing loss (n=1).

Discussion

Central nervous system involvement in PGM1-CDG patients has not been considered a symptom of PGM1 enzyme deficiency, due to the fact that the majority of patients initially described in the literature presented with normal intelligence. The occurrence of neurological symptoms in a few reported patients has mostly been explained as a consequence of the hypoglycemic episodes and insufficient or late treatment. Recently, several reports have been published on PGM1-CDG patients with varying severity of neurological symptoms (Ondruskova *et al*, 2014; Lowenthal *et al*, 2015; Wong *et al*, 2016; Zeevaert *et al*, 2016; Nolting *et al*, 2017; Ding *et al*, 2018). These individual reports as well as the variable manifestation of hypoglycemia accompanied with CNS involvement made us question whether the observed cases with CNS symptoms are truly all caused by hypoglycemia induced brain damage or rather they could be related protein hypoglycosylation affecting the brain.

Other common types of CDG such as PMM2-CDG, ALG1-CDG, ALG6-CDG characteristically present with neurological involvement such as seizures, developmental delay and hemiplegia. (Ferreira *et al*, 2018). However, the full explanation for the underlying cause of CNS involvement in these disorders is still lacking, especially since one could theoretically expect metabolic compensation by the maternal metabolism in fetal life during early brain development in CDG patients. Apart from one patient whose brain imaging revealed a slightly hypoplastic pituitary (Ding *et al*, 2018), no obvious brain abnormalities were detected by imaging in other PGM1-CDG patients.

It is important to note that most MPI-CDG patients do have early hypoglycemia, similar to that seen in many PGM1-CDG patients, while neurologic problems in MPI-CDG are extremely rare. Hypoglycemia in young PGM1-CDG patients is mostly due to severe hyperinsulinism. Late onset ketogenic hypoglycemia in PGM1-CDG is mostly due to a problem in glycogenolysis (Scott *et al*, 2014), and easily treatable by a frequent feeding regimen. In general, glycogen storage disorders are also not associated with CNS involvement. Only a few patients are known with hypocortisolism, which is, in most cases, treatable by cortisol supplements. Therefore, therapy resistant hyperinsulinism and recurrent hypoglycemia can't be the single explanation for CNS involvement in PGM1-CDG patients.

The absence of neurological symptoms in PGM1-CDG patients had previously been explained by the presence of PGM1 isoenzyme PGM2, which predominantly acts as a ribomutase, as well as other enzymes such as phosphomannomutases (PMM1, PMM2), which all have a certain capacity to catalyze the conversion of glucose-1-P to glucose-6-P. However, PGM1 remains the major catalyzer of the inter-conversion of these two phosphate sugars, raising the question whether the other enzymes are able to fully compensate for its deficiency.

In Table 1, we summarize the symptoms of 17 previously reported patients, all suffering from neurological symptoms ranging from mild presentation such as learning disabilities to severe ones such as seizures. More than 40% of the reported patients (17/41) showed mild to moderate developmental delay and intellectual disability. Since a few patients had severe hypoglycemic episodes, obviously we cannot rule out the role of these episodes in abnormal CNS development. However, other patients with severe hypoglycemia

presented with no CNS involvement (Supplementary Table 1), while four patients had neither untreated nor recurrent hypoglycemia episodes, nor other explanation for their learning disability.

A possible explanation for these patients' neurologic involvement could be the fetal hypoglycosylation of brain specific proteins, abnormal fetal migration, or significant lack of phosphorylated sugars in the CNS due to the PGM1 enzyme deficiency, similar to the neurological involvement seen in most other CDGs. Also, asymptomatic or unreported severe hypoglycemic episodes should not be dismissed. Theoretically other (second) mutations, modifier genes or differences in PGM1 compensation by isoenzymes could play a role as well. Importantly, there is a vast phenotypic variability of patients with PGM1-CDG, which does not correlate either with genotype or with PGM1 activity. We propose that similarly, there is a lack of correlation between the presentation of hypoglycemia and manifestation of CNS symptoms in PGM1-CDG, which should not be overlooked and requires deeper understanding.

Due to the fact that PGM1-CDG is one of the few treatable CDGs, early diagnosis based on the associated congenital malformations and aggressive treatment of the mostly hyperinsulinemic hypoglycemia are crucial for the patients' normal development.

Based on our review, we suggest that neurological involvement should be considered as a primary symptom in PGM1-CDG and the psychomotor development has to be specifically assessed during the diagnostic process.

Conflict of interest

Authors declare they have no conflict of interest.

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Table 1. List of patients presenting with CNS involvement

Patient	Publication	Age in years	Mutations	Congenital malformations	Learning disability	Developmental delay	Neurological symptoms	Hypoglycaemia	Insulin	Cortisol levels	Diet or treatment for hypoglycemia	Galactose or lactose supplement
1	Ondruskova <i>et al</i> , 2014	10	c.1010C>T c.1508G>A p.Thr337Met p.Arg503Gln	Cleft palate	+	Significant motor skills delay	Mild neurological impairment, borderline IQ with a decline over the years (IQ 78>66)	Low fasting glucose levels accompanied with ketonuria	N/A	N/A	+	Lactose, no improvement
2	Loewenthal <i>et al</i> , 2015	14	c.112A>T p.Asn38Tyr <i>homozygous</i>	Pierre Robin Sequence	+	NR	NR	Severe recurrent ketotic	Normal	Decreased during fasting	Hydrocortisone supplement, did not completely resolve hypoglycemic episodes	NR
3	Loewenthal <i>et al</i> , 2015	17	c.112A>T p.Asn38Tyr <i>homozygous</i>	Cleft palate	+	NR	NR	Resolved spontaneously	N/A	Mild	NR	NR
4	Loewenthal <i>et al</i> , 2015	13.5+	c.112A>T p.Asn38Tyr <i>homozygous</i>	Bifid uvula	+	NR	NR	Severe recurrent ketotic	Normal	Decreased during fasting	Hydrocortisone supplement, did not completely resolve hypoglycemic episodes	NR
5	Zeevaert <i>et al</i> , 2016	8 ⁺	c.1162G>A c.1547T>C p.Glu388Lys p.Leu516Pro	Facial dysmorphism, Cleft palate	NR	NR	Recurrent, Arms and left leg paralysis Hemiplegia (normal MRI)	Several asymptomatic episodes	Relative Hyperinsulinism	Low to normal morning cortisol	Hydrocortisone, complex carbohydrate supplements did not prevent hypoglycemic episodes	Galactose 0.5g/kg for 4 weeks
6	Wong <i>et al</i> , 2016 [*]	8 ⁺	c.361G>C p.Gly121Arg <i>homozygous</i>	Bifid uvula and cleft palate	NR	+	Intellectual disability,	+	N/A	N/A	NR	-
7	Wong <i>et al</i> , 2016	3	c.689G>A p.Gly230Glu <i>homozygous</i>	Cleft palate	+	+	Intellectual disability	+	Normal	Normal	Frequent feeding	Galactose 1g/kg/day
8	Wong <i>et al</i> , 2016 [*]	11	c.787G>T c.1551C>A p.Asp263Tyr p.Tyr517X	Bifid uvula and cleft palate	+	+	Intellectual disability	+	N/A	N/A	NR	NR

9	Wong <i>et al</i> , 2016	2	c.1598G>T p.R515L <i>homozygous</i>	Cleft palate Multiple VSD	NR	+	NR	+	N/A	NR	NR	Galactose 1g/kg/day
10	Wong <i>et al</i> , 2016*	33	c.787G>T c.788A>G p.Asp263Tyr p.Asp263Gly	Bifid uvula	+	+	Intellectual disability,	+	N/A	N/A	NR	NR
11	Wong <i>et al</i> , 2016	2	c.157-158delinsG c.1507C>T c.661C>T p.Gln53Glyfs*15 p.Arg503X p.Arg221Cys	Bifid uvula and cleft palate	+	+	Intellectual disability, Strabismus, abnormal eye movement, seizures	+	Hypersulinism	N/A	Frequent feeding	Galactose 1g/kg
12	Wong <i>et al</i> , 2016*	5	c.184G>C p.Asp62His <i>homozygous</i>	Bifid uvula	+	+	Intellectual disability,	+	Normal	N/A	Frequent feeding	Galactose 1g/kg/day
13	Wong <i>et al</i> , 2016*	6	c.184G>C p.Asp62His <i>homozygous</i>	Bifid uvula and cleft palate	+	+	Speech delay	+	Normal	N/A	Frequent feeding	Galactose 1g/kg/day
14	Wong <i>et al</i> , 2016	21	c.1264C>T c.1588C>T p.Arg422Trp p.Gln530X	Bifid uvula and cleft palate	NR	NR	Abnormal eye movement intermittent nystagmus, strabismus	+	Normal	Normal	Frequent feeding	Galactose 1g/kg/day
15	Nolting <i>et al</i> , 2017	10	c.771delT p.Phe257Leufs*20 <i>homozygous</i>	Cleft palate, Pierre Robin Sequence	NR	+	Motor and fine motor delay, weakness of legs, hearing loss	-	N/A	NR	NR	Galactose 1g/kg/day plus short time uridine 150mg/kg/day
16	Ding <i>et al</i> , 2018	4	c.119delT	-	-	-	Brain MRI revealed thinning pituitary	Low fasting glucose levels accompanied with ketonuria	Low insulin levels	Normal	Frequent feeding	Refused due to therapy expenses
17	Ding <i>et al</i> , 2018	7	c.1172G>T c.1507C>T	Cleft palate and micrognathia	+	Significant motor skills delay	Speech delay, mild intellectual disability, Mildly abnormal EEG	Recurrent ketotic	Normal	Low cortisol levels, normal ACTH	Frequent feeding, uncooked corn starch	Galactose (dosage not indicated)

deceased

*: patient first reported by Tegtmeier *et al*, 2014

N/A: not available

NR: not reported

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Highlight

- PGM1 deficiency, a disorder of glycogenolysis and glycosylation was initially described as a disease without neurological involvement.
- Our review of the literature revealed that more than 40% of PGM1 patients (16 out of 38 patients) have CNS symptoms without explanation.
- Neither patients with glycogen storage disorders nor patients with hyperinsulinism are known with such a high rate of brain involvement. Additionally almost all other CDGs have neurologic involvement and ID as their feature.
- Clinicians should be aware of the high risk of neurologic problems in PGM1 deficiency, when treating patients and counsel families.