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Case Report

Outcome of creatine supplementation therapy in phosphoglucomutase-1 deficiency associated congenital disorders of glycosylation: Novel insights

Anastasia Ambrose [a], Morganne McCabe [a], Clara Hung [a], Iveta Sosova [b,c], Peter Seres [d], Saadet Mercimek-Andrews [a,e,f,g,*]

[a] Department of Medical Genetics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[b] Alberta Newborn Screening and Biochemical Genetics Laboratory, University of Alberta Hospital, Alberta Precision Laboratories, Edmonton, Alberta, Canada
[c] Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada
[d] Department of Radiology and Diagnostic Imaging, Faculty of Medicine and Dentistry University of Alberta Edmonton Alberta, Canada
[e] Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada.
[f] Women and Children's Health Research Institute, University of Alberta, Edmonton, Alberta, Canada
[g] Alberta Health Services, Edmonton Zone, Alberta, Canada

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ABSTRACT

Background: Biallelic pathogenic variants in *PGM1* result in phosphoglucomutase 1 (PGM1) deficiency that is one of the congenital disorders of glycosylation (CDG) (PGM1-CDG). Phenotypic spectrum includes congenital malformations, and muscular, cardiac, hepatic, endocrine and hematologic phenotypes. Current treatment consists of D-galactose therapy that results in clinical and biochemical improvements. To improve fatigue, and exercise intolerance, we started creatine supplementation therapy.

Material and methods: We reviewed electronic patient chart. We applied Nijmegen Pediatric CDG Rating Scale (NPCRS) and The Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F). We measured creatine metabolism biomarkers.

Results: This is a 29-year-old female with PGM1-CDG, confirmed diagnosis by clinical exome sequencing. She has been treated with D-galactose therapy which did not improve her fatigue and exercise intolerance. She was started on creatine supplementation therapy at the age of 27 years which led to decreased daytime sleeping, increased exercise capacity and improvements in her NPCRS, and FACIT-F. Her plasma guanidinoacetate was low. She had elevated urine galactitol on D-galactose therapy.

Discussion: PGM1-CDG associated myopathy is likely due to combination of several factors including abnormal muscle carbohydrate metabolism, abnormal N-glycosylation of proteins involved in the muscle functions and creatine transport and altered muscle energy homeostasis. It was previously shown that creatine supplementation therapy improves myopathy in patients with mitochondrial cytopathies. We think that the use of creatine supplementation therapy coincided with improvements in fatigue and exercise intolerance subjectively and objectively in our patient.

1. Introduction

Congenital disorders of glycosylation (CDG) are a group of rare inherited metabolic diseases that are characterized by defects in the post-translational modification of proteins, specifically in the attachment and processing of carbohydrate chains, called glycans. Biallelic pathogenic variants in *PGM1* (OMIM# 171900) result in phosphoglucomutase 1 (PGM1) deficiency (PGM1-CDG) (OMIM# 614921). PGM1 catalyzes the reversible conversion between glucose-1-phosphate and glucose-6-phosphate and plays critical roles in glycolysis, glycogenolysis, and glycogenesis [1,2]. There is a disrupted intracellular glucose and galactose metabolism, and impaired assembly and remodeling of N-linked glycans in PGM1-CDG.

There are less than 100 patients with PGM1-CDG reported in the medical literature [3]. The phenotypic spectrum includes congenital malformations, and muscular, cardiac, hepatic, endocrine and

* Corresponding author at: Department of Medical Genetics, University of Alberta, 8–39 Medical Sciences Building, 8613 114 Street, Edmonton, AB T6G 2H7, Canada.
E-mail address: saadet@ualberta.ca (S. Mercimek-Andrews).

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hematologic phenotypes [4,5]. Transferrin isoelectric focusing shows increased asilotransferrin and/or disialotransferrin and decreased tetrasialotransferrin [4]. Patients with PGM1-CDG is treated with D-galactose therapy, a monosaccharide that restores glycosylation by replenishing the UDP-glucose and UDP-galactose [2,4,6].

N-glycosylation is the post translational modification process for creatine transporter, encoded by *SLC6A8*. This process is important for trafficking of creatine to the plasma membrane as well as its transport [7]. Creatine is phosphorylated to phosphocreatine, and both play a critical role in cellular energy metabolism. Phosphocreatine is converted to creatine to replenish adenosine diphosphate to adenosine triphosphate (ATP) in the mitochondria. Creatine is taken up by high energy requiring organs such as skeletal muscle and the brain. Creatine supplementation therapy can improve high-intensity, isometric, anaerobic, and aerobic power, highlighting its potential therapeutic benefits [8–10,12]. Creatine supplementation therapy has been used in patients with primary mitochondrial diseases with myopathic phenotype [8–14].

We report a patient with PGM1-CDG (previously reported in the medical literature [3,15–17]) who has had significant fatigue and muscular phenotype leading to lack of physical activities and extended hours of daytime sleeping. We initiated creatine supplementation therapy and monitored her treatment outcome in this study.

2. Material, methods & results

The patient signed a case report consent form to allow us to present their results in this study. We reviewed Electronic Patient Chart for the medical history, family history, physical examination, biochemical investigations, neuroimaging, and molecular genomic investigations.

The 2D T1-weigthed and 2D T2-weighted images as well as chemical shift image (CSI) multi-voxel brain magnetic resonance spectroscopy (MRS) were acquired on 3 Tesla Siemens Skyra (Erlangen, Germany) at University of Alberta Hospital, Edmonton. Standard of care T1-weighted images with fluid inversion recovery (FLAIR) acquired in sagittal plane were used for tissue segmentation (gray matter (GM)/white matter (WM)/cerebral spinal fluid (CSF)). T2-weighted images (acquired in axial oblique plane) were used for assessment of voxel placement during analysis. CSI MRS (semi-adiabatic localization by adiabatic selective refocusing (sLASER) sequence, axial-oblique plane, resolution 6.25 × 6.25 × 10 mm, 8 × 8 voxel matrix, TR = 1520 ms, TE = 135 ms) was used to assess metabolites (creatine compound and choline compound) in white matter regions of basal ganglia. CSI MRS data were analyzed using FSL-MRS [re; first, T1-weighted images were segmented to GM/WM/CSF using fsl_anat (FSL v 6.0.7.11) [22] and this segmentation was provided as one of the inputs for FSL-MRS fitting. Basis set for the CSI sequence was generated using MRI Cloud (https://braingps.mricloud.org/mrs-cloud) [23,24]. Region of interest was defined as a mask (in CSI space) using fsleyes, including only voxels with WM content >80 % and with good spectra quality, excluding any voxels in ventricles. Spectra fitting was done for the masked region of interest. Based on the report generated by FSL-MRS fitting, we report a ratio of creatine compound (Creatine+Phosphocreatine, Cr + PCr) over choline compound (Glycerophosphocholine+Choline-containing Compounds, GPC + PCh).

2.1. Case report

This is a 29-year-old female with PGM1-CDG who was previously reported as part of Frontiers in Congenital Disorders of Glycosylation Consortium (FCDGC) [3,15–17]. Briefly, she has history of neonatal hypoglycemia (glucose 1.5 mmol/L), cleft palate (surgically repaired at age 1 month), dilated cardiomyopathy and mitral valve insufficiency in echocardiography, gastroesophageal reflux disease (GERD), generalized myalgia, muscle cramps, fatigue, exercise intolerance, and progressive muscle weakness. She had difficulty in standing from a seated position and in climbing stairs. Her physical examination revealed generalized muscle weakness throughout her entire body, particularly in the proximal muscles. Her muscle bulk was normal. Her tone was decreased in upper extremities and was spastic in lower extremities. Her muscle stretch reflexes were + 3 in the upper extremities and + 2 in the lower extremities at the age of 18 years. Her muscle biopsy (left vastus lateralis) showed mild to moderate nonspecific myopathic changes. Hematoxylin and eosin staining identified mildly increased variation in fiber size, sparse small or atrophic fibers, occasional nuclear clumps and regenerating fibers, rare necrotic fibers, rare fibers containing eosinophilic cytoplasmic bodies, and minimal inflammation. Gomori's modified trichrome staining identified occasional ragged red fibers. Succinate dehydrogenase histochemistry identified rare fibers with mildly increased reactivity. NADH-TR histochemistry identified rare fibers with increased reactivity, rare fibers with moth-eaten or targetoid appearance. Cytochrome oxidase histochemistry identified rare fibers devoid of reactivity. ATPase histochemistry identified sparse type 1 and 2 fiber atrophy, and type 2c immature fibers hardly found. Esterase histochemistry identified rare small fibers with increased reactivity. Immunohistochemistry identified CD45 sparse positive inflammatory cells, CD68 occasional positive macrophages, CD4 occasional positive T-cells, CD8 rare positive cytotoxic T-cells, and Desmin rare fibers with focally increased immunoreactivity. Her biochemical investigations are summarized in Table 1.

Her clinical exome sequencing identified a heterozygous pathogenic (c.787G > T; p.Asp263Tyr) and a heterozygous likely pathogenic (c.988G > C; p.Gly330Arg) variants in *PGM1* (NM_002633.2). After her diagnosis, she was started on D-galactose supplementation therapy (14 g/day) and her dose was increased to 20 g three times a day as per her tolerance. Despite this treatment, she has continued having fatigue, generalized myalgia, muscle cramps, exercise intolerance, and progressive muscle weakness. She was sleeping all day (approximately 21 h/day) due to these symptoms. We started her on creatine supplementation therapy (2 g three times a day, 120 mg/kg/day initially, increased to 3 g three times a day, 180 mg/kg/day after one year of therapy). Her treatment is summarized in Table 2.

She underwent following assessments using: 1) The Nijmegen Pediatric CDG Rating Scale (NPCRS), a clinical tool designed to evaluate the severity and progression of CDG by assessing neurological, systemic, and developmental features [18]; 2) The International Cooperative Ataxia Rating Scale (ICARS), which quantifies the severity of ataxia based on postural, limb, speech, and oculomotor impairments [19]; 3) The 6-min walk test, a functional exercise test that measures walking endurance and mobility by assessing the distance covered in six minutes [20]; 4) The Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F), a patient-reported questionnaire that evaluates fatigue severity and its impact on daily activities and quality of life [21].

At the age of 27 years, she underwent continuous glucose monitoring using the Dexcom G6 sensor to assess if she has any hypoglycemia which identified hypoglycemia overnight (between 2.2 and 2.5). She was started on cornstarch (32 g) at bedtime, but did not tolerate and discontinued after few weeks.

She underwent three neuropsychological assessments, and the results are summarized in Supplemental Table 1. Her total composite score was at 3rd percentile (69 ± 6; borderline intellectual disability) using the Stanford-Binet Intelligence Scale: Fourth Edition (SBIV) at the age of 4 years. Her general cognitive ability revealed extremely low range of intellectual functioning (0.2 percentile) using Weschler Intelligence Scale for Children-4th edition (WISC-IV) at the age of 10 years. Her Full-Scale IQ score was 71 (3rd percentile; Borderline range) using Wechsler Adult Intelligence Scale – IV (WAIS-IV) at the age of 28 years.

Her echocardiography revealed mildly dilated aortic valve annulus (25 mm), aortic root dilation (37 mm), ascending aorta dilation (37 mm), decreased medial mitral valve annulus velocity, mild left ventricular dilatation, mildly decreased left ventricular systolic function and 41 % ejection fraction at the age of 24 years prior to her PGM1-CDG diagnosis. Her echocardiography showed bicuspid aortic valve with mild regurgitation, aortic root dilation (39 mm), borderline left

Table 1
Biochemical investigations.

	Metabolites (reference range)	5 years pre-creatine therapy	4 years pre-creatine therapy	3 years pre-creatine therapy	Two weeks creatine supplementation therapy	1 year creatine supplementation therapy	2 years creatine supplementation therapy
Creatine metabolism biomarkers	Plasma creatine (7.1–96.5 μmol/L)	NP	NP	NP	283.8	247.7	279.9
	Plasma guanidinoacetate (1.1–3.3 μmol/L)	NP	NP	NP	0.6	0.6	0.8
	Urine creatine (3–178 mmol/mol creatinine)	NP	NP	NP	Above reportable range	Above reportable range	Above reportable range
	Urine guanidinoacetate (4–83 mmol/mol creatinine)	NP	NP	NP	25	17.7	23.9
Galactose metabolism biomarkers	RBC Galactose-1-Phosphate Uridyltransferase (≥ 24.5 nmol/h/mg Hb)	NP	NP	NP	NP	25.9	NP
	RBC galactose-1-Phosphate (≤ 0.9 mg/dL)	NP	NP	NP	NP	< 0.3	NP
	Urine galactitol (< 13 mmol/mol Cr)	NP	NP	NP	NP	104	NP
Chemistry	Plasma CK (<200 U/L)	1075	1121	3056	1194*	531	NP
	Plasma AST (<40 U/L)	NP	109	NP	54*	58	NP

Abbreviations
AST = aspartate transaminase; CK = creatine kinase; NP = not performed.
* 6 months creatine therapy.

Table 2
Treatments and their doses are summarized in Table 2.

Treatment/ Age	27 y	27 y 2 mo	27 y 7 mo	28 y 4 mo	28 y 11 mo	29 y 6 mo
D-galactose	5 g five times/d	20 g two times/d	20 g three times/d	20 g three times/d	20 g three times/d	20 g three times/d
Creatine	None	2 g three times/d	2 g three times/d	3 g three times/d	3 g three times/d	3 g three times/d

Abbreviations: d = day; mo = month(s); y = year(s).

ventricular dilatation, and 53 % ejection fraction at 1.5 year of D-galactose and 5 months of creatine supplementation therapies at the age of 27 years. Her repeat echocardiography on creatine supplementation therapy showed bicuspid aortic valve, mild left ventricular dilatation and 48 % ejection fraction at 3.5 year of D-galactose and 2 years of creatine supplementation therapies at the age of 29 years.

Her NPCRS was 13 at the age of 26 years. Her NPCRS was improved to 11 (maximum score of 82, with higher scores indicating greater disease severity) on D-galactose supplementation therapy. Her NPCRS score improved to 5 on one-year of creatine therapy and to 4 at two years of creatine therapy. Her fatigue assessments using the FACIT-F improved on the creatine supplementation therapy. The results of these assessments are summarized in Table 3. She underwent two 6- min walk test during her appointments on creatine supplementation therapy, but we did not have a baseline assessment due to COVID-19 pandemic. However, she and her parents provided information that she was able to walk between living room and her bedroom few times a day at home. On creatine supplementation, she started doing chair exercise, aquatic exercise and walking for 1 to 1–1/2 h few times per week outside. Additionally, she did not require naps during the daytime and was able to stay awake from 10:00 am to 8:00 pm. She walked 216 m unaided, taking a seated break lasting 17 s in her 6-min walk test on one year of creatine supplementation therapy. She maintained the same distance requiring a single 35-s break at two-year of creatine supplementation therapy.

Her brain MRS (performed on 2 weeks of creatine supplementation therapy) revealed similar ratio of Cr + PCr)/(GPC + PCh (in both basal ganglia white matter and basal ganglia not white matter) compared to the age and sex matched control (26 years old female with cystathionine beta synthetase deficiency) at the age of 27 years (Fig. 1) (Supplemental Table 2).

Table 3
Results of Nijmegan Pediatric CDG rating scale (NPCRS) and Functional Assessment of Chronic Illness Therapy (FACIT) scale are summarized in Table 3.

	7 months pre-creatine treatment	5 months pre-creatine treatment	2 weeks pre-creatine treatment	5 months creatine treatment	1 year creatine treatment	2 years creatine treatment
Functional Assessment of Chronic Illness Therapy (FACIT) scale						
FACIT-F TOI	NP	NP	24	NP	65	72
FACIT-G	NP	NP	47	NP	81	85
FACIT-F	NP	NP	53	NP	104	117
Nijmegan Pediatric CDG rating scale (NPCRS)						
	13	13	11	13	5	4
International Co-Operative Ataxia Rating Scale (ICARS)						
	NP	NP	NP	NP	2	9

Abbreviations: CDG = congenital disorders of glycosylation; FACIT-F = functional assessment of chronic illness therapy- fatigue; FACIT-F TOI = functional assessment of chronic illness therapy- fatigue total outcome index; FACIT-G = functional assessment of chronic illness therapy- general; NP = not performed.

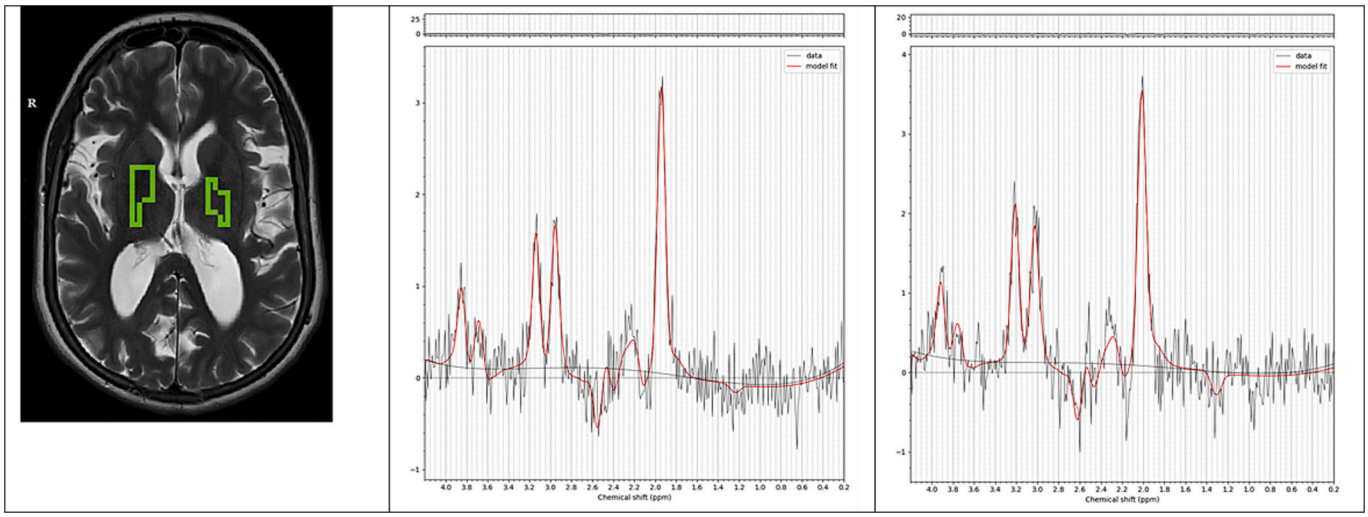

Fig. 1. Brain magnetic resonance spectroscopy (chemical shift imaging, sLASER with TE = 135 ms). Region of interest in white matter is shown overlaid on T2 weighted image for the patient in the left panel. Fitted spectra are shown for the patient (29-year-old female, middle panel) and control (26-year-old female, right panel).

3. Discussion

We report a patient with PGM1-CDG who has fatigue and muscular phenotype and a favorable outcome on creatine supplementation therapy. D-galactose therapy was reported to improve clinical and biochemical features in PGM1-CDG [4,5]. These improvements include normalization of liver function tests, coagulation parameters, and increased glycoprotein levels such as TSH, TBG and IGF3BP [25]. D-galactose therapy reduced the frequency of hypoglycemic episodes, improved abnormal transferrin isoelectric focusing, and increased intracellular levels of UDP-glucose and UDP-galactose in cultured skin fibroblasts [25]. About one-third of patients reported a positive effect on exercise intolerance and fatigability on D-galactose therapy [25]. Her ejection fraction improved from 41 % to 48 % and there was no improvement in the dilated cardiomyopathy on the combined D-galactose and creatine supplementation therapies. However, we are not certain if the improvement in the ejection fraction is significant and if creatine supplementation therapy contributed to this improvement. As we did not perform echocardiography prior to starting creatine supplementation therapy, we will not be able to know its contributions to the cardiac phenotype. Unfortunately, aspartate aminotransferase (AST) and creatine kinase (CK) levels did not normalize on D-galactose therapy. Persistently elevated AST and creatine kinase levels may suggest unresolved myopathy on D-galactose therapy alone [25]. Our patient did not report any improvement in muscle pain and fatigue on D-galactose therapy. Additionally, AST and CK levels remained elevated on D-galactose therapy. For this reason, we started her on creatine supplementation therapy which led to decreased daytime sleeping, increased exercise capacity and improvements in her NPCRS, and FACIT-F.

PGM1-CDG has previously been reported as a metabolic myopathy [4,26–29]. Muscular phenotype include exercise intolerance, fatigability, muscle weakness, cramps, and rhabdomyolysis [2,4,6,16,25,30–38]. One patient has been previously reported to have muscle pain and cramps following exercise [38]. A myopathic gait and muscle wasting have been described in few patients [1,39]. Electromyography (EMG) showed a myopathic pattern in three patients [1,38,39]. Muscle biopsy revealed myopathic changes and/or accumulation of fat or glycogen in 10 patients with PGM1-CDG [2,5,30,31,38,39]. PGM1-CDG associated myopathy is likely multifactorial: 1) Due to satellite cellopathy, where muscle disorders are due to pathogenic variants in myopathogenes (e.g. *ENO3, FLAD1, PGM1* and *PRKAG2*) potentially causing satellite cell dysfunction [26]; 2) Due to altered glycosylation patterns of muscle function-related proteins. ACTB (actin beta) is essential for cytoskeletal integrity and cellular motility and undergoes both N-linked (Asn12) and multiple O-linked glycosylation (https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACTB&keywords=ACTB, accessed January 21, 2024). AGRN (agrin) is central to the formation and maintenance of the neuromuscular junction (NMJ) and relies on extensive N-linked (e.g., Asn135, Asn250) and O-linked glycosylation for proper interaction with receptors like MUSK (https://www.genecards.org/cgi-bin/carddisp.pl?gene=AGRN&keywords=AGRN, accessed January 21, 2024). Impaired glycosylation of AGRN may compromise NMJ integrity, leading to reduced muscle signaling and contributing to muscle weakness. FRYL (FRY like transcription coactivator) is a regulator of the actin cytoskeleton and polarized cell extensions and requires N-linked glycosylation (Asn1919) (https://www.genecards.org/cgi-bin/carddisp.pl?gene=FRYL&keywords=FRYL, accessed January 21, 2024). Dysregulated glycosylation in PGM1-CDG may impair ability of FRYL to maintain muscle architecture. All protein interactions of PGM1 with muscle-associated genes are summarized in Supplemental Table 3; 3) Due to the defective N-glycosylation affecting the function of genes important for muscles such as *DES* (Asn342), *FHL1* (Asn77), *FKRP* (Asn172, Asn209), *ANO5* (Asn366), *SLC22A5* (Asn57, Asn64, Asn91), *LDHA* (Asn84), *GAA* (Asn140, Asn233, Asn390, Asn470, Asn652, Asn882, Asn925), *SELENON* (Asn126, Asn190, Asn483, Asn505, Asn531), and *RYR1* (Asn2774) (Supplemental Table 4); 4) Due to defective N-glycosylation affecting creatine transporter, which undergoes post translational modification process at Asn192, Asn197 and Asn548 (https://www.genecards.org/cgi-bin/carddisp.pl?gene=SLC6A8, accessed January 20, 2025). It was shown that non-glycosylated creatine transporter had about 2 times lower capacity for creatine transport compared to fully glycosylated creatine transporter [7]. The authors concluded that N-linked glycans are used for the correct trafficking of creatine transporter to the plasma membrane [7]. Creatine supplementation can improve myopathy via high-intensity power output and increases activation of glycolysis and glycogenolysis in patients with mitochondrial cytopathies [12]. As PGM1-CDG is one of the N-glycosylation defects and results in myopathy, we thought that we can try creatine supplementation therapy. Our patient showed subjective and objective improvements in her fatigue and myopathy coincided with the creatine supplementation therapy. To the best of our knowledge, we report for the first time the use of creatine supplementation therapy in one patient with PGM1-CDG. We think that

it would be beneficial to try creatine supplementation therapy in all patients with CDG who have fatigue and myopathic features to see if it will be useful to improve these symptoms.

Muscular phenotype has been reported in patients with arginine-glycine amidinotransferase (AGAT), creatine transporter and guanidinoacetate methyltransferase (GAMT) deficiencies, also called creatine deficiency disorders (CDD). Patients with CDD present with proximal muscle weakness, cramps, muscular hypotonia and myopathic abnormalities on electromyography [40–48]. This is due to creatine and/or guanidinoacetate deficiencies (especially in AGAT deficiency) in those patients with CDD. Individuals with AGAT deficiency have low levels of guanidinoacetate in urine, plasma, or CSF [49]. It is also known that high dose creatine therapy decreases guanidinoacetate production by negative feedback of AGAT. Interestingly, we identified low levels of plasma guanidinoacetate in our patient from the beginning of creatine supplementation therapy. The first plasma guanidinoacetate measurement was performed after two week of creatine supplementation therapy. We are not certain, if low plasma guanidinoacetate is due to creatine supplementation or due to glycosylation abnormalities. The AGAT and GAMT are O-glycosylated and there are no protein-protein interactions between PGM1 and AGAT and GAMT. Creatine and guanidinoacetate in urine and plasma should be collected prior to creatine supplementation therapy to understand if there is a decreased production of creatine and guanidinoacetate in PGM1-CDG or in other CDG if creatine supplementation therapy is planned.

Blood galactose-1-phosphate and urine galactitol levels were found to be normal in patients after 12 weeks of D-galactose therapy [25]. Galactose-1-phosphate levels were low in the cultured skin fibroblasts in patients with PGM1-CDG which was normalized on the D-galactose therapy [6]. In our patient, we identified elevated urine galactitol and normal red blood cell galactose-1-phosphate on the -galactose therapy. Elevated galactitol can lead to cataracts through the accumulation of galactitol in the lens, as seen in disorders of galactose metabolism [50]. To the best of our knowledge, we report for the first time elevated urine galactitol on D-galactose therapy in a patient with PGM1-CDG. We wonder if long-term D-galactose therapy may cause cataract and should be closely monitored in patients with PGM1-CDG.

Our study had several limitations including: 1) We have a single case on creatine supplementation therapy, and we are not certain if all patients will improve; 2) We did not measure urine and plasma guanidinoacetate and creatine levels to prior to start of creatine supplementation therapy; 3) We did not perform brain MRS to see improvements in creatine levels in brain on the creatine supplementation therapy; 4) Long-term side effects of creatine supplementation therapy including weight gain and kidney stones have been reported in patients with AGAT deficiency (Battini et al., 2017). However, a placebo controlled clinical trial for creatine supplementation (10 g/day) resulted in severe diarrhea, severe nausea and limb swelling were reported in <3 out of 175 patients with amyotrophic lateral sclerosis (Groeneveld et al). Despite these limitations, we think that our report is valuable to improve fatigue and muscular phenotype in patients with PGM1-CDG using creatine supplementation therapy.

In conclusion, we report one patient with PGM1-CDG on creatine supplementation therapy coinciding with improvements in her fatigue and exercise intolerance. We report for the first time elevated urine galactitol in a patient with PGM1-CDG which requires further investigations and monitoring of cataract as long-term treatment complication. We report secondary abnormalities in creatine metabolism which is likely secondary to abnormal N-glycosylation of creatine transporter. Due to use of creatine supplementation therapy in different inherited metabolic diseases with muscular phenotype, we think that patients with CDG who have muscular phenotype might benefit from creatine supplementation therapy.

CRediT authorship contribution statement

Anastasia Ambrose: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation. **Morganne McCabe:** Writing – review & editing, Methodology, Investigation. **Clara Hung:** Writing – review & editing, Methodology, Investigation. **Iveta Sosova:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Peter Seres:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis. **Saadet Mercimek-Andrews:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2025.101212.

Data availability

All data generated or analyzed during this study can be found within the published article and its supplemental files.

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