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Limitations of galactose therapy in phosphoglucomutase 1 deficiency

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ABSTRACT

Introduction: Phosphoglucomutase 1 deficiency (PGM1 deficiency) has been identified as both, glycogenosis and congenital disorder of glycosylation (CDG). The phenotype includes hepatopathy, myopathy, oropharyngeal malformations, heart disease and growth retardation. Oral galactose supplementation at a dosage of 1 g per kg body weight per day is regarded as the therapy of choice.

Results: We report on a patient with a novel disease causing mutation, who was treated for 1.5 years with oral galactose supplementation. Initially, elevated transaminases were reduced and protein glycosylation of serum transferrin improved rapidly. Long-term surveillance however indicated limitations of galactose supplementation at the standard dose: 1 g per kg body weight per day did not achieve permanent correction of protein glycosylation. Even increased doses of up to 2.5 g per kg body weight did not result in complete normalization.

Furthermore, we described for the first time heart rhythm abnormalities, i.e. long QT Syndrome associated with a glycosylation disorder.

Mass spectrometry of IGFBP3, which was assumed to play a major role in growth retardation associated with PGM1 deficiency, revealed no glycosylation abnormalities. Growth rate did not improve under galactose supplementation.

Conclusions: The results of our study indicate that the current standard dose of galactose might be too low to achieve normal glycosylation in all patients. In addition, growth retardation in PGM1 deficiency is complex and multifactorial. Furthermore, heart rhythm abnormalities must be considered when treating patients with PGM1 deficiency.

1. Introduction

Phosphoglucomutase 1 deficiency (PGM1 deficiency) has been defined as a glycogenosis and congenital disorder of glycosylation (CDG) related to a great variety of biochemical and clinical symptoms. Phenotypical characterization is still incomplete, pathomechanisms are only partly understood and although therapeutic approaches have been proposed, further detailed research and investigation are indispensable.

By converting glucose-1-phosphate into glucose-6-phosphate, phosphoglucomutase 1 (PGM1) enables the liver to release glucose from glycogen in order to maintain glucose homeostasis (Fig. 1). In the reverse reaction, PGM1 catalyzes glucose-6-phosphate conversion into glucose-1-phosphate for glycogen biosynthesis and is related to the UDP-galactose pool needed for protein N-glycosylation [1]. PGM1 also

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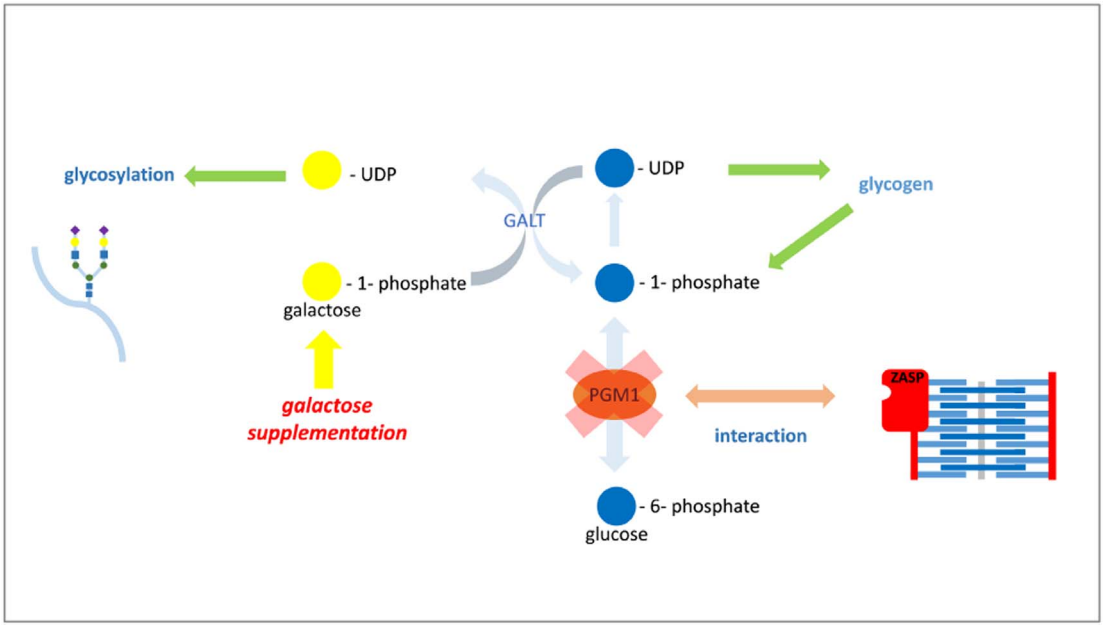

Fig. 1. Schematic representation of phosphoglucomutase 1 (PGM1) key role in metabolism and protein interaction.
In PGM1 deficiency, malfunction of the enzyme causes a wide range of clinical symptoms such as hepatopathy, uvula bifida, myopathy, cardiomyopathy and growth retardation [1].
PGM1 serves as a binding factor to the ZASP in heart muscle cells. The deficient enzyme causes dilated cardiomyopathy [2].
In PGM1 deficiency, glucose-6-phosphate (blue) cannot be generated from glycogen, which causes hypoglycemia and exercise- induced rhabdomyolysis [3].
By galactose supplementation (yellow) the PGM1 pathway is bypassed and the formerly deficient protein glycosylation is compensated [1].

interacts with *Z*-band alternatively spliced PDZ motif protein (ZASP) in heart muscle cells [2].

In this paper, we report on a patient with a novel *PGM1* mutation receiving galactose supplementation expanded by temporary uridine intake and additional growth hormone therapy. Results of this first long-term surveillance reveal the positive effects and limitations of galactose supplementation in PGM1 deficiency.

Mass spectrometry data on subunits of the growth hormone complex provide first insights into the glycoprotein profile of this PGM1 deficient patient and give explanations on therapeutic limitations.

2. Methods

2.1. Informed consent and ethical approval

Informed consent of the parents was obtained. Ethical approval was granted by the local Ethics Committee.

2.2. Glycosylation assays

Isoelectric focusing (IEF), as well as immunoprecipitation followed by sodium dodecyl sulfate-polyacrylamide-gel electrophoresis (SDS-PAGE) were performed as described elsewhere [1,4].

High performance liquid chromatography (HPLC) of serum transferrin was carried out following the manufacturer's protocol employing the “CDT in serum - HPLC” kit from Chromsystems (Gräfelfing, Germany).

Electrospray ionization mass spectrometry (ESI-MS) was performed as described previously [5].

2.3. Cells and tissues

Patient's leukocytes were obtained and isolated as outlined before [1].

2.4. Enzyme assays and PGM1 western blotting

A modified Beutler test using dried blood spots on Guthrie heel-prick test cards was used. Specific phosphoglucomutase 1 activity profile was gained by spectrometric measurement of the enzyme activity in extracts of leucocytes as stated elsewhere [1].

Investigation of phosphoglucomutase 1 expression by western blotting was carried out as described elsewhere [1] using different antibodies (Ab 55,616 and Ab 188,869; Abcam, Cambridge, UK).

2.5. Genetic analysis

Sanger Sequencing of *PGM1* was performed on the patient's and the parents' genomic DNA.

Genomic DNA obtained from patient's leucocytes was isolated and analyzed for long-QT syndrome (LQTS) gene mutations, in particular the LQT 1–3, 5–7 and 8 subforms (ion channel genes: *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *HCNJ2*, *CACNA1C*) as previously described [6]. The complete coding sequences were analyzed.

2.6. IGF ternary complex analysis

2.6.1. Affinity purification and western blotting of serum IGFBP-3

IGFBP-3 was isolated from 2.5–5 mL serum samples by immunoaffinity chromatography on columns of anti-IGFBP-3 IgG (R-100, prepared in-house) immobilized onto agarose (Affi-Gel 10 (Bio-Rad #1536046)). Bound IGFBP-3 was eluted with 0.1 M acetic acid, 0.5 M NaCl, pH 2.8. Samples were further purified on a 4.6 × 250 mm C18 column (Jupiter 5 µm, 300 Å; Phenomenex 00G-4053-E0), using a 15–60% gradient of acetonitrile in 0.1% trifluoroacetic acid over 30 min at 1.5 mL/min.

Western blotting was performed as previously described [7].

2.7. IGFBP-3 mass spectrometry

Purified IGF-BP3 was reduced with dithiothreitol followed by carbamidomethylation, and then digested with a mixture of trypsin and

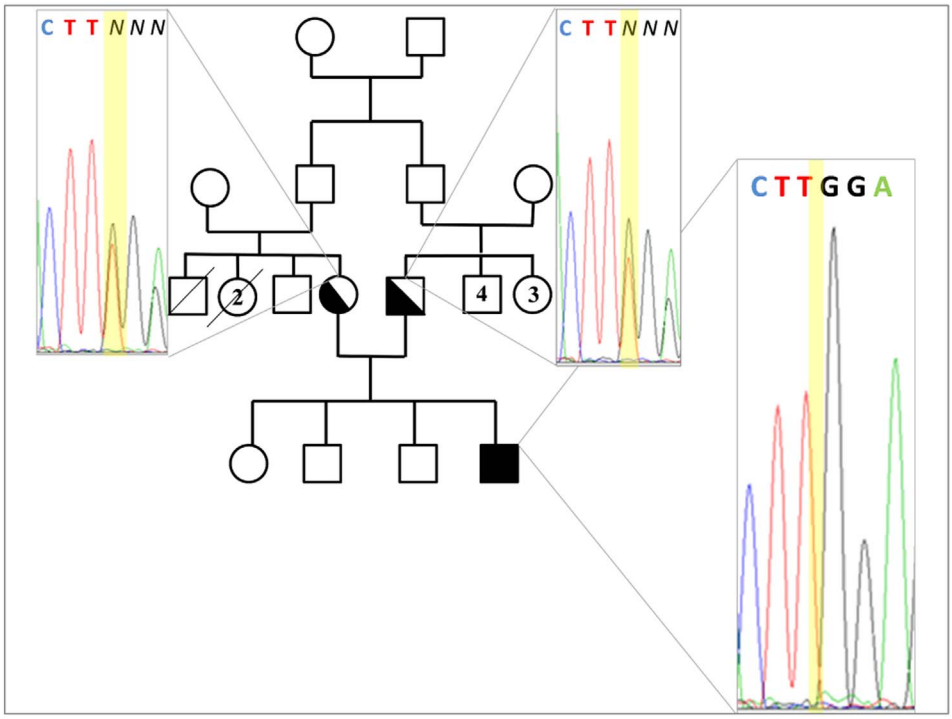

Fig. 2. Pedigree of the patient's family.
Sanger sequencing performed on the patient and his consanguineous parents revealed a homozygous 1 base deletion in the phosphoglucomutase 1 gene (c.771delT) resulting in a frameshift and a premature stop codon further downstream.

lysylendopeptidase in 0.1 M Tris HCl, pH 8.0. The solution pH was then adjusted at pH 5.5 and treated with an *Arthrobacter* neuraminidase for desialylation. Enrichment of glycopeptides was carried out according to a method described previously [8]. Briefly, the digest was mixed with a 15 μL packed volume of Sepharose CL4B (GE Healthcare Life Sciences, Pittsburgh, PA) in 1 mL of an organic solvent of 1-butanol/ethanol/H_2O (4:1:1, v/v). After gentle shaking for 30 min, the gel was washed twice with the same organic solvent. The gel was then incubated with an aqueous solvent of ethanol/H_2O (1:1, v/v) for 5 min, and the solution phase was recovered and dried using a vacuum concentrator. After drying the eluate, the enriched glycopeptides sample was dissolved in 1 μL of 0.1% (v/v) trifluoroacetic acid and mixed with 1 μL of 2% (w/v) 2,5-dihydroxybenzoic acid dissolved in a 50% (v/v) acetonitrile solution, and then placed on a sample target and dried for MS. Matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF) mass spectrometry (MS) was carried out on a Voyager DE Pro mass spectrometer with a nitrogen pulsed laser (337 nm) (AB Sciex, Framingham, MA). Measurements were carried out in positive ion and linear TOF mode (Supplementary Fig. 13).

2.8. Galactose and uridine therapy

D-Galactose (D-galactose, provided by Dr. Schär Medical Nutrition GmbH, Germany) dissolved in water was administered at a total dosage of 1 g per kg body weight per day split into five separate portions. After 3.5 months, the daily intake was doubled and then further increased up to 2.5 g per kg body weight another 3 months later.

Uridine (Uridinum, Fagron GmbH & Co. KG, Germany) at a daily total dosage of 150 mg per kg body weight divided into five separate rations was added to the galactose supplement starting from week 38 for a period of 6 weeks.

In week 47, galactose supplementation was interrupted for 10 weeks and then reinitiated at a daily dosage of 1 g per kg body weight.

Changes in the glycosylation profile of serum transferrin were monitored by frequent HPLC and IEF. Serum transaminases and blood coagulation parameters were analyzed and the patient's body height was measured frequently.

3. Results

3.1. Patient

The patient is the 10-year-old son of consanguineous Turkish patients and was born after 39 weeks of gestation. Birth weight was 2810 g (10th percentile) and body length was 48 cm (3rd percentile). He presented with cleft palate and Pierre-Robin sequence requiring surgery during the first year of life (Supplementary Fig. 1), dysmorphic ears, ventricular septal defect with spontaneous closure, maldescensus testis and myopathy. Walking started at the age of 15 months. Auditory tests were pathological in the newborn period and hearing aids were necessary up to the age of 4.5 years.

Fine motor skills were impaired. Weakness of legs limited fast running.

At the age of four, elevated transaminase levels with a GOT of 139 U/L (< 45 U/L), GPT of 45 U/L (< 40 U/L) and GLDH of 9.8 U/L (< 5 U/L) were detected. Observation of serum transaminases during the following years showed permanent enzyme elevation with peaks of GOT at 289 U/L, GPT at 55 U/L and GLDH at 40.9 U/L.

Body length remained below the 3rd percentile and IGF1 and IGFBP-3 levels were below normal. At the age of 5 2/12 years, the patient's skeletal age was estimated at 4 years. Growth hormone therapy (Norditropin) was introduced at the age of 5 and a half years. Daily dosage was raised from 0.45 mg up to 1 mg (Supplementary Fig. 2).

Cardiac examination first revealed a QTc of 458 ms (reference: < 440 ms), which initially required no treatment. More recent electrocardiogram analysis showed a QTc of 534 ms so that bisoprolol therapy was introduced. Consequently, QTc in electrode II shortened to values within upper reference ranges at 440 ms and V2-4 stayed elevated at 483 ms (Supplementary Figs. 3–6).

Echocardiography did not reveal dilated cardiomyopathy but showed a slightly enlarged left ventricle (LVed 42 mm; + 0.4) with a normal ejection fraction.

3.2. Glycosylation assays

Isoelectric focusing (IEF), sodium dodecyl sulfate-polyacrylamide-gel electrophoresis (SDS-PAGE) as well as high performance liquid chromatography (HPLC Chromsystems) of serum transferrin revealed an abnormal transferrin glycosylation pattern (Supplementary Fig. 7).

Mass spectrometry (ESI-MS) of serum transferrin showed abnormal glycoforms, which decreased under galactose treatment (Supplementary Fig. 8).

3.3. Enzyme assays and western blotting for PGM1

In the modified Beutler test for PGM1 deficiency, all known PGM1 deficient patients showed enzyme activity below 18 U/dL [1]. PGM − activity in our patient was 10 U/dL.

Phosphoglucomutase 1 activity in the patient's leucocytes was decreased (Supplementary Fig. 9).

Western blots for PGM1 and the control protein β-actin revealed the absence of phosphoglucomutase 1 in the patient's leucocytes (Supplementary Fig. 10).

3.4. Genetic analysis

Sanger sequencing revealed a homozygous deletion in exon 5 (c.771delT, F257Lfs*20, reference sequence NM_002633.2). Parents were heterozygous for this mutation (Fig. 2).

Genetic analysis for presence of a congenital Long QT Syndrome revealed no mutations in the coding sequences of the major cardiac genes for repolarization, i.e. *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2* and *CACNA1C*.

3.5. Galactose and uridine therapy

HPLC analyses of transferrin glycosylation revealed an improvement of protein glycosylation after three weeks of daily galactose supplementation (1 g per kg body weight) (Fig. 3).

After four months, HPLC indicated an undulant stagnation of transferrin glycosylation with tetrasialo-transferrin fluctuating between 70 and 80% (reference: > 85%).

Doubling the daily intake to 2 g galactose per kg body weight improved the glycosylation pattern of the patient's serum transferrin. Further increase to 2.5 g per kg body weight kept the glycosylation profile fluctuating close to physiological ranges. Complete and steady correction of deficient glycosylation was not achieved.

Additional supplementation of uridine has been reported to fully normalize glycosylation in fibroblasts [1], but did not improve the serum transferrin glycosylation profile in the patient.

Interruption of galactose supplementation resulted in the reoccurrence of deficient glycosylation patterns comparable to pretreatment values.

Restart of galactose supplement at a dosage of 1 g per kg body weight per day showed a quick improvement of protein glycosylation, remaining beneath normal ranges.

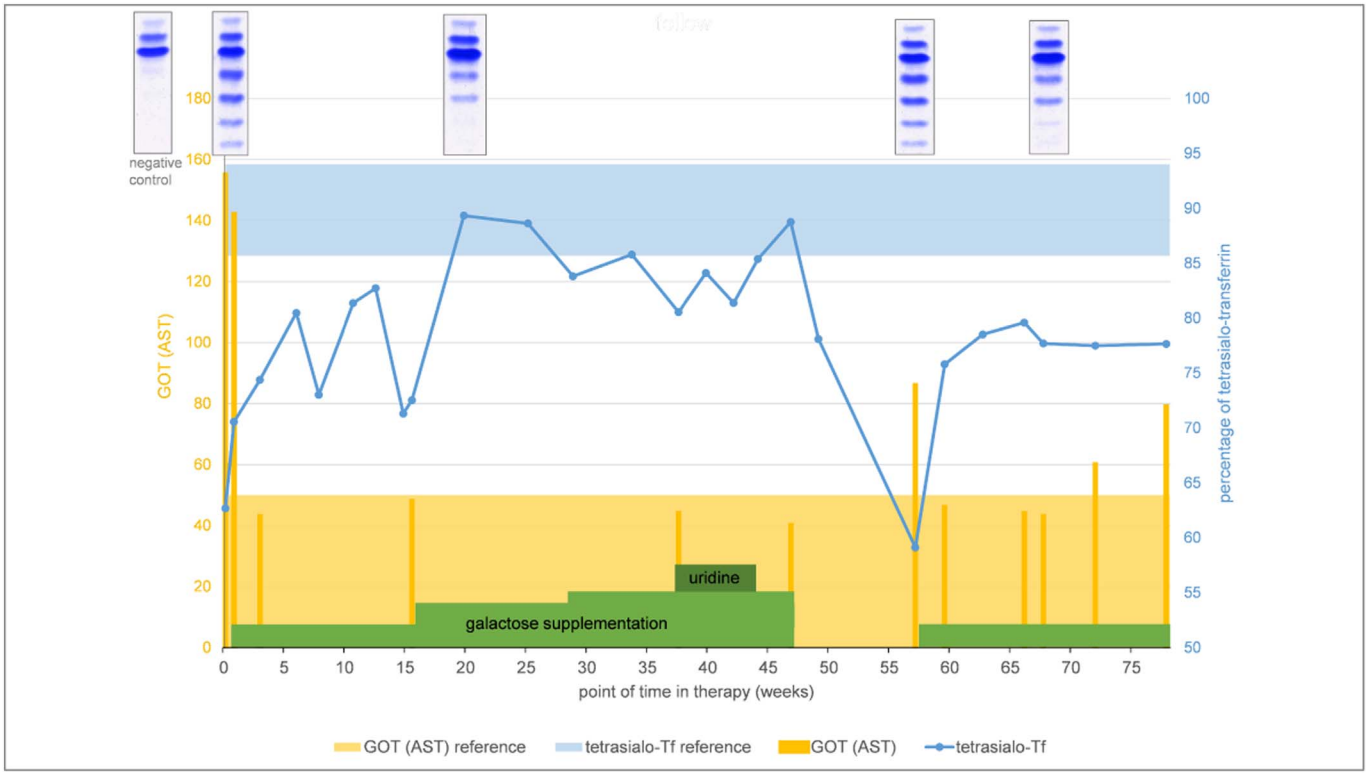

Fig. 3. Changes in glutamate-oxaloacetate transaminase (GOT) levels and protein glycosylation under galactose and temporary uridine supplementation monitored by frequent analysis of aspartate transaminase levels, HPLC and IEF of serum transferrin (Tf).

Elevated aspartate transaminase levels decreased with galactose supplementation and rose during interruption of therapy.

Deficient glycosylation patterns showed quick improvement after galactose intake, but levels of tetrasialo-Tf (blue line) and hypoglycosylated transferrin isoforms (sum of glycoforms with 0–3 sialic acids, not shown) remained stagnating without reaching physiological rates (reference according to [9]: asialo-Tf: below level of detection, monosial-Tf: below level of detection, disialo-Tf: 1.1 ± 0.72, trisialo-Tf: ± 2.60, tetrasialo-Tf: 89.84 ± 4.16, pentasialo-Tf: 6.4 ± 3.80).

Dosage increase led to nearly normalized rates (tetrasialo-Tf range: light blue range), but failed to entirely correct the glycosylation deficiency. We could not show an additional effect of uridine.

Interruption of galactose supplementation led to pretreatment glycosylation patterns. Partial recovery of transferrin glycosylation was achieved by a restart of galactose therapy at a daily intake of 1 g per kg body weight.

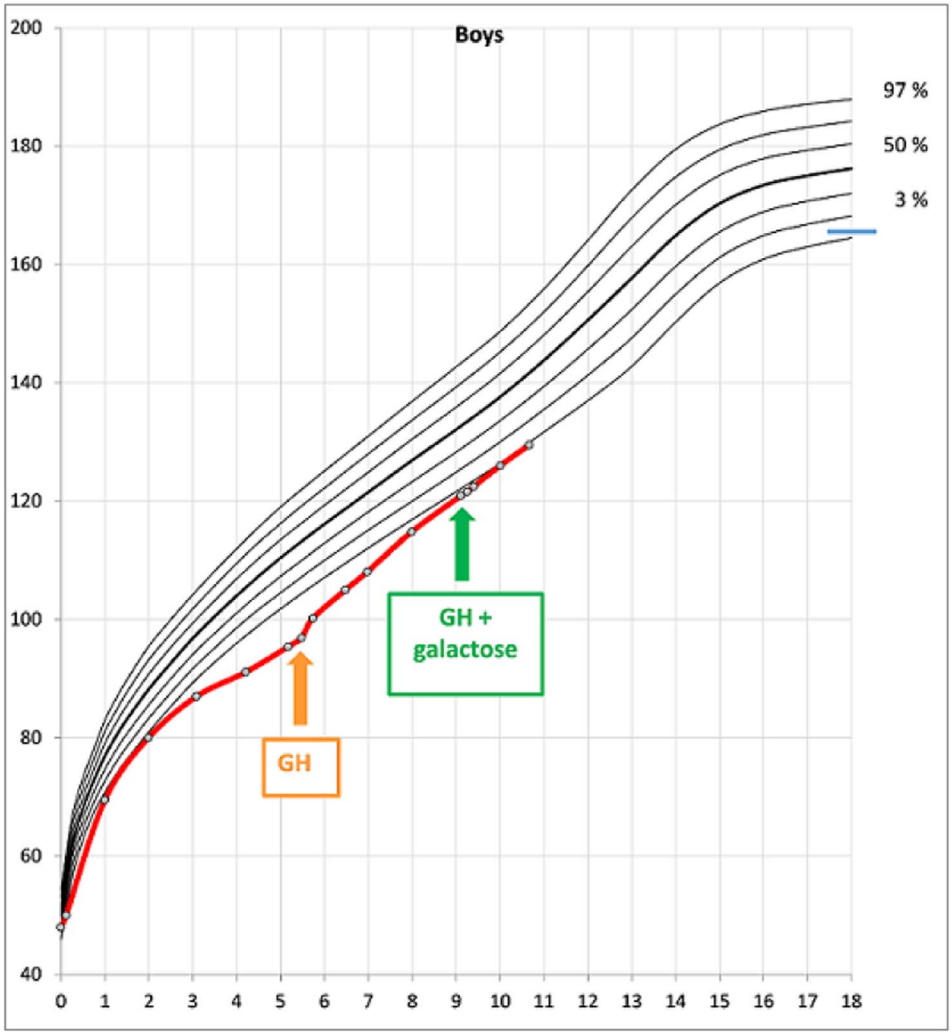

Fig. 4. Body height entered in growth curves for Turkish children aged 0 to 18 years according to reference values [10].
At the age of 5 6/12 years, the patient was introduced to growth hormone therapy (orange) gradually increasing the dosage up to 1 mg per kg body weight. Growth rate was improved and catch-up growth was observed. Additional galactose intake did not show further improvement (green). The patient's calculated target height is indicated by a blue line.

Other parameters, such as serum transaminases and antithrombin III rates, were reduced and remained within physiological ranges most of the time. After supplement interruption, values returned to pretreatment ranges (GOT 146 U/L (< 50 U/L), GPT 61 U/L (< 40 U/L)) and improved quickly after the restart of dietary galactose supplementation at a daily dosage of 1 g per kg body weight (GOT 44 U/L (< 50 U/L), GPT 15 U/L (< 40 U/L)). However, transient elevations of serum transaminases were observed intermittently during therapy at the standard dosage.

3.6. Growth hormone therapy

Growth rate was low since birth and remained below the 3rd percentile during early childhood (Fig. 4). Growth hormone therapy had a beneficial effect with catch-up growth reaching the 3rd percentile. Galactose did not cause further improvement of the growth rate during the observed interval.

3.7. IGF ternary complex analysis

Whole sera western blots showed typical doublet band for IGFBP-3 (glycosylation isoforms) at about 38–40 kDa, a faint band at about 36 kDa (unknown) and a major proteolysed IGFBP-3 band at about 30 kDa. Analysis revealed normal patterns with no difference among the samples (Supplementary Fig. 11).

In the purified IGFBP-3 western blot, the untreated patient sample (P1) had an additional band underneath the 30 kDa proteolysed band in the purified IGFBP-3, possibly the amino-terminal fragment IGFBP-3 [1–159] [14] (Supplementary Fig. 12). This fragment is expected to contain glycosylation at sites 1 and 2 (N89 and N109), in pretreatment sample P1 possibly differently glycosylated. It was absent in the controls and appeared to decrease when the patient was treated. However, it was not evident in P1 whole serum.

Mass spectra of tryptic glycopeptides from IGFBP-3 both, before and during therapy, did not show abnormally glycosylated species (Fig. 5).

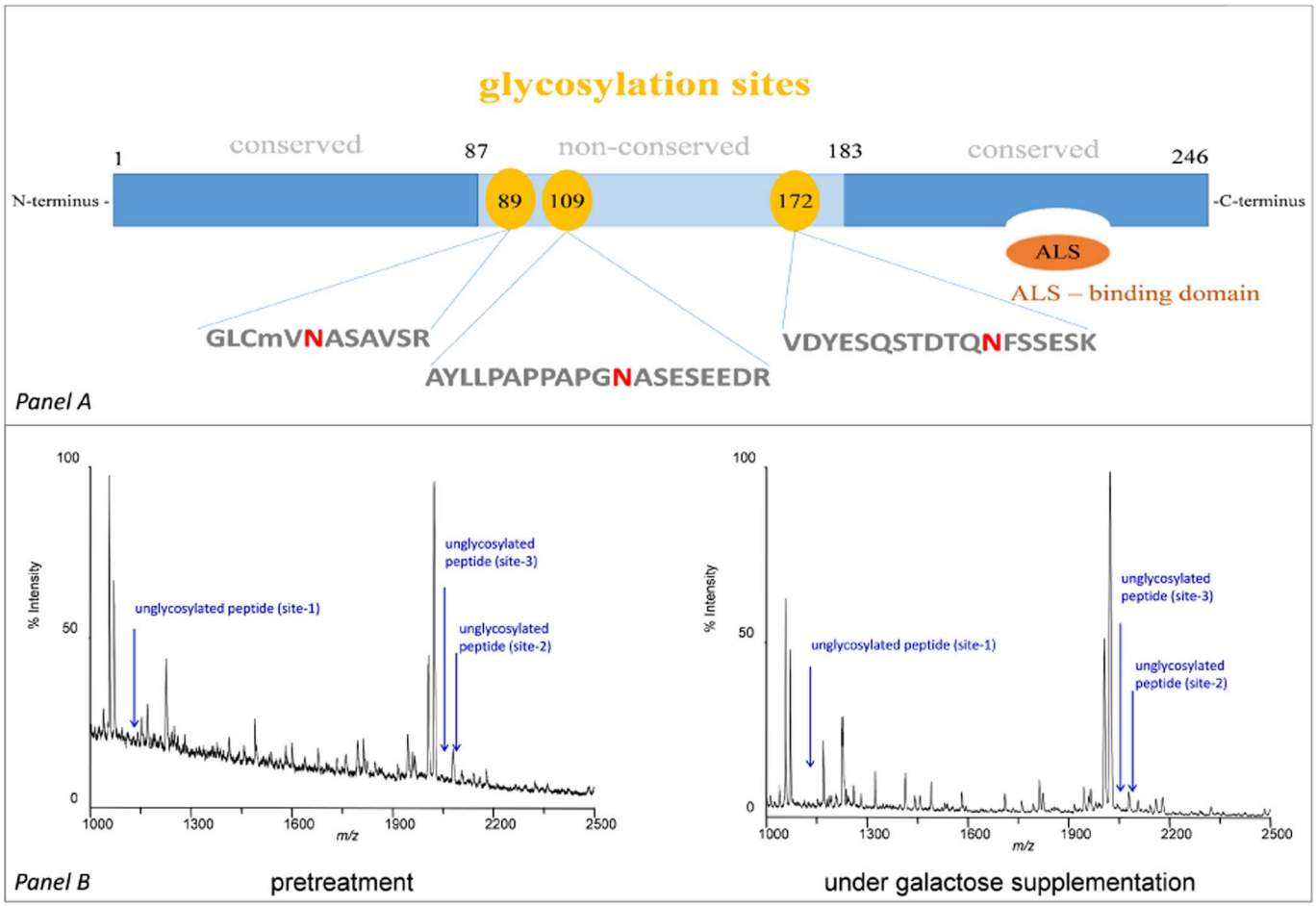

Fig. 5. Panel A: Schematic representation of IGFBP-3 structure showing glycosylation sites and ALS binding domain. The glycoprotein IGFBP-3 is an important component of the ternary IGF transport complex (IGF-I/IGF-II, IGFBP-3, ALS) determining the bioavailability of the IGFs [11]. The three N-glycosylation sites are located in the non-conserved central or linker domain, while the binding site for ALS is located in a highly conserved C-terminal domain [12]. Hypoglycosylated IGFBP-3 shows increased cell binding activity compared to normally glycosylated protein [13]. Since the same basic amino acids required for cell binding are also responsible for ALS binding, the competition between cell surface molecules and ALS for the IGFBP-3 binding domain presumably leads to dissociation of the ternary IGF-IGFBP-3 complex [11].
Panel B: Mass spectra of IGFBP-3 in patient's serum before and under galactose supplementation. Mass spectrometry of IGFBP-3 did not detect unglycosylated peptides, neither before nor under galactose supplementation.

4. Discussion

Galactose supplementation has been proposed as a treatment option for PGM1 deficiency with reports on favorable effects regarding protein glycosylation, endocrine malfunctions, hypoglycemic episodes and growth retardation [1,15,16].

The results of our single case study question the efficacy of the previously recommended therapeutic regimen and add further important details to the already varied phenotype observed in PGM1-CDG.

4.1. Effects of galactose therapy

In our patient, glycosylation was not restored completely by treatment with the current standard dosage of 1 g galactose per kg bodyweight per day [15,16]. Even higher doses of up to 2.5 g per kg body weight per day were not successful in correcting glycosylation permanently.

In SLC39A8 deficiency, a disorder of manganese transport and glycosylation, daily galactose supplementation was increased up to 3.75 g per kg body weight resulting in normalization of the glycosylation profile without any observable side effects [17]. Given these findings, it is possible similar doses might be needed in PGM1 deficiency in order to increase the UDP-galactose pool sufficiently. This might achieve the desired correction of serum protein glycosylation and needs to be evaluated in the future. However, high doses of galactose may lead to disruption of the Leloir pathway of galactose metabolism and the accumulation of toxic metabolites, which is why clinical application needs to be well-considered [20].

Furthermore, additional uridine substitution showed no positive effect on our patient. This is in contrast to previously reported findings obtained on cultured human fibroblasts in which uridine substitution was able to improve glycosylation [1]. Besides, negative effects of long-term uridine administration were observed in murine models. Notably, long-term uridine application induced glucose intolerance and fatty liver disease [22]. These findings warrant cautious application of additional uridine substitution in PGM1 deficiency, since the potential effects of uridine application might worse pre-existing symptoms of PGM1 deficiency.

Similarly to previously reported cases [16], levels of initially elevated transaminases improved under galactose intake. Still, transient elevations were observed intermittently during long-term surveillance. This fluctuation might also respond to higher doses of galactose as suggested above.

4.2. Long QT Syndrome in PGM1 deficiency — first description and possible link with glycosylation

Cardiac symptoms observed in congenital glycosylation disorders

are usually limited to structural heart disease, most often dilated cardiomyopathy [24]. To our knowledge, our patient presenting with a QTc of 534 ms (reference < 440 ms) is the first case of Long QT Syndrome (LQTS) associated with an inborn error of glycosylation. LQTS is a channelopathy characterized by a prolonged ventricular repolarization period of the action potential [18]. Correspondent genetic mutations in common LQTS genes were excluded.

Norring et al. already suggested a link between abnormal N-glycosylation and consequently affected electrocardial signaling in CDG [19]. Recent studies now illustrate the impact of aberrant sialylation on cardiac ion channel gating and action potential. In vitro data combined with in silico modeling showed that reduced sialylation alters potassium and sodium currents leading to prolonged duration of cardiac action potential and a shortened refractory period [21].

Thus, the Long QT Syndrome might be attributable to hypoglycosylation in PGM1 deficiency. The link between hypoglycosylation and an impaired conduction system of the heart is highly relevant for screening and prophylactic therapy in PGM1 deficient patients.

4.3. Growth retardation in PGM1 deficiency — need for further research

Most PGM1 deficient patients present with growth retardation and show reduced levels of IGF-I and its binding protein IGFBP-3 [1]. IGF-binding proteins carry the majority of IGFs in the circulation thereby determining bioavailability and extravascular determination [7]. Up to date, deficient glycosylation of those binding proteins, such as IGFBP-3, was presumed to cause reduced growth hormone complex stability, resulting in decreased half-life and concentration in PGM1 deficiency and consequently growth failure [1]. MPI-CDG patients suffering from growth retardation were successfully treated with mannose supplementation improving protein glycosylation, growth hormone levels and body height [23]. However, we did not observe any positive effects of galactose substitution on the growth of our patient.

We employed mass spectrometry of the insulin-like growth factor complex component IGFBP-3 in order to find evidence regarding the current theory of growth retardation in PGM1 deficiency. Analysis detected neither unglycosylated peptides containing glycosylation site-1, or 3, nor abnormal glycoforms at the three glycosylation sites. Thus, contradicting former hypothesis, sole hypoglycosylation of the growth factor complex component is not a suitable explication for growth retardation in PGM1 deficiency. In fact, it appears to be a complex etiology compromising glucose metabolism as well as various glycoproteins involved in the hormone cascade [25].

However, mass spectrometry appears to be a very useful analytical method to map the glycoprotein profile of each CDG patients in order to characterize the individual deficit and – based on that – evaluate effects of supplementary therapy.

5. Conclusion

The results of this single case study stress the need for individualized therapy in PGM1 deficiency. In our patient, the current standard dose of galactose did not achieve complete normalization of glycosylation as well as other laboratory parameters. In addition, the previously suggested pathomechanism of growth retardation in this disorder seems to be more complex than thought and might in fact not be due to abnormal glycosylation of IGFBP3. Finally, Long QT Syndrome is a novel phenotypical feature of PGM1 deficiency and should be regarded as a potentially life threatening manifestation of this inborn error of metabolism.

Abbreviations

PGM1	phosphoglucomutase 1
CDG	congenital disorder of glycosylation
ZASP	*Z*-band alternatively spliced PDZ motif protein
IEF	isoelectric focusing
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide-gel
HPLC	high performance liquid chromatography
ESI-MS	electrospray ionization mass spectrometry
LQTS	Long QT Syndrome
IGF	insulin-like growth factor
IGFBP-3	insulin-like growth factor-binding protein-3
GOT	glutamate-oxaloacetate transaminase
GPT	glutamate-pyruvate transaminase
GLDH	glutamate dehydrogenase
QTc	corrected QT interval
LVed	left ventricular end-diastolic diameter
MPI-CDG	Mannosephosphate Isomerase-Congenital Disorder of Glycosylation
PMM2-CDG	Phosphomannomutase 2-Congenital Disorder of Glycosylation
rhIGF-I	recombinant human Insulin-like growth factor-I

Declarations

Ethics approval and consent to participate

This study is a therapy on an individual basis and was approved by the local bioethics committee (Ethik Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität) on May 31, 2013.

Consent for publication

A consent for publication was obtained from the patient's parents.

Competing interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgmr.2017.07.010.

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