News on Clinical Details and Treatment in PGM1-CDG

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Abstract Phosphoglucomutase 1 deficiency has recently been reported as a novel disease that belongs to two different classes of metabolic disorders, congenital disorders of glycosylation (CDG) and glycogen storage diseases.

This paper focuses on previously reported siblings with short stature, hypothyroidism, increased transaminases, and, in one of them, dilated cardiomyopathy (DCM). An intronic point mutation in the PGM1-gene (c.1145-222 G>T) leads

to a complex alternative splicing pattern and to almost complete absence of PGM1 activity.

Exercise-induced muscle fatigue, chest pain, and rhabdomyolysis persisted into adulthood. Fainting occurred during the first minutes of strong exercise due to glucose depletion and serum heart troponin was increased. A second wind phenomenon with an improvement in exercise capacity after some minutes of training was observed. Regular aerobic training improved fitness and helped to avoid acute damage. DCM improved during therapy.

Glycosylation deficiency was most prominent in childhood. Glycosylation improved with age and further improved with oral galactose supplementation even in adulthood. Optimal improvement of glycosylation-dependent phenotypes should be achieved by early and permanent galactose treatment.

However, in case of mutations in ZASP, DCM can develop as a consequence of impaired binding of PGM1 to the heart-specific isoform of ZASP, independently of overall glycosylation efficiency. Thus, even if mutations in PGM1 impair the function of the ZASP-PGM1 complex, supplementation of galactose cannot be expected to restore that function. Therefore, knowledge of PGM1 deficiency in a patient should prompt surveillance of early signs of DCM and specific treatment if necessary.

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Abbreviations

CDT	Carbohydrate-deficient transferrin
DCM	Dilated cardiomyopathy
ER	Endoplasmic reticulum
FS	Fractional shortening
HPLC	High-performance liquid chromatography
IEF	Isoelectric focusing
IGF-1	Insulin-like growth factor 1
LVIDD	Left ventricular internal dimension in diastole

PGM1	Phosphoglucomutase 1
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
TF	Transferrin
ZASP	Z-band alternatively spliced PDZ-motif protein

Introduction

N-glycosylation is a common cotranslational modification of proteins and starts with the preassembly of oligosaccharides on dolichol, a lipid anchor in the ER membrane. The preassembled oligosaccharide is transferred en bloc by oligosaccharyltransferase to glycosylation consensus sites of the nascent protein. The glycoprotein is transferred to the Golgi by vesicular transport where the glycans are further processed. Congenital disorders of glycosylation (CDG) are a group of metabolic disorders affecting the synthesis and attachment (CDG-I) or the processing (CDG-II) of the glycan (Marquardt and Denecke 2003).

PGM1 deficiency is a novel treatable metabolic disorder and combines glycosylation abnormalities found in CDG-I and CDG-II (Tegtmeyer et al. 2014). Phosphoglucomutase functions in glycolysis and glycogenesis by catalyzing interconversion of glucose-1-phosphate and glucose-6-phosphate. Therefore, the liver is unable to maintain a normal glycemia, and muscles are not able to use glycogen as an effective energy source.

The clinical phenotype of PGM1 deficiency ranges from hypoglycemia, hepatopathy with elevated transaminases, cardiomyopathy, exercise intolerance, muscle weakness, rhabdomyolysis, growth retardation, hypogonadotropic hypogonadism to uvula bifida and/or cleft palate (Tegtmeyer et al. 2014).

The two patients described in this paper are siblings, a boy and a girl, mentioned as 5.1 and 5.2 in our previous publication (Tegtmeyer et al. 2014). Both show the typical clinical PGM1 phenotype. We present a more detailed analysis of the molecular defect, the biochemical consequences, and new observations on the effect of age on PGM1 deficiency-related glycosylation efficiency and discuss the specific treatment of DCM.

Materials and Methods

Patients

The parents of the patients are 2nd cousins (see Supplemental Fig. 1), healthy, and of normal height (mother: 165 cm, 60th percentile; father: 170 cm, 17th percentile; <http://iea.de/perz/>).

Patient 1, a boy, was born at term with normal body weight and length. After birth, a soft cleft palate was noted and closed by surgery 2 months later. Lumbar lordosis and disproportionate dwarfism were diagnosed at age 4, and disproportionate growth persisted to adulthood with an upper/lower body segment ratio of 1.43, i.e., more than 4 SD above the mean (Tanaka et al. 2004). At age 7, mild dilated cardiomyopathy was noticed. In recent years, during the first two minutes of strong exercise, he repeatedly experienced chest pain, breathing difficulties, and a feeling of nearly fainting. These symptoms disappeared with prolonged exercise and could be ameliorated by training. Three episodes of rhabdomyolysis with red urine were reported but only when strong exercise was started after a training pause of several weeks.

In the past, ravenous appetite sometimes occurred, and at the age of 12, a low glycemia (after overnight fasting) was found (2.8 mmol/l). The patient and his sister report a high consumption of milk products.

Currently, at the age of 25, the patient's height is 166 cm (<3rd percentile) with a normal body weight of 76 kg. The echogenicity of the liver is increased with reduced portal vein flow of 13 cm/s (reference mean $\pm$ SD = 20.4 ± 4.7 cm/s). Echocardiography showed a slightly enlarged left ventricle (LVIDD 60 mm, reference range is 41.5–57 mm, see supplement) with good systolic function (FS 31%, reference range ($\pm$ 2 SD) males 26.9–47.3%).

Patient 2, a girl, was born after 40 weeks of pregnancy with a length of 49 cm and a body weight of 3570 g. Immediately after birth, a Pierre–Robin sequence (with cleft hard and soft palate) and preauricular tissue were noted. A ventricle septum defect disappeared within the first year of life.

At the age of 18 months, dilated cardiomyopathy was diagnosed with a shortening fraction of 12% (Fig. 1). Captopril and metildigoxin increased the fractional shortening to the lower end of the normal range (Fig. 1). Metildigoxin was continued, and 18 months later, cardiac function was stable. However, in primary school, the cardiological situation got worse. Endomyocardial biopsies at 7.4 years did not show signs of acute or chronic myocarditis or virus infection, by histology/immunohistology and molecular biology. Storage diseases such as hematochromatosis, amyloidosis or M. Fabry were excluded. Some glycogen accumulation was shown by PAS staining in patient 2 but not patient 1. Cardiomyocytes with a considerable variety in size and hyperchromatic, pleomorphic nuclei and interstitial fibrosis were observed in patient 2 (Supplemental Fig. 2a–c). Electron microscopy of the biopsy revealed vacuolization, reduction in myofibrils, and fibrosis (Fig. 1a, b). Cardiac catheter examination disclosed mitral, tricuspid, and aortic valve insufficiency. She was listed for cardiac transplantation. After adding

Fig. 1 Dilated cardiomyopathy in patient 2. (a, b) Electron microscopy demonstrating vacuolization (red “V”), fibrosis (red “F”) and reduction in myofibrils. (c) Drug therapy and course of DCM. Reference range for fractional shortening (FS; gray shaded, mean over all age classes ± 2 SD: 26.1–47.2%) was obtained from 48 females

aged 8.1–17.8 (Punn et al. 2012). Dilated cardiomyopathy is represented as left ventricular inner diastolic diameter (LVIDD); a reference range (yellow shaded, mean ± 2 SD) for LVIDD was determined as described in supplemental material

L-thyroxin (for correction of hypothyroidism) and at 7.5 years enalapril, metoprolol, and hydrocortisone to her medication, she showed an enormous improvement, getting back to normal range of FS within 7 month (Fig. 1). However, LVIDD still was above the 2 SD range and in following years developed at such higher level in parallel to the normal growth of the left ventricle (Fig. 1).

Early dwarfism was recognized (Supplemental Fig. 3; however, not disproportionate, in contrast to her brother), and kyphoscoliosis. Currently, at the age of 21, the patient’s height is 150 cm (<3rd percentile) and weight is 51 kg (between 10th and 25th percentiles). Fasting hypoglycemia was found at several moments (e.g., 1.6 mM at 2 years).

Growth hormone was given to both patients for a short period of time (see Supplemental Fig. 3). Growth hormone deficiency had been excluded, but a reduced growth hormone sensitivity due to hypoglycosylation was assumed, with low IGF-1 (0.4 $\mu\text{g/ml}$ at 7 years, reference range 0.5–3 $\mu\text{g/ml}$).

For additional patient details, see Supplement.

IEF (Isoelectric Focusing) and SDS-PAGE (Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis)

IEF and SDS-PAGE of serum TF were performed as described (Nichues et al. 1998).

HPLC (High-Performance Liquid Chromatography)

HPLC of carbohydrate-deficient transferrin (CDT) was performed as described (Biffi et al. 2007).

Cell Culture

A skin biopsy was taken from the patients after informed consent of the parents. Fibroblasts were cultured in Dulbecco’s modified Eagle medium (Sigma), and 10%

Fig. 2 Age dependency of glycosylation efficiency and galactose treatment effect in patient 2. Isoelectric focusing and SDS-PAGE of serum transferrin of a PMM2-CDG patient, healthy control (C) and patient 2 (“P/7.4”: patient 2 at age 7.4 years). The numbers 0–4 at IEF indicate transferrin isoforms with four, three, two, one, or no sialic acid, while in SDS-PAGE 0, 1, and 2 indicate transferrin isoforms with 0, 1, or 2 occupied glycosylation sites. *Lower panel*: quantification by HPLC. *Horizontal blue and red shading* indicate the reference ranges for tetrasialotransferrin and hyposialotransferrin, respectively (Grundahl et al. 2012). Doubleband of patients disialotransferrin, known as “C2” variant (Helander et al. 2001), is explained in the

Supplement. Note change from strong glycosylation deficiency at young age (7.4 years) to milder glycosylation deficiency as adult (19.0 years) in all panels (also in her brother; not shown). Further improvement in glycosylation during galactose treatment is shown in the *gray-shaded* region around age 20. Galactose treatment consisted of 1 g/kg/day galactose powder dissolved in water and divided into 5 doses. Transferrin isoform relative concentrations were obtained by HPLC. Hyposialotransferrin is the sum of isoforms with 0–3 sialic acids (*red line*). Tetrasialotransferrin normalizes under therapy (*blue line*; pentasialotransferrin not shown)

Fig. 3 Glucagon test. Baseline glycemia was determined 15 min before the test. Glucagon injection at timepoint 0 was followed by determination of glycemia every 10 min

fetal calf serum (Invitrogen, Darmstadt, Germany) and 1% L-glutamine-penicillin-streptomycin (PAA) were added.

Cell Isolation

Fibroblasts (80–90% confluence) were washed with phosphate buffered saline (PBS) and trypsinized. Cell pellets were washed in PBS and after centrifugation for 5 min at room temperature put in HEPES–sucrose buffer (0.2 M sucrose, 0.02 M HEPES pH 7.3) containing protease inhibitors (complete, Roche; 10 µg/ml pepstatin A, 10 µg/ml PMSF).

Gene and Protein Analysis

For detailed mutation analysis of PGM1 and transferrin, see supplemental data. Also read the supplement for the Western Blot description.

Functional Tests: Glucagon Test and Galactose Kinetics

Blood samples were taken after an overnight fast to determine the initial values. For the glucagon test, 1 mg GlucaGen (Novo Nordisk Pharma GmbH, Mainz, Germany) was injected intravenously, and blood samples were taken every 10 min for 1 h. The kinetics of blood glucose has been tested.

Determination of galactose kinetics in whole blood was performed as described in Tegtmeier et al. (2014). Galactose powder was supplied by falcento AG, Kreuzlingen, Switzerland

Results

Analysis of Serum TF Glycosylation

Reduced glycosylation of transferrin in our patients, including an unusual mixture of CDG-I and -II patterns, has been discussed earlier (Tegtmeier et al. 2014). Subsequently, we discovered that both patients showed considerably improved glycosylation with increasing age. HPLC quantification demonstrates that hyposialylated transferrin isoforms (i.e., specifically those with two, one, or no sialic acid) are clearly further reduced by galactose treatment (Fig. 2). Tetrasialotransferrin increased to 87 % under galactose (normal range: 85.6–94% [mean $\pm$ 2 SD, Grundahl et al. 2012]). After stopping galactose supplementation, glycosylation efficiency returned to pretreatment values. For quantification of transferrin isoforms by HPLC of patient 1, see Supplemental Table 1.

Mutation analysis

The patients mutation in *PGM1* at g.55020 from G>T (c.1145-222 G>T) creating a new splice site has been described by Tegtmeier et al. (2014). While the normal donor splice site at exon 7 is not mutated, nevertheless the new splice site is used instead with high preference in splicing to exon 8 acceptor. However, beyond the published result, while, at first glance sequencing data looked somewhat noisy, a more detailed analysis demonstrated, that two new splice variants containing additional intron sequences occur (Exon 7a or Exon 7b, see Supplemental Fig. 4). While real-time quantification had demonstrated patients' total PGM1-mRNA level about 2% of normal (Tegtmeier et al. 2014), we demonstrate here that the regular transcript in fact is reduced to about 1/400, i.e., 0.25% of normal control. Details of the transcript analysis, the effect of nonsense-mediated decay, and quantification of the correctly spliced transcript are given in the supplementary material (Supplemental Figs. 4 and 5). Western blot does not show protein at all (Tegtmeier et al. 2014). Corresponding to low mRNA level, only less than 0.3% of normal PGM1 protein was expected.

Glucagon Test and Galactose Kinetics

Glucagon test and galactose kinetics were performed with patients and a healthy control. A diagnostic glucagon test was performed in order to check gluconeogenesis and to reveal abnormalities compared to our healthy control. The patient's fasting glycemia was lower than in our healthy control (healthy control: 108 mg/dl, patient 2: 66 mg/dl and patient 1: 78 mg/dl), and glucose concentrations reached a lower level and showed a delayed reaction compared to our healthy control (Fig. 3). Since patients with a PGM1 deficiency cannot efficiently obtain glucose from their glycogen stores, the increase of blood glucose is probably mainly due to gluconeogenesis.

Discussion

PGM1 deficiency is a novel treatable metabolic disorder which combines CDG and glycogenosis. Regular supplementation of oral galactose shows a remarkable biochemical improvement of glycosylation, and complex carbohydrates stabilize blood glucose (Tegtmeier et al. 2014). We here report further data on the sib pair 5.1/5.2 of that publication. In particular, we observed that the serum TF hypoglycosylation was more pronounced in childhood than in adulthood (Fig. 2). A similar phenomenon of

pronounced hypoglycosylation in early childhood that improved over time and could be further improved by galactose supplementation has been observed in UDP-galactose transporter deficiency (Dörre et al. 2015). It can be argued that the growing organism has a higher demand for glycosylation of all those proteins of the growing body, while the adult needs to keep steady state only and limited substrate allows higher percentage of normal glycosylated proteins in steady state. Thus, for CDG that lead to reduced speed of glycan production, one might generally expect a stronger hypoglycosylation in children than in adults.

Improved glycosylation should also improve IGF1 function and growth (Tegtmeyer et al. 2014). In addition, mutations in *XYLT1* have been shown to cause short stature (Schreml et al. 2014). The encoded protein xylosyltransferase (XT1) is necessary to start proteoglycan production with the common linker: protein-Ser-O-Xyl-Gal-Gal-GlcA, i.e., requiring two galactose molecules. Thus, PGM1 deficiency causing low levels of activated galactose may promote short stature also via inefficient proteoglycan production. It is not clear yet how much different pathways contribute to short stature. It may be possible that different degree of CDG-I vs. CDG-II component and total glycosylation efficiency, as seen in both patients, depending on age and galactose supply (Fig. 2), affect the pathways differently. Such differences may also be related to the degree of disproportionate growth. In addition to galactose, puberty-adjusted growth hormone or rhIGF-1 therapy may further improve growth (Mauras et al. 2000). It has been demonstrated in more recent literature that the typical growth spurt during puberty is associated with a doubling of GH amplitude and corresponding increase in IGF-1. Most significant effects using therapeutic GH for treatment of short stature were obtained when this normal doubling of GH was also mimicked in therapy by increasing GH to 0.7 mg/kg b.w. per week (Mauras et al. 2000). Recently, it has been suggested that early installation of rhIGF-1 therapy may efficiently improve growth in another congenital disorder of glycosylation, PMM2-CDG (Miller et al. 2013). Therefore, early start of rhIGF-1 therapy and an increased dosing scheme during puberty may help to improve outcome.

The rationale for galactose treatment is that protein misglycosylation in PGM1 deficiency is caused by the decrease of UDP-galactose. Galactose supplementation provides additional galactose and fills up the UDP-Gal pool: Gal-1-P+ UDP-Glc→UDP-Gal+Glc-1-P (Tegtmeyer et al. 2014). Determination of galactose kinetics in whole blood was performed in order to see galactose absorption in a patient with PGM1 deficiency compared to a healthy control (Supplemental Fig. 6). Blood galactose was measured for patient 2 and healthy control during the test. A second galactose kinetic test was performed while under galactose treatment. After oral galactose consumption of 0.3 g/kg body

weight, whole blood values of the control increased up to 0.7 mmol/l, while patient 2 only showed concentrations of up to 0.2 mmol/l. Lower galactose peak concentrations in the patient may result from reduced absorption in PGM1 deficiency or from a stronger first pass effect in the liver so that an increase of galactose in the blood can almost not be measured. A permanent galactose treatment might fill up pools, and indeed under this condition, a galactose bolus resulted in higher galactose concentrations.

The reported feelings of discomfort during exercise on a bike in untrained condition were not correlated to electrocardiogram changes. However, on a treadmill, perceived exertion up to a point of muscle fatigue, chest pain, and breathing difficulties and exercise even beyond that point were similar as in patients with myophosphorylase deficiency (MD, McArdle's disease). McArdle's disease patients develop a second wind after 6–9 min of continuous exercise which results from an increased capacity for oxidative phosphorylation and an increased availability of extramuscular fuels (Haller and Vissing 2002). Since phosphoglucomutase deficiency and McArdle's disease both block the production of glucose from glycogen, the same second wind mechanism might be assumed. In McArdle disease, where glycogen usage is impaired in muscles only (defect of myophosphorylase), but not in the liver, it has been shown that during exercise, muscles use more blood born glucose and liver fills up the blood glucose. In PGM1-patients, however, also the liver cannot quickly deliver glucose from glycogen, so that increased use of blood born glucose by PGM1-deficient muscles meets reduced possibilities of PGM1-deficient liver to stabilize blood glucose, resulting in acute reduction of blood glucose. Thus, there is strong evidence that hypoglycemia, which already may occur in PGM1-patients without doing strong exercise by simply overnight starving (Tegtmeyer et al. 2014), will be exaggerated by strong exercise and can explain the fainting experienced by our patient. Fainting did not occur on a cycle ergometer but only on a treadmill. Generally, heart rate is higher on a treadmill than with cycling (Tsintzas et al. 2003), and blood glucose falls in the first minutes on a treadmill even stronger than at cycling, causing a nearly fainting in our patients.

Dilated cardiomyopathy can result from mutations in the protein ZASP (Vatta et al. 2003). An association of mutations in the ZASP protein (exon 4, 6, or 10) and the binding of PGM1 was first described by Arimura et al. and suggested an involvement of a deficient ZASP-PGM1 interaction in the pathogenesis of dilated cardiomyopathy (Arimura et al. 2009). In patient 1, we could now demonstrate that under strong exercise on a treadmill that lead to rhabdomyolysis, also the marker for damage of the heart muscle, troponin I, increased to a level at the warning threshold for myocardial infarction (0.04 ng/ml, peak

extrapolated with value at timepoint of blood sampling – about 1 week after exercise – to the time after exercise). Severe DCM can be effectively treated with standard medication; however, in addition, improvements of citrate cycle by anaplerotic supplements and training, both improving oxidative energy production, are suggested to reduce dependency on PGM1-ZASP interaction and thus to reduce likelihood for developing clinical relevant DCM. Indeed, we now discovered that rhabdomyolysis occurred at a specific strong level of exercise but only if there was a training pause of several weeks, and the patient observed that regular (moderate) training had a protective effect.

Regular supplementation with oral galactose induced a considerable biochemical improvement of glycosylation. Early detection, e.g., with the diagnostic scheme for PGM1 deficiency created by Tegtmeier et al. (2014), and early galactose supplementation can ameliorate some aspects of this disease. We discussed earlier that simply knowledge of PGM1 deficiency may allow to prevent some consequences, e.g., rhabdomyolysis and sudden death by guidance to avoid strong exercise. However, by regular surveillance, it will also be possible to detect signs of DCM development early and to initiate a specific therapy to prevent clinical obvious DCM.

Compliance with Ethics Guidelines

Author Contributions

Esther Schrapers did most of the experiments, retrieved the data from decades, analyzed data, drafted, and revised the manuscript.

Laura C. Tegtmeier was involved in several experiments, e.g., galactose kinetics.

Gunter Simic-Schleicher discovered the patients and provided many data.

Volker Debus provided the data on DCM.

Janine Reunert supported and supervised experiments.

Sebastian Balbach was involved in glucagon test and galactose kinetics.

Karin Klingel did light and electron microscopy incl. interpretation.

Ingrid Du Chesne was involved in analysis of mutation.

Anja Seelhöfer supported detailed analysis of transcript.

Manfred Fobker analyzed the clinical chemistry data.

Thorsten Marquardt supervised the study, drafted, and revised the manuscript.

Stephan Rust supervised the study, supported detailed analysis of transcript, analyzed data, drafted, and revised the manuscript.

Thorsten Marquardt and Stephan Rust have contributed equally to the manuscript.

All authors contributed to and reviewed the manuscript.

Conflict of Interest

Esther Schrapers, Laura C. Tegtmeier, Gunter Simic-Schleicher, Volker Debus, Janine Reunert, Sebastian Balbach, Karin Klingel, Ingrid Du Chesne, Anja Seelhöfer, Manfred Fobker, Thorsten Marquardt, and Stephan Rust declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for inclusion in the study.

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