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Case Report

Individual Treatment Trial of *PIGV*-Associated Mabry Syndrome with D-Mannose in a Young Child

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Abstract

We describe the first individual treatment trial with D-mannose in a young girl with PIGV-CDG. PIGV-CDG belongs to the GPI anchor deficiencies leading to intellectual disability, dysmorphic features, epilepsy, and, less frequently, organ malformations. A hallmark of the GPI anchor deficiencies is the elevated serum alkaline phosphatase (AP). Our patient carried the germline homozygous *PIGV* variant c.1022C>A, p. (Ala341Glu), the most commonly reported pathogenic variant leading to *PIGV*-CDG so far. We aimed to improve the impaired enzymatic function of *PIGV* through elevated substrate levels by giving D-mannose orally. We monitored the clinical status, developmental progress as well as serum AP levels. Our patient experienced no side effects. Standardized developmental testing showed better developmental progress during the 21-month treatment period with D-mannose than in the 12 months following the discontinuation of treatment. The D-Mannose treatment might have had a positive effect on the development of our patient with PIGV-CDG.

More Information

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Introduction

Pathogenic biallelic germline variants in *PIGV* lead to the PIGV-congenital disorder of glycosylation (PIGV-CDG) also known as Hyperphosphatasia with mental retardation syndrome (HPMRS-1, OMIM #239300). It belongs to the genes associated with the clinical entity of Mabry syndrome. Affected individuals exhibit developmental delays, intellectual disability, dysmorphic features (hypertelorism, flat facial profile, brachytelephalangy), elevated serum alkaline phosphatase (AP) (hyperphosphatasia), epilepsy, and less frequently

Hirschsprung disease, organ malformations such as renal or anorectal malformations [1].

PIGV encodes the mannosyltransferase II that is involved in the synthesis of the GPI anchor by catalyzing the attachment of the second mannose to the GPI anchor [2]. Germline variants leading to PIGV-CDG involve transcripts with impaired enzyme function [3] leading to deficient GPI anchor synthesis and therefore reduced binding of the GPI anchor substrates. One of these substrates AP leads to the characteristic elevated serum AP level. Rodríguez de los Santos, et al. established a mouse model for inherited GPI anchor deficiencies with a patient-specific hypomorphic mutation in *PIGV.* This mouse model exhibits a motor and cognitive phenotype as well as alterations in sociability, mirroring the human phenotype [4].

Case presentation

Our patient was born mature (40 + 4 weeks of gestation) with a slightly low birth weight (2900 g, 7th percentile). At the age of 6 days, she developed a BRUE (brief resolved unexplained event) with cyanosis as well as marked hypotonia and was diagnosed with a hypoplastic aortic arch and aortic isthmus stenosis. She was delayed in her development in all trajectories (walking at the age of 18 months independently, grasping with the full hand, and using 2 meaningful words at the age of 30 months) and showed pronounced restlessness as well as muscular hypotonia. Later, she developed febrile seizures (3 episodes in the 2nd year of life), and EEGs showed a high beta activity. NGS panel analysis showed the homozygous variant c.1022C>A, p. (Ala341Glu) in the *PIGV* gene, the so far in the literature and in ClinVar most commonly reported pathogenic *PIGV* variant (ClinVar# 1284). Chromosome analysis as well

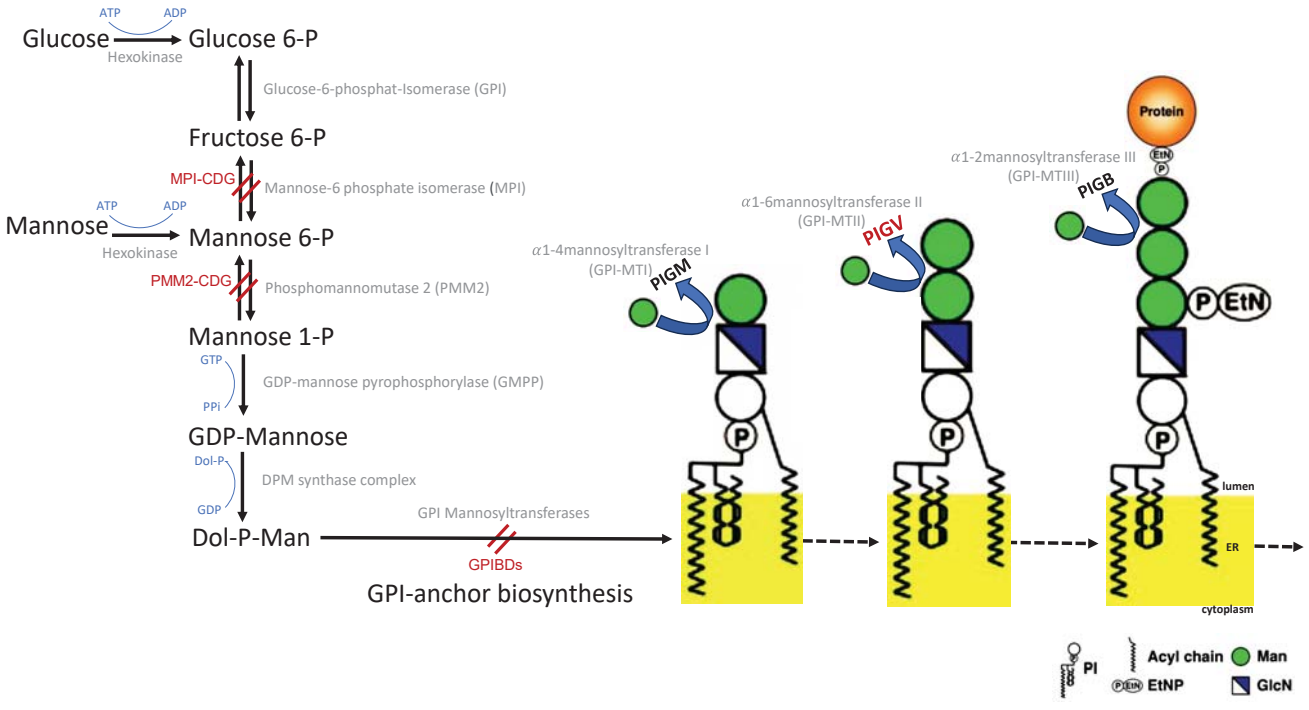
as array CGH were normal. She was presented first to our ambulatory syndrome clinic at the age of 30 months with the typical facial features of patients with Mabry syndrome including a flat facial profile, prominent sutura metopica, hypertelorism, broad nasal bridge, wide mouth, interdental spaces, and nail dysplasia without brachytelephalangy [5,6]. Fasting serum alkaline-phosphatase (ALP) was elevated: 1008-1144 U/l, mean 1073 U/L, being the key laboratory indicator of the compromised GPI biosynthesis.

Treatment and discussion

The biosynthetic pathway for GPI is mediated by the sequential addition of glycosyl residues and other components to the phosphatidylinositol (PI). Therefore, inborn GPI deficiencies (IGDs) belong to the large group of congenital disorders of glycosylation (CDGs). For 2 types of CDG syndrome, mannose phosphate isomerase- (MPI) and phosphomannomutase 2 (PMM2) deficiency, patients benefit from dietary supplementation of mannose [7-9]. In MPI deficiency, exogenous mannose can bypass the reduced endogenous Man-6-P production through phosphorylation by hexokinase (Figure 1). In PMM2 deficiency, where Man-6-P is the substrate, increasing mannose concentrations can counteract the reduced enzyme activity. Man-1-P, the product of PMM2, is further transformed by GDP-mannose pyrophosphorylase (GMPP) into GDP-mannose, which itself is the substrate of dolichol-phosphate mannosyltransferase (DMP). The product of DMP is Dol-P-Man, which is transferred by mannosyltransferases of the GPI biosynthesis pathway to build the common core of the GP-Ianchor [10,11]. Similarly, we hypothesized, that an increased substrate (D-mannose) concentration could result in increased levels of Dol-P-Man in patients with a hypomorphic mutation in *PIGV* as well, although potentially in a lesser effect, because of the wildtypes in PMM2, GMPP, and DMP in the previous biosynthesis steps.

D-mannose is a widely used substance to prevent cystitis and urinary tract infections. It is available over-the-counter, can be taken orally, and has a generally mild side effect profile with the most common side effect being diarrhea. A serious side effect was published only in association with intravenous administration of high-dose, 1 g/kg/day D-mannose [12]. Also, there is thorough pediatric experience with the usage of D-mannose based on the metabolic treatment of children with MPI and PMM2 [13-15].

After informed consent of the parents we initiated the D-mannose therapy with a slow stepwise dose escalation to avoid diarrhea, starting at 100 mg/kg/day. We targeted 3 doses: 0,6 g/kg/day, 0,8 g/kg/day, and finally 1 g/kg/day. Based on the parental report, our patient was more alert and concentrated in the first few months of treatment receiving 0,6 g/kg/day of Dmannose. She made small developmental steps throughout the 21-month treatment period, followed by a marked slowing of her developmental velocity after discontinuing D-mannose



(modified from Kinoshita T *et al* 2008, Niehues R & Hasilik M *et al* 1998, Taday R *et al.* 2020)

Figure 1: Mannose metabolic pathway and main steps in the GPI anchor biosynthesis featuring mannose residues. For 2 types of CDG syndrome, mannose phosphate isomerase- (MPI) and phosphomannomutase 2 (PMM2) deficiency, mannose can bypass the enzymatic defect and contribute to the GDP-mannose pool. In the further biosynthetic pathway of GPI Dol-P-Man is transferred by the mannosyltransferases I-III (PIGM, PIGV and PIGB) to build the common core of the GPI-anchor.

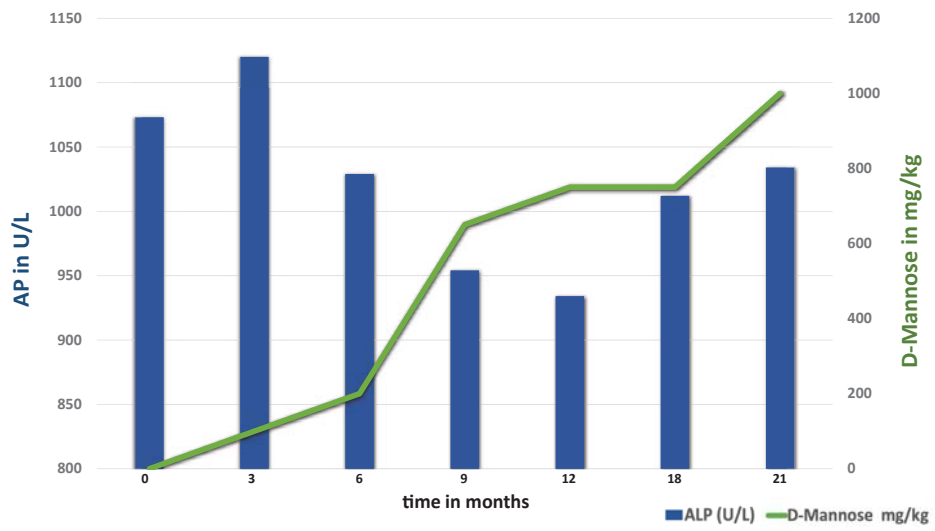


Figure 2: Changes in serum AP in relation to D-Mannose dose given throughout the treatment period Serum AP showed no clear decrease with higher doses of D-mannose given.

based on the standardized developmental assessments (Münchener Funktionelle Entwicklungsdiagnostik, MFED, *Munich functional developmental assessment*). At the start of the therapy, she showed a developmental age of 14 - 19 months at the biological age of 30 months. At the end of the D-mannose therapy, she showed a developmental age of 15 - 24 months at the biological age of 50 months. Upon the follow-up 1 year after discontinuation of D-mannose, she showed a developmental age of 15-24 months. She experienced no epileptic seizures throughout the complete period in our care. D-mannose was well tolerated, and no diarrhea or other side effects were observed. The complete treatment period was 21 months. Fasting serum AP was measured repeatedly throughout the treatment trial. The lowest level of AP was 934 U/L (13% decrease from the starting mean level of 1073 U/L), measured under the dose 0,6 g/kg/day after 6 months of administration, and was paradoxically slightly higher under higher doses of D-mannose: 1012 U/L under 0,8 g/kg/day as well as 1034 U/L under 1 g/kg/day (Figure 2).

Conclusion

We described the first individual treatment trial with D-mannose in a young patient with PIGVCDG. There were no side effects reported under treatment. Our patient showed better developmental progress in the 21-month period under D-mannose than in the 12-month period after discontinuing treatment. Long-term D-Mannose treatment might have positive effects on the development of patients with PIGV-CDG. Further studies, especially including more patients as well as regarding dose-finding, are required to allow a clearer judgment on the effect of D-mannose treatment in PIGV-CDG.

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