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Mannose phosphate isomerase-congenital disorder of glycosylation leads to asymptomatic hypoglycemia

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ABSTRACT

Background: Mannose phosphate isomerase deficiency-congenital glycosylation disorders (MPI-CDG) is a rare autosomal recessive disorder caused by pathogenic variants in the *MPI* gene and characterized by digestive, hepatic, and endocrine-related symptoms. Herein, we reported a case of a 4-month-old baby with MPI-CDG confirmed by genetic testing.

Case summary: Based on the age of the child and the present clinical symptoms (feeding difficulties, intractable diarrhea, vomiting, hepatosplenomegaly, recurrent hypoglycemia, coagulation disorder, and hypoproteinemia under the premise of anti-infection therapy), congenital glycosylation disorder was suspected, which was then confirmed by genetic testing. Her father carried a heterozygous deletion variant of exons 1–2 of the *MPI* gene, while her mother carried a heterozygous variant of C. 422C > T variant. It was suspected that a biallelic pathogenic variant of the *MPI* gene caused the CDG.

Conclusion: MPI-CDG should be considered in infancy with unexplained hypoglycemia and recurrent digestive and endocrine system involvement. Also, if evident symptoms are present, a gene examination should be performed, as this could speed up the diagnosis assuring timely treatment.

1. Introduction

N-linked Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndromes, are a group of multisystem autosomal recessive disorders caused by enzymatic defects in the synthesis and processing of oligosaccharides on asparagine (N)-linked glycans or glycoproteins [1]. CDG are a genetically and clinically heterogeneous group of over a hundred diseases classified as (a) protein N-glycosylation defects, (b) protein O-glycosylation defects, (c) glycolipid and GPI-anchored synthesis defects, and (d) multiglycosylation pathways [2]. Clinical features of CDG are characterized by slow development, severe liver disease and neurological signs, while mannose phosphate isomerase deficiency-congenital glycosylation disorders (MPI-CDG) are among the few CDG with no or mild neurological involvement.

MPI-CDG was first discovered by Jaekenet and clinically characterized by protein-losing enteropathy, hypoglycemia, congenital hepatic fibrosis, and antithrombin deficiency [3]. It is the CDG that can be treated with oral mannose (CDG-Ib, OMIM602579), and is due to deficiency of an enzyme located in the cytoplasm, which catalyzes the isomerization of fructose-6-phosphate to mannose-6-phosphate. Mannose can also enter cells from free mannose via a specific transporter [4]. Thus, mannose supplementation has been successfully used to treat MPI deficiency.

MPI-CDG has been reported in a few patients compared to other types of CDG; yet, it is also believed that many patients remain undiagnosed. Serum transferrin isoelectric focusing (IEF) method remains the preferred choice for the diagnosis of n-glycosylated disorders associated with sialic acid deficiency [5], but its inability to differentiate between types of N-linked CDG allows for a definitive diagnosis by genetic testing.

Herein, we reported a case of a 4-month-old baby with MPI-CDG confirmed by genetic testing.

2. Clinical report

A 4-month-old female infant was admitted to the hospital for a duration of 20 days due to hypoglycemia. Multiple fasting blood glucose

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measurements revealed levels below 2.8 mmol/l, with random fluctuations ranging from 2.0 to 4.6 mmol/l. Her eating habits were generally normal, although she experienced diarrhea more than ten times per day in small amounts, without mucus or blood present. The patient exhibited appropriate mental status and was born full term with a GIPI (gastrointestinal polyposis index), scoring a perfect Apgar score of 10 at birth. She had a birth weight of 3150 g, body length of 63.0 cm, body mass of 16.1 kg, and BMI of 16.l kg/mˆ2; she could hold her head up but lacked the ability to turn over independently. Both parents were healthy and non-consanguineous (not closely related by blood), and there were no abnormalities reported during pregnancy. Physical examination findings include: weight measuring at the tenth to twenty-fifth percentile (wt:6.3 kg); height measuring at the twenty-fifth to fiftieth percentile (Ht:62 cm); normal cranial appearance with no abnormal facial features observed; liver palpable two centimeters below the rib cage exhibiting softness and sharp edges without any signs of tenderness upon pressure application; spleen palpable one centimeter below the rib cage. The biochemical examination upon admission revealed a serum insulin level of 8.01uIU/ml (2.6–24.9), glucose level of 3.63 mmol/L (3.9–6.1), C-peptide level of 2.22 ng/mL, blood β-hydroxybutyric acid level of 41.11umol/L, albumin level of 33.48 g/L, and total protein level of 49.5 g/L, with no other significant abnormalities observed. The final diagnosis was hyperinsulinemic hypoglycemia accompanied by impaired liver function, for which informed consent was obtained from the parents to retain a volume of 2 ml venous blood from both the child and parents for genetic-related examination.

One week post-discharge, the child presented with fever, poor appetite, and cough. She received treatment at an external medical facility for 7 days before being readmitted to our hospital. Physical examination revealed a weight of 6.4 kg (10th–25th percentile), height of 63 cm (25th–50th percentile), stable vital signs, diminished mental responsiveness, reduced skin elasticity and subcutaneous fat deposition; flat and soft fontanelle; normal skull appearance without any abnormal facial features; coarse breath sounds bilaterally without rales; unremarkable cardiac findings; flat and soft abdomen with the liver palpable 3 cm below the costal margin exhibiting a soft texture and sharp edges but no tenderness on palpation. The spleen was palpable approximately 1 cm below the rib cage. On admission, blood glucose level measured at 3.0 mmol/L prompting immediate feeding instructions to the family which were declined by the child who subsequently vomited. Thirty minutes later, blood glucose was retested at 3.8 mmol/L followed by continuous monitoring thereafter due to concerns of life-threatening complications. Three hours later, blood glucose dropped to critically low levels at 1.8 mmol/L necessitating urgent intervention for risk mitigation purposes after obtaining consent from the patient's family whereby administration of intravenous infusion containing 10 % glucose solution commenced at a rate of 5 mg/kg/min.

Due to food refusal and vomiting, a gastric tube was left in place and 60 ml of formula +20 ml of 10 % glucose water was administered nasally once every 2 h. Subsequently, the blood glucose fluctuated from 2.8 to 4.7 mmol/l, and when it was lower than normal, the blood glucose was maintained normal by oral sugar water and pumping 10 % glucose injection. At the same time, serum insulin was 15.53uIU/ml (reference range: 2.6–24.9), glucose was 2.7 mmol/L (reference range:3.9–6.1), C peptide was 4.69 ng/mL(normal range:1.1–4.4), and blood β-hydroxybutyrate was 41.11umol/L (normal range:30–300) (support: hyperinsulinemic hypoglycemia). The child also had a hypercoagulable state with 680*10ˆ9/L platelets (normal range:167–453) and 1.78 mg/l D-dimer ↑(normal range:0–0.55), and heparin sodium was taken to counteract platelet agglutination. The liver function test was low albumin, 23.60 g/L↓(normal range:39–54), with mild generalized swelling, 4 cm below the rib cage of the liver and 1 cm below the rib cage of the spleen, followed by albumin 5 g infusion. The clinical symptoms of the child improved slightly with the above treatment, but the reexamination indexes were still not optimistic.

Based on the child's age and current clinical symptoms (including feeding difficulties, intractable diarrhea, vomiting, hepatosplenomegaly, recurrent hypoglycemia, coagulation disorder, and hypoproteinemia under strict infection control measures), a suspicion of congenital glycosylation disorder arose which was subsequently confirmed through genetic testing.

During the follow-up period, oral mannose was effectively absorbed in the gastrointestinal tract at a dosage of 150 mg/kg/dose administered four times daily. The child's blood glucose levels remained stable within the range of 3.8–4.8 mmol/l. Notably, both diarrhea and ageusia resolved, while albumin levels and coagulation function gradually returned to normal ranges. Furthermore, there was a significant reduction in elevated serum transaminase levels.

As part of the treatment plan, the child received prescribed oral mannose therapy along with regular monitoring of liver and coagulation function.

The child was prescribed oral mannose therapy and regular liver and coagulation function tests.

2.1. Follow-up

When the baby turned nine months, her height was 67 cm (P3–10) and weight was 8 kg (P10–25). Her growth was behind that of normal children of the same age. She had no hypoglycemia or gastrointestinal discomfort but elevated serum transaminases in the indicators on regular follow-up. Her parents refused to perform other tests, such as transferrin.

2.2. Genetic testing

The affected child was found to carry two biallelic mutations in the *MPI* gene: NM_002435, exon 1–2 heterozygous deletion (exon1–2 del) and NM_002435, c.422C > T (p.A141V). Sanger sequencing and qPCR showed that the child's father carried the heterozygous deletion variant of exon 1–2 of the *MPI* gene, and the mother carried the c.422C > T heterozygous variant (Fig. 1A). The *MPI* gene exon 1–2 heterozygous deletion and c.422C > T were new and unreported variants. According to the criteria proposed by the ACMG, the *MPI* exon 1–2 deletion was classified as "Likely pathogenic" as evidenced by PVS1 and PM2_supporting (PVS1: this variant is an exonic deletion that may result in loss of gene function; PM2_supporting: the variant was absent from the controls databases), c.422C > T was also classified as "Likely pathogenic" as evidenced by PM2_Supporting and PM3 and PP3_Strong (PM2_supporting: the variant was absent from the controls databases; PM3: the loci are derived from the parents respectively, which is consistent with the inheritance pattern of recessive genetic disorders; PP3_Strong: multiple protein function prediction software such as REVEL, SIFT, PolyPhen_2, MutationTaster and GERP+ predict harmful results). AlphaFold was used to predict the protein structure of *MPI* (Fig. 1B). By analyzing the protein structure, we found that the variant c.422C > T (p.A141V) in *MPI* changed alanine to valine at the mutant site but did not change the structure of the hydrogen bond. Nevertheless, variations in the amino acid side chains may still affect the protein's function.

3. Discussion

MPI-CDG patients usually present with gastrointestinal symptoms, hypoglycemia, and congenital hepatic fibrosis without neurological involvement. The clinical manifestations of MPI-CDG were first reported by Pelleatier et al. [6]. Subsequently, Schollen and colleagues [7] identified a 1-bp insertion in the *MPI* gene in the same patient, confirming its compound heterozygosity and autosomal recessive inheritance. It was also confirmed that the MPI-CDG phenotype is caused by a mutation in the mannose phosphate isomerase gene on chromosome 15q24, which encodes mannose phosphate isomerase [7]. The *MPI* gene contains eight exons with a size of 5 KB [7]. The MPI gene is highly conserved between species, with 84 % homology between human and

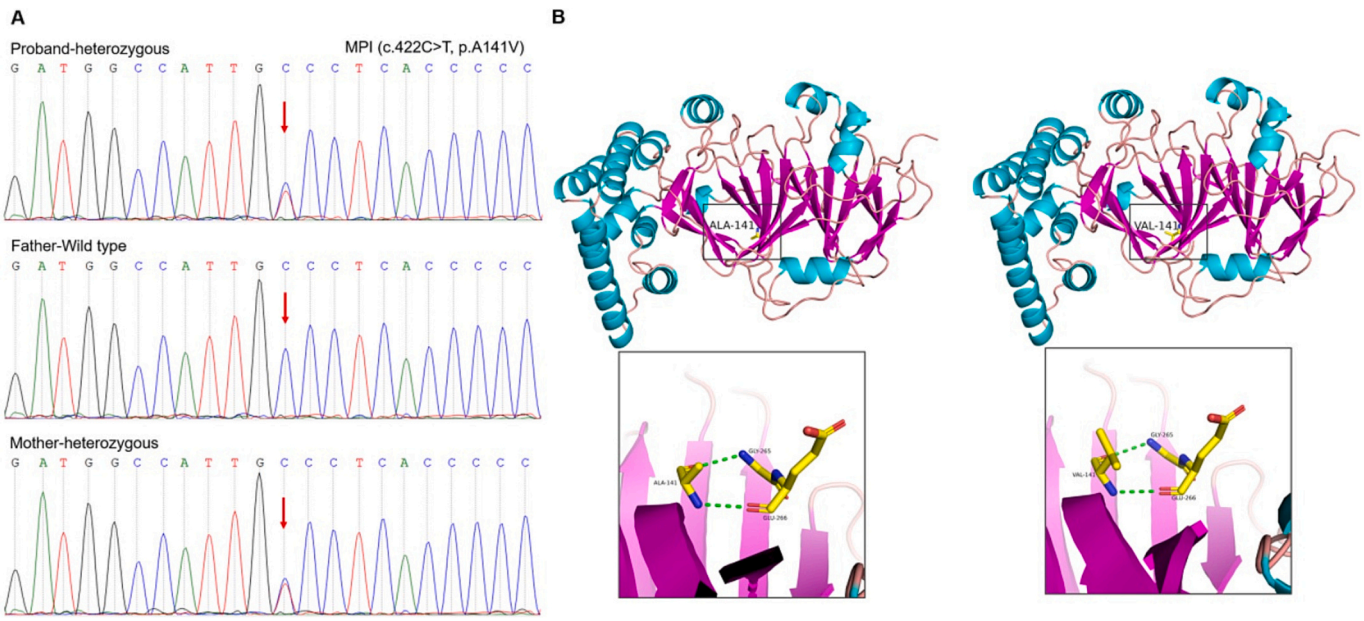

Fig. 1. Sanger sequencing of the trios confirmed the *MPI* variant and MPI protein modelling. (A) Patient: heterozygous mutation (NM_002435, c.422C > T, p. A141V), which was inherited from her mother. (B) Left, wild type (WT); right, the model of the A141V mutant. An expanded view of the wild and mutant types is shown at the bottom. Ala 141 formed two hydrogen bonds (green dashed lines) in the wild type with Gly 265 and Glu 266. In the mutant, valine replaced alanine, resulting in a change in the amino acid side chain but no change in hydrogen bonding.

mouse and 39 % with Candida at the protein level. Experimental animal studies have shown abnormalities in the formation of the yolk sac vasculature system in MPI knockout mice during embryonic life, as well as abnormal mannose and ATP levels in vivo [8].

Delonlay et al. [9] reported clinical, biological and molecular analysis of 26 patients with CDGI. Two MPI-CDG patients suffered from severe liver disease, protein-losing enteropathy and hyperinsulinemic hypoglycemia without neurological involvement [9]. In MPI-CDG, liver involvement is the most common typical triad of symptoms in MPI-CDG associated with digestive endocrine symptoms [10]. Only in two sisters described by Helander et al., the disease was found incidentally in adulthood and without symptoms such as liver and intestinal disease [11]. Involvement of the liver often presents as mild liver disease, hepatomegaly, and hepatic fibrosis. Mannose supplementation can improve clinical and biological parameters; however, patients can still develop progressive liver fibrosis [12]. The most important complications in adulthood are esophageal varices and portal hypertension. Jassenat et al. [13] described a case requiring liver transplantation for hepatopulmonary syndrome associated with portal hypertension, which was successful, with overall clinical improvement after transplantation, recovery of pulmonary function, and normalization of electrcofocal patterns, such as coagulation parameters and transferrin [13].

MPI-CDG has significant clinical heterogeneity. Westplat et al. reported brothers with the same genetic mutation; one died of cirrhosis at the age of 5 years, while the other had no further symptoms after childhood but did not receive treatment; he is currently living a normal life [14]. Hyperinsulinemic hypoglycemia(HH) has also been reported in MPI-CDG [15]. Still, the exact cause of hyperinsulinemia in CDG patients remains unclear. Some hypotheses include hypoglycosylation of membrane receptors, such as the flavourea receptor SURI, which is important for insulin release [16]. Hypoglycosylation of mouse pancreatic cells has also been described by Cabezasetal et al. to alter insulin secretion [17]. Mannose supplementation has shown good results in patients with hyperinsulinemic hypoglycemia(HH) and patients with unknown underlying causes of hypoglycemia [17]. However, excessive accumulation of mannose 6 phosphate (M6P) can lead to intracellular energy depletion, and the “honeybee effect” was first described by Delafuent et al. [18]. but when in excess, it inhibits the activity of hexokinase, glucose phosphate isomerase and glucose-6-phosphate dehydrogenase, decreasing glycolysis and leading to intracellular ATP depletion and subsequent energy depletion [19]. Oral mannose has no significant side effects, and Sharmaetal et al. recommended that mannose should be used with caution during pregnancy, although no embryonic deaths have been reported [20].

The gastrointestinal response of the children in this paper was not overly pronounced, but there was intermittent vomiting, persistent diarrhea and low food intake. Morena-Barrio et al. described patients with Crohn’s disease and MPI enteropathy present at one month, with typical clinical signs and histological manifestations, who received various anti-inflammatory treatments for 13 years with poor results, and whose symptoms resolved rapidly after the introduction of mannose treatment [21]. Martinhernandes et al. also mentioned the normalization of histological biopsies after mannose treatment in children with villi atrophy [22]. Yet, Pdelonglay et al. also described that heparin can be used as a substitute for mannose in some patients, especially in the treatment of enteropathy [23].

Those with symptoms related to their immune system have also been reported in MPI-CDG [24](Table 1). The patient presented with recurrent respiratory infections and abnormal IgM levels but none of the classic symptoms associated with MPI-CDG. Oral mannose therapy led to a fast improvement in serum IgM levels in the patient. Similar changes in serum IgM levels were reported in our patients, and a regular check was required after mannose supplementation. (See Table 2.)

Long-term follow-up of patients with MPI-CDG with significant symptoms in childhood and given mannose therapy, some of them remain normal with age into adulthood, but the long-term prognosis varies from person to person [25].

The patient’s characteristics, in this case, were as follows: [1] recurrent attacks of hyperinsulinemic-hypoglycemia and diarrhea since infancy; [2] elevated liver enzymes and prolonged coagulation; [3] hypoproteinemia and edema with proteins likely lost through the gastrointestinal tract; [4] a heterozygous missense mutation in deletion exons 1–2 and exon 4 (c. 422C > T) of the *MPI* gene that came from the parents separately, which is in accordance with autosomal recessive inheritance; [5] clinical symptoms were significantly improved by oral exogenous mannose. Based on the clinical manifestations and genetic

Table 1
Overview of Currently Known Mutations in MPI-CDG Patient.

Ref	PMI mutations and(or) enzymatic activity	Case number	Case age
Niehues R et al. [1998]	c.166-167insC,c.656G > A	1	11 m
Van Diggelen et al. [1998]	c.152 T > C,c.152 T > C	1	?
Babovic-Vuksanovic et al. [1999]	IVS4-1G > C,c.1252G > A	1	3 m
de Lonlay P et al. [1999]	c.764 A > G,c.1193 T > Cheterozygote mutations T255C and I398T	1	3 m
Westphal et al. [2001]	636G > A(R219Q),419 T > C (I140T) , 1131 A 3 G/636G > A (R219Q),419 T > C(I140T)	2	5y/ 2.5y
D. Penel-Capelle et al., [2003]	compound heterozygosity for the Y129C and R152Q mutations	1	7y
K. Mention et al. [2007]	carried one homozygote mutation, R295H,	1	2 m
R. Y. J. Tamminga et al. [2008]	c.656G > A (R129Q),	1	4y
Mirian C.H. Janssen et al.[2013]	c.455G.A/c.41 A.C	1	15y
Anders Helander et al.[2014]	c.656G > A,c.656G > A	1	32y
Asma Deeb& Abdulla Al Amoodi.[2018]	(p.Ala288Val) at the MPI gene Both parents are carriers	1	4y
Chris Mühlhausen et al.[2020]	c.655C > T/p.Arg219Trp, c.1178G > C/p. Gly393Ala.	1	15
Kinza Noman et al. [2020]	D131N (c.391G > A) mutation in the PM1 gene	1	6 m
Tawhida Y. et al. [2020]	c.487 A > T(p.K163X),c.656G > A (p.R219Q) /c.884G > A(p.R295H), c.1193 T > C (p.I398T)	2	2.5y/ 14 m
Patryk LipiNski et al. [2021]	c.1193 T > C(p.Ile398Thr/c.656G > A,(p.Arg219Gln)	2	2y/12 m
Diederik De Graef et al.[2022]	c.656 G > A (p.Arg219Gln) , c.170 G > T (p. Gly57Val)	1	11y
Siliang Lu et al. [2023]	exon 4 (c.455G > T, p.R152l) and an exon 7 (c.884G > A, p.R295H)	1	2y

Table 2
Oral mannose doses and side effects in MPI-CDG patients in literatures.

Publish Years	Author	Dose	Side effect
2019	de la Morena-Barrio ME [21]	1400 mg/ time, 2 times/ day	No adverse events
2021	Lebredonchel E [26]	170 mg/time, 4 times/day	No adverse events
2020	Abdel Ghaffar TY [27]	1 g/kg/day	No adverse events
2020	Mühlhausen C [28]	0.75 g/kg/day	No adverse events
2022	De Graef D [24]	150 mg/kg, 3 times/day	No adverse events
2020	Abdel Ghaffar TY [27]	0.8 g/kg/day	Abdominal pain and mild diarrhea form intolerance
1998	Ralf Niehues [4]	150 mg/kg, 5 times/day	No adverse events

testing results, the patient was diagnosed with MPI-CDG.

4. Conclusions

In our case, the child had the onset of asymptomatic hypoglycemia in infancy, and typical MPI-CDG clinical manifestations accompanied the subsequent infection. The genetic report suggested that he carried two new biallelic mutations in the *MPI* gene. However, the clinical presentation of this disease is highly heterogeneous, which may account for the underdiagnosis. The disease is life-threatening if not treated with timely mannose supplementation. Therefore, a quick and accurate diagnosis is critical. Prenatal genetic counseling and genetic testing in suspected cases can help to clarify the diagnosis as early as possible. Lifelong oral mannose is essential in the later stages of treatment, but it is also important to monitor blood glucose and regular blood tests, coagulation, liver function and liver imaging.

Ethics approval

This study was approved by the ethic committee of Hunan Provincial Peoples' Hospital, the First Afliated Hospital of Hunan Normal University.

Consent to participate

Informed consent was obtained from the patient for publication of this case report details.

Consent to publish

Parents/guardians gave their written consent for their child's personal or clinical details along with all identifying images to be published in this study.

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Informed consent

Informed consent was acquired from the patients AND that the patients consented to the publication of all images, clinical data, and other data included in the manuscript.

CRediT authorship contribution statement

Cheng Luo: Conceptualization. **Danxia Peng:** Conceptualization. **Yanyan Li:** Formal analysis. **Shuping Liu:** Writing – original draft. **Qiong Wu:** Writing – original draft. **Xuan Xu:** Writing – review & editing. **Jie Wen:** Data curation.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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