

Mannose treatment improves immune deficiency in mannose phosphate isomerase–congenital disorder of glycosylation: case report and review of literature

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Abstract: Mannose phosphate isomerase–congenital disorder of glycosylation (MPI-CDG) is a CDG presenting with a clinically recognizable presentation, including early hypoglycemia, coagulation defects, and gastrointestinal and hepatic symptoms. We report on a female patient with biallelic pathogenic mutations in the *MPI* gene who 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 and transferrin glycosylation in our patient. The patient did not experience severe infections after the initiation of treatment. We also reviewed the immune phenotype in patients so far reported with MPI-CDG.

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Plain Language Summary

Using a type of sugar called mannose to strengthen the immune system of a person living with a rare disease called MPI-congenital disorder of glycosylation

Mannose phosphate isomerase–congenital disorder of glycosylation (MPI-CDG for short) is a rare, inherited disease that mainly affects the liver and digestive system. People with MPI-CDG typically develop signs and symptoms of the condition during childhood. Common symptoms of MPI-CDG include low blood sugar, blood clotting problems, poor growth, low weight, swelling of the lower legs or hands, digestive problems, and liver problems. Early diagnosis is crucial for people with MPI-CDG, as it is a potentially life-threatening, but treatable disease. Given that there are a small number of people with MPI-CDG, especially those with symptoms related to their immune system, it is important to highlight specific cases to raise awareness.

This article summarizes a specific case study of a female child with MPI-CDG. This individual did not experience the usual signs and symptoms of the disease. However, she had multiple infections affecting her respiratory tract, and had abnormal levels of antibodies in her blood.

The patient was treated with mannose, a type of sugar that is related to fructose and glucose. After 12 months of treatment, levels of antibodies stabilized. Furthermore, she did not experience any more severe infections after starting treatment with mannose. Tests designed to measure levels of glycosylation, called glycosylation transferrin testing, showed improvement in glycosylation to almost normal levels.

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In conclusion, this case report adds to the current knowledge about the disease and raises awareness that patients can present with immunological problems. It also shows that mannose treatment can be an effective treatment to improve the immune system and glycosylation in MPI-CDG.

Keywords: CDG, glycosylation, mannose, MPI, recurrent infections, therapy

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Introduction

Congenital disorders of glycosylation (CDGs) are a heterogeneous group of rare genetic disorders, which disrupt the glycosylation process important for many cellular functions. Specifically, this process involves the enzymatic activation and assembly of oligosaccharides (glycans) added to various proteins and lipids.¹ Mannose phosphate isomerase–congenital disorder of glycosylation (MPI-CDG) affects protein N-glycosylation, due to biallelic pathogenic variants in the *MPI* gene that leads to MPI enzyme deficiency. MPI-CDG is characterized by a clinically recognizable phenotype, including severe recurrent hypoglycemia, a complex coagulopathy with bleeding tendency and increased risk for thrombotic episodes, as well as protein losing enteropathy and various hepatic symptoms. Neurological symptoms are typically absent. MPI converts fructose-6-phosphate into mannose-6-phosphate, providing the necessary mannose-6-phosphate for glycosylation. Treatment with high dose oral mannose supplementation has been shown to be an effective therapy for MPI-CDG patients, as MPI enzyme deficiency can in part be substituted by hexokinase function.² In this article, we present an MPI-CDG patient with recurrent respiratory infections and decreased immunoglobulin levels with a favorable response to oral mannose therapy and review the literature on immune abnormalities in MPI-CDG.

Case presentation

Our patient is an 11-year-old girl, born at 38 weeks gestation via induced vaginal delivery, with normal birth weight of 3.7 kg and length of 49 cm. Parents were nonconsanguineous. Early development and growth profile were normal. She presented with respiratory symptoms at 5 years of age, and subsequently has had 20 confirmed cases of pneumonia, both bacterial and viral. She has been hospitalized on three separate occasions,

including one admission to the intensive care unit, the first time at age 8. Initially, asthma exacerbations were also suspected due to recurrent hypoxemia and atelectasis on imaging. However, she did not respond to standard treatment. Additional evaluations included a flexible bronchoscopy that revealed tracheomalacia, normal pulmonary function tests, and normal sweat chloride test. Due to her abnormal presentation, an immune disorder was suspected, and at 10 years of age, she was referred for genetic evaluation.

The patient appeared well developed and well nourished, without dysmorphic features. Whole exome sequencing (WES) revealed compound heterozygosity in the *MPI* gene for a known c.656 G > A (p.Arg219Gln) pathogenic variant and a novel c.170 G > T (p.Gly57Val) variant of uncertain significance (VUS). In addition, she had a heterozygous c.2282_2285delCAGT pathogenic variant in the *FLG* gene, associated with an increased risk for asthma.³ The VUS (p.Gly57Val) in the *MPI* gene has not been previously published as pathogenic or benign to our knowledge. *In silico* analysis supports that this missense variant has a deleterious effect on protein structure/function. According to the GnomAD database, the VUS is located in a region where five other pathogenic or likely pathogenic variants are reported (https://gnomad.broadinstitute.org/gene/ENSG00000178802?dataset=gnomad_r2_1).

Initial laboratory studies showed a decreased immunoglobulin M (IgM) level at 32 mg/dl (range 53–194 mg/dl) while other immunoglobulins (IgG, IgA, IgE) were normal. Alanine transaminase (ALT) was increased at 94 U/l (range 10–35 U/l). However, aspartate transaminase (AST), alkaline phosphate (AP), glucose, antithrombin III, and factor XI activity were all within normal range. Both ultrasound of the abdomen and liver elastography were normal. Carbohydrate-deficient transferrin testing showed elevation of the mono-oligo/

di-oligo ratio at 0.26 (≤ 0.06) and a-oligo/di-oligo ratio at 0.017 (< 0.011), indicating an abnormal CDG type 1 pattern. Decreased enzyme activity in leukocytes confirmed the diagnosis of MPI-CDG. Phosphomannoisomerase (MPI) enzyme activity in leukocytes was 370 nmol/h/mg in our patient, compared with > 1300 nmol/h/mg in controls.

The patient is enrolled in the Frontier in CDG Consortium (FCDGC) natural history study (institutional review board (IRB): 19-005187; <https://clinicaltrials.gov/ct2/show/NCT04199000?cond=CDG&draw=2&rank=4>). Written and informed consent was obtained from the legally authorized representatives of the subject prior to study initiation. To address whether standard of care therapy for MPI-CDG patients could decrease infection frequency and improve immune function, our patient was started on a low dose of oral mannose at 100 mg/kg TID. At therapy initiation, she had a severity score of 3 according to the Nijmegen Pediatric CDG Rating Scale (NPCRS). After 4 months, hemoglobin A1c (HbA1c) remained normal at 5.7% (4.6–5.9%), and carbohydrate-deficient transferrin testing revealed improving mono-oligo/di-oligo ratio of 0.18 (≤ 0.06) and normal a-oligo/di-oligo ratio of 0.005 (≤ 0.011). The mannose dose was increased to 150 mg/kg TID after 6 months of treatment. After 1 year of treatment, carbohydrate-deficient transferrin testing improved further with mono-oligo/di-oligo ratio of 0.10 (≤ 0.06) and normal a-oligo/di-oligo ratio of 0.005 (≤ 0.011). HbA1c was elevated at 6.5 (4.8–5.6%). IgM levels remained decreased at 30 (53–164 mg/dl). Complete blood count (CBC) and comprehensive metabolic panel (CMP) were normal. Previously elevated ALT levels returned to normal range. She has not had any infections after the initiation of the mannose therapy for the observation period of a year.

Discussion

Immunoglobulin glycosylation is frequently abnormal in different N-linked glycosylation defects, and decreased levels of immunoglobulins are also common.⁴ Interestingly, patients with lower levels of immunoglobulins in CDG – like PMM2-CDG or ALG6-CDG patients – do not always present with classic symptoms of immunodeficiency, but do have more frequent ‘trivial’ infections, including upper respiratory disease, recurrent ear infections, or lung disease.⁵ In a survey of 122 patients with PMM2-CDG about half of these patients

reported frequent infections: especially affecting the gastrointestinal tract. Infections correlated with more severe non-immune PMM2-CDG signs.⁵ Compared with classic immunodeficiencies in association with CDG, infections did not last longer and were not lethal. However, recurrent infections did have clinical relevance: the infections triggered an increase in immune reaction with redirecting glycosylation toward immune proteins from other essential proteins. This could lead to more under-glycosylation of endocrine and coagulation factors, leading to secondary life-threatening complications like hypoglycemia, seizures, bleeding, or stroke.⁶ Other CDGs have proven immunological defects, such as MOGS-CDG and ALG12-CDG, in which defective glycosylation of immunoglobulin G (IgG) has been proven. Those patients are more prone to infection due to the reduced efficacy and shortened half-life of IgG.^{7,8} A similar defective glycosylation of immunoglobulins could contribute to the immune phenotype in MPI-CDG. Further investigation by glycoproteomics might improve our understanding of the molecular defects contributing to the clinical phenotype of the disease.

Immunological involvement in MPI-CDG has not been systematically studied. Several children with MPI-CDG were described with recurrent infections with frequent fever episodes, even sepsis, but no obvious immune abnormalities.⁹ Immunoglobulin deficiency has been observed as a consequence of protein losing enteropathy, which was reported to lead to low immunoglobulin levels and severe infections in MPI-CDG patients (in these cases decreased levels of IgG levels were characteristic).^{10,11} Atypical infections were reported in a patient with bronchiolitis obliterans, cryptosporidial diarrhea, and a high frequency of respiratory infections; a patient with sepsis and severe infectious diarrhea; and another patient with *Ascaris lumbricoides* and *Giardia lamblia* infections.^{2,12–14} Only five of the nine patients reported in the literature were treated with mannose. Three showed significant clinical improvement after initiation of therapy. Two patients had a lethal outcome, succumbing to sepsis and liver failure, respectively^{10–14} (Table 1).

Many cells surface proteins important in cellular immunity are glycosylated. One of these proteins is ICAM1, which is highly abundant on the vascular endothelial surface and important in the inflammatory response.^{15,16} In a mice model of

Table 1. Clinical presentation of MPI-CDG cases with immune abnormalities.

| | Case 1 Pelletier <i>et al.</i> ⁹ | Case 2 Pelletier <i>et al.</i> ⁹ | Case 3 Pelletier <i>et al.</i> ⁹ | Case 4 Pelletier <i>et al.</i> ⁹ | Case 5 Pelletier <i>et al.</i> ⁹ | Case 6 Damen <i>et al.</i> ¹⁰ | Case 7 de Lonlay <i>et al.</i> ¹¹ | Case 8 Kelly <i>et al.</i> ¹⁴ | Case 9 Penel-Capelle <i>et al.</i> ¹² | Case 10 Abdel-Ghaffar <i>et al.</i> ¹³ |
|---|--|--|--|--|--|---|---|--|---|--|
| Abnormal coagulation | - | - | - | - | - | + | + | + | + | - |
| Hypo-glycemia | - | + | + | + | + | + | + | - | + | - |
| Liver involvement | - | + | + | + | + | + | + | + | + | + |
| Presence of PLE | - | + | + | + | + | + | + | + | + | + |
| Infection types | Pneumonia (bacterial and viral) | Fever, leucocytosis, and sepsis | Fever, leucocytosis, and sepsis | Fever, leucocytosis, and sepsis | Fever, leucocytosis, and sepsis | Diarrhea | Recurrent cholangitis | Bacterial, fungal, parasitic | Diarrhea | Diarrhea |
| Unusual pathogen | - | - | - | - | - | Not found | - | <i>C. albicans</i> , <i>Cryptosporidium</i> , <i>Helicobacter pylori</i> , <i>Enterobacter spp.</i> | <i>Salmonella</i> | <i>Ascaris lumbricoides</i> and <i>Giardia lamblia</i> |
| Immune abnormality | Decreased IgM, normal IgG and IgA | Decreased normal IgM and IgA | Decreased IgG, normal IgM and IgA | Decreased IgG, normal IgM and IgA | Decreased IgG, normal IgM and IgA | Decreased IgG, normal IgM and IgA | Decreased Ig levels | Studies normal | Unknown | Unknown |
| Pathogenic variants in MPI gene | Arg219Gln Gly57Val | Unknown | Unknown | Unknown | Unknown | Unknown | Ser102Leu Met138Thr | Unknown | Tyr129Cys Arg152Gln | Lys163X Arg219Gln |
| MPI-CDG, mannose phosphate isomerase-congenital disorder of glycosylation; PLE, protein losing enteropathy. | | | | | | | | | | |

MPI-CDG, MPI-deficient mice who were treated with zymosan to trigger inflammatory response had a decreased neutrophil reaction, and decreased ICAM-1 response to acute peritonitis.¹⁶ MPI-deficient mice when supplemented with mannose for 7 days restored ICAM-1 expression on mesenteric endothelial cells and transendothelial migration of neutrophils during zymosan-induced inflammation.¹⁶

Based on animal studies in the literature, one would expect improvement of immunologic symptoms in MPI-CDG patients on mannose supplementation therapy.^{16,17} Clinical studies further demonstrate long-term efficacy and safety of mannose treatment.¹⁸ In our patient, IgM levels and glycosylation were both improved after 4 months and remained stable for a year during follow-up. Carbohydrate-deficient transferrin tests showed improving Mono-oligo/Di-oligo Ratio of 0.18 (≤ 0.06) and normal A-oligo/Di-oligo Ratio of 0.005 (≤ 0.011), while HbA1c remained within acceptable range (6.5%). Most importantly, the patient has not had any infection after initiation of mannose treatment, showing the clinical benefit of mannose treatment on frequent infections in MPI-CDG. A possible limitation could be that our patient had less exposure to pathogens from staying at home due to the COVID-19 pandemic. Epidemiologic studies indicate social distancing and other lockdown strategies reduce the incidence of viral respiratory diseases and hospitalization in the pediatric population.¹⁹

Liver involvement is the most frequent symptom in MPI-CDG, and gastrointestinal symptoms are also among the most common features of the disease. MPI-CDG can present with a mild or asymptomatic phenotype, though only two siblings have been described without liver or intestinal disease.^{2,20} Gastrointestinal involvement can also present in adolescence as described by de la Morena-Barrio *et al.*²¹ Our patient is unique as she has not shown liver abnormalities nor gastrointestinal symptoms during her course of disease. The slight increase of serum ALT at initial laboratory investigation could be a sign of liver involvement in our patient and the ALT levels normalized after mannose treatment. Our patient has a relatively high residual enzyme activity in blood, which might mirror a less severe overall phenotype. It is possible that some milder cases of MPI-CDG remain undiagnosed while these patients could benefit from safe and effective mannose treatment.

Conclusion

Mannose treatment improves glycosylation and decreases the incidence of infections in our case thus supporting the efficacy of this treatment in MPI-CDG patients presenting with immune deficiency.

The unique phenotype in our patient illustrates the heterogeneity of the disease and shows the clinically recognizable presentation is not necessarily present in all cases. MPI-CDG can result in immunodeficiency and can be a cause of unexplained recurrent and atypical infections.

Author contributions

Diederik De Graef: Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Jehan Mousa: Data curation; Investigation; Writing – review & editing.

Marta Biderman Waberski: Conceptualization; Data curation; Writing – review & editing.

Eva Morava: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement

The patient is enrolled in the Frontier in CDG Consortium (FCDGC) natural history study (institutional review board (IRB) 19-005187; <https://>

clinicaltrials.gov/ct2/show/NCT04199000?cond=C DG&draw=2&rank=4). Written informed consent was obtained from the legally authorized representatives of the subject prior to study initiation. Informed consent for publication of this case report was also obtained from the legally authorized representatives of the subject as the subject is a minor.

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