Successful Liver Transplantation and Long-Term Follow-up in a Patient With MPI-CDG

AUTHORS: Mirian C.H. Janssen, MD, PhD,[a,b] Ruben H. de Kleine, MD,[c] Arie P. van den Berg, MD, PhD,[d] Yvonne Heijdra, MD, PhD,[e] Monique van Scherpenzeel, PhD,[f,g] Dirk J. Lefeber, PhD,[f,g] and Eva Morava, MD, PhD[h]

Departments of [a]Pediatrics, [b]Internal Medicine, [e]Pulmonary Diseases, and [f]Neurology, and [g]Laboratory of Genetic, Endocrine, and Metabolic Disease, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; Departments of [c]Hepatobiliary Surgery and Liver Transplantation, and [d]Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, Netherlands; and [h]Tulane Hayward Genetics Centre, New Orleans, Louisiana

KEY WORDS
congenital disorder of glycosylation, MPI-CDG, liver transplantation

ABBREVIATIONS
CDG—congenital disorder of glycosylation
PMM—phosphomannomutase
PMM2-CDG—Phosphomannomutase 2 deficiency congenital disorder of glycosylation
TIEF—transferrin isoelectric focusing

Dr Janssen interpreted data and designed and wrote the article; Dr Kleine interpreted data and reviewed and revised the manuscript; Dr van den Berg interpreted data and reviewed and revised the manuscript; Dr Heijdra performed the analyses of pulmonary function tests and reviewed and revised the manuscript; Dr Scherpenzeel analyzed the biochemical data and reviewed and revised the manuscript; Dr Lefeber designed the biochemical studies, analyzed the biochemical data, and reviewed and revised the manuscript; Dr Morava interpreted data and designed and wrote the article; and all authors approved the final manuscript as submitted.

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Address correspondence to M.C.H. Janssen, MD, PhD, Department of Pediatrics and Internal Medicine 463, Radboud University Medical Centre, PO Box 9101, 6500 HB, Nijmegen, The Netherlands. E-mail: mirian.janssen@radboudumc.nl

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abstract

Hepatopathy is the most common feature in the Congenital Disorders of Glycosylation (CDG). More than 70 subtypes have been identified in this growing group of inborn errors. Most defects present as multisystem disease, whereas phosphomannose isomerase deficiency (MPI-CDG) presents with exclusive hepato-intestinal phenotype. MPI-CDG has been considered as one of the very few treatable disorders of glycosylation; several patients showed significant improvement of their life-threatening protein-losing enteropathy and coagulation disorder on oral mannose supplementation therapy. However, patients who have MPI-CDG develop progressive liver insufficiency during a later course of disease. A patient who had MPI-CDG developed progressive liver fibrosis, despite oral mannose supplementation and repeated fractionated heparin therapy. She showed mannose therapy-associated hemolytic jaundice. She developed severe dyspnea and exercise intolerance owing to pulmonary involvement, necessitating liver transplant. After transplantation her physical exercise tolerance, pulmonary functions, and metabolic parameters became fully restored. She is still doing well 2 years after transplantation now. In conclusion, we here report on the first successful liver transplantation in CDG. *Pediatrics* 2014;134:e279–e283

Congenital disorders of glycosylation (CDG) are caused by defects in the synthesis and attachment of glycans to proteins and lipids. One discriminates between N-linked and O-linked glycosylation depending on how a glycan chain is linked to a protein (linked to an "N" or "O" atom of a particular amino acid). N-glycosylation goes through the cytoplasm, endoplasmic reticulum, and Golgi apparatus, whereas O-linked glycosylation is localized to the Golgi. Until now, some 30 defects in protein N-glycosylation have been described; 20 are related to assembly (CDG-I) and 8 to processing (CDG-II).[1–3] Most CDG show an abnormal transferrin isoelectric focusing (TIEF). Glycosylated proteins, including transport proteins like ceruloplasmin, α-1-antitripsin, or hormones and regulators, like thyroglobuline and thyroid stimulating hormone, show the same glycosylation abnormalities and demonstrate abnormal function. Because N-glycosylation of serum proteins occurs mostly in the liver, many secretory proteins are involved by an abnormal N-glycosylation, leading to abnormal liver function and systemic consequences as well.

Phosphomannomutase (PMM) 2 deficiency (PMM2-CDG) is the most common form of CDG, presenting with a type 1 TIEF pattern. Over 700 patients have been reported with PMM2-CDG,[1] presenting with a severe multisystem involvement, including liver disease, endocrine and coagulation abnormalities, and multiple neurologic symptoms. No curative therapy is available in PMM2-CDG. Phosphomannose isomerase deficiency (MPI-CDG) is the third most common CDG presenting with a type 1 TIEF pattern. Symptoms include recurrent episodes of vomiting, protein-losing enteropathy, bleeding diathesis and recurrent thrombosis, liver disease, and hypoglycemia. High doses of oral mannose therapy have proven beneficial for many patients who have this life-threatening disorder but cannot always prevent liver cirrhosis.[4–8] Here we report the first successful liver transplantation in a patient who has therapy-resistant MPI-CDG.

CASE DESCRIPTION

Our female patient was born at term without any complications as the first child of healthy non-consanguineous parents, with appropriate growth parameters. No perinatal abnormalities were noted. Motor development and early growth were normal. She was hospitalized for recurrent episodes of vomiting, diarrhea, and hepatomegaly. When she was 2 years old she was diagnosed with failure to thrive, congenital hepatic fibrosis, and portal hypertension, with hepatic vein thrombosis. Protein-losing enteropathy was treated with low-fat diet and repeated albumin infusions. The patient was diagnosed with MPI-CDG (CDG type 1B, OMIM 602579) at the age of 15 years. The diagnosis was based on 2 key findings: a characteristic isoelectric focusing pattern of the patient's serum transferrin, and a very low level of phosphomannose isomerase activity in fibroblasts (77 nmol/h per mg protein; normal range, 1250–2800 nmol/h per mg protein). She was found to be compound-heterozygous for the p.R152Q/p.Q14P (c.455G>A/c.41A>C) mutations in the MPI gene. Oral mannose supplementation (1 g/kg/day) was successful in controlling her coagulation abnormalities, but this treatment had to be stopped because of persistent diarrhea, abdominal pain, and jaundice owing to hemolysis. At the age of 25 years there was progressive edema and ascites caused by hypoalbuminemia, treated with diuretics, albumin infusions, and intravenous fractionated heparin.[9] This resulted in a stable period. Repeated mannose therapy, even at a low dose of 100 mg/kg/day, led to improvement of the metabolic abnormalities, but progressive hemolytic jaundice appeared again. At the age of 28 years, she experienced recurrent hepatic encephalopathy, severe upper abdominal pain requiring morphine, constipation, and a severely decreased exercise tolerance. A year earlier she could swim, study, and go to work every day. This rapid-onset fatigue and dyspnea bounded her to a wheelchair and to continuous use of oxygen.

Laboratory examination revealed an intermittently elevated ammonia, slightly decreased albumin, normal renal function, and decreased coagulation factors. Chest radiograph was normal. High-resolution CT scan of the chest revealed no abnormalities. CT scan of the abdomen showed a cirrhosis pattern with a hypotrophic right and a hypertrophic left half of the liver. Besides splenomegaly, large collaterals and tapering of the portal vein suggestive of partial thrombosis were present. A frank aneurysm of 1.5 cm was seen in the gastroduodenal artery. Two separate aneurysms in the splenic artery (1.5 and 3.0 cm) were also detected. Gastroscopy showed no varices. Liver biopsy demonstrated congenital hepatic fibrosis (Fig 1). Because of the severely decreased exercise tolerance, echocardiography was performed; it showed minimal signs of pulmonary arteriovenous shunting. Ejection fraction was normal and there were no valve abnormalities. Estimated pulmonary artery peak pressure and right atrium pressure were normal. The exercise echocardiography demonstrated no abnormalities, except for the minimal arteriovenous shunting. Perfusion-ventilation scanning of the lungs was normal; there were no signs of pulmonary embolism. Pulmonary function investigations showed no obstruction or restriction. Saturation

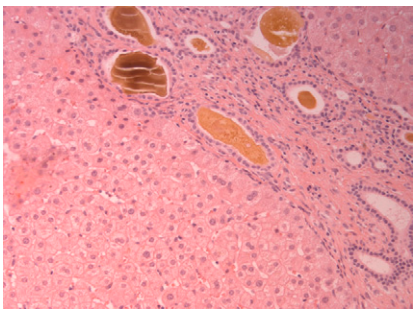

FIGURE 1
Histology of the liver biopsy before transplantation. Congenital hepatic fibrosis with ductal plate malformation/formation of von Meyenburg complexes (multiple and nodular cystic lesions). Substantial fibrosis with partial formation of nodules (considered F3 fibrosis).

was normal. There was a mildly decreased diffusion capacity. Cycling ergometry (maximal test based on heart frequency and lactate) at 100 W showed 58% of the predicted value without ventilatory restriction or an increased alveolar-arterial oxygen pressure difference but an aberrant oxygen pulse plot (Fig 2).

Orthotopic Liver Transplantation

Because of progressive liver failure with recurrent hepatic encephalopathy, therapy-resistant CDG, and possible hepato-pulmonary syndrome, the patient was accepted for liver transplantation with a nonstandard exception. She received a full-size graft from a heart-beating donor. Aggressive buffering of her lactate acidosis was pursued throughout the procedure. The portal vein was partially occluded by a mural thrombus. The graft functioned immediately. The aneurysms were not amenable to surgery during transplantation. She was extubated on postoperative day 2 and returned to the ward on day 3 with continuous oxygen. Therapeutic anticoagulant therapy with low molecular heparin was started after the prothrombin time dropped to below 20 seconds. The aneurysms of the gastroduodenal and splenic artery were embolized on postoperative day 8 to prevent spontaneous rupture.[10] No contrast leakage was seen during the procedure. The patient developed bilateral psoas hematomas that needed a surgical removal. Subsequently *Staphylococcus aureus* sepsis attributable to a splenic abscess occurred that was treated by CT-guided drainage and prolonged administration of antibiotics.

RESULTS AFTER TRANSPLANTATION

Clinical Symptoms

After she recovered from these complications, our patient showed a profound improvement. She was able to

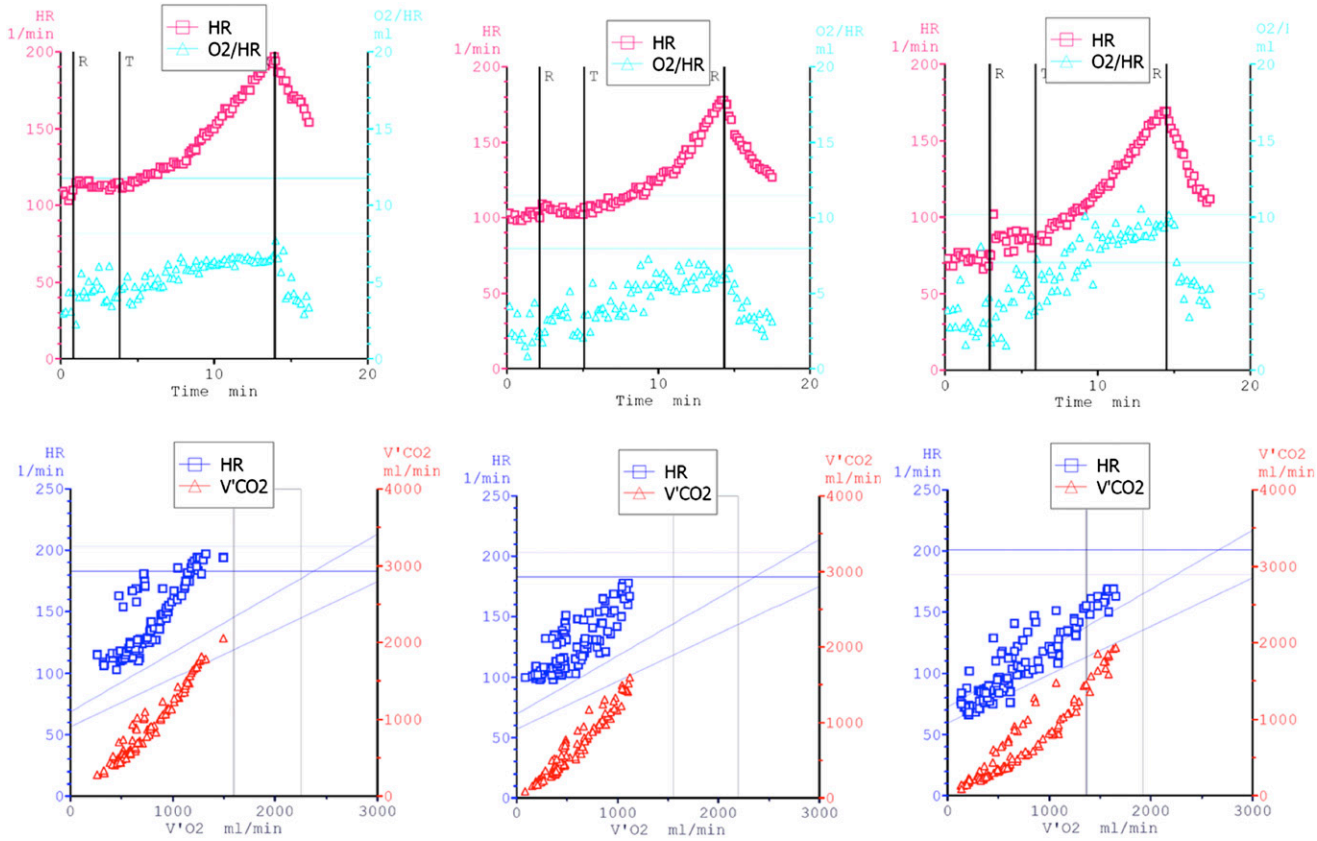

FIGURE 2
02 plot before and after transplantation. Upper panel, in blue the oxygen pulse (02/heart rate[HR]). Lower panel, heart rate against V02 (oxygen consumption). Before transplantation during minimal exercise there was already a plateau in the oxygen pulse. After transplantation the 02 pulse did not decrease anymore.

restart normal nutrition, stopped oxygen support, had no muscle fatigue, and reported no pain anymore. The gastrointestinal function was fully restored. Gradually the exercise tolerance improved to normal, allowing her to ride the bicycle and start swimming again. At this time, 2 years after transplantation, she is still doing well.

Metabolic Laboratory Examination

The main improvement was a complete normalization of the coagulation factors after transplantation. Enzymatic activity of phosphomannose isomerase in leukocytes remained deficient (1.7 mU/mg protein before and 1.8 mU/mg protein after transplantation; reference, 12.3 to 43.7). Analysis of the N-glycosylation by TIEF (not shown) and sensitive mass spectrometry (Fig 3) showed near normalization on mannose therapy and a completely normal distribution of transferrin subfractions after liver transplantation.

Additionally, we studied the underglycosylation of a non–liver-derived glycoprotein. Analysis of B-cell–derived immunoglobulins in plasma before transplantation showed a low percentage of non-glycosylated IgGs, to a similar extent as samples from a patient who has PMM2-CDG and ALG6-CDG. After transplantation, no improvement could be observed in IgG glycosylation.

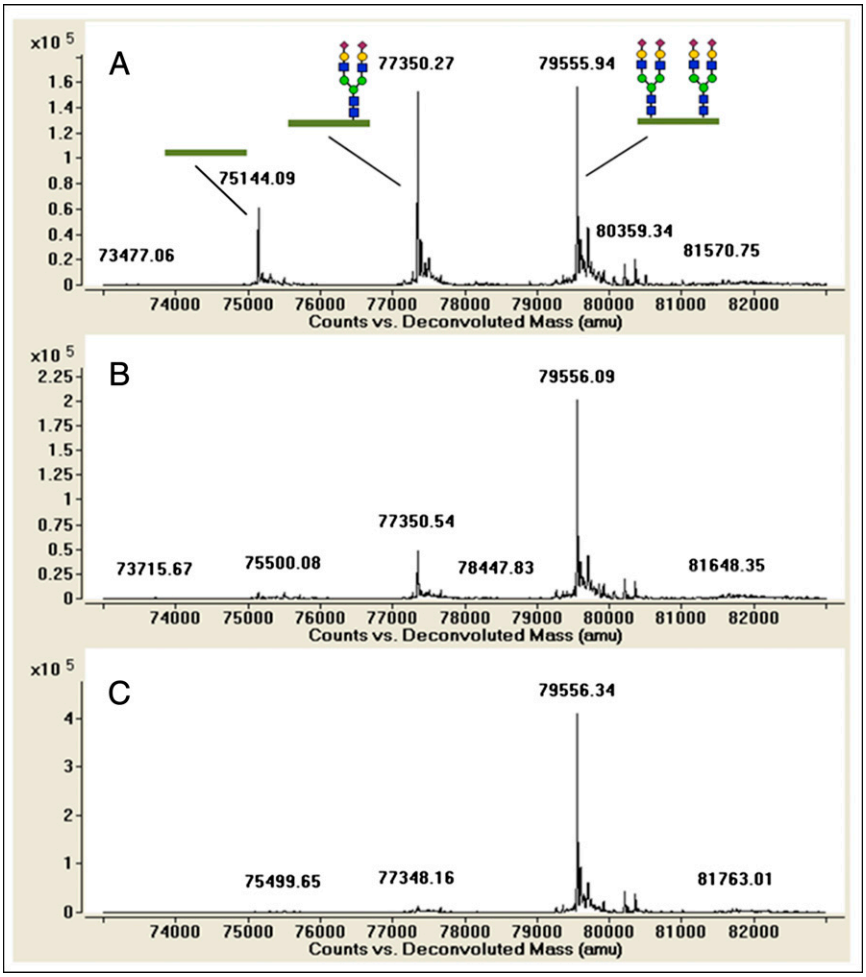

FIGURE 3
Transferrin glycosylation profiles. Transferrin glycosylation profile A, before treatment; B, during mannose treatment; and C, after liver transplantation without mannose treatment. The brown bar represents transferrin. A, Before treatment, loss of 1 and 2 glycans of transferrin was observed. B, On mannose therapy, a relatively mild loss of 1 glycan was shown. After transplantation, normal glycosylation of transferrin was found.

Pulmonary Investigations

Figure 2 demonstrates the oxygen pulse-plot before and after transplantation. Before transplantation, already during minimal exercise, there was a plateau in the oxygen pulse. After transplantation the oxygen pulse did not decrease anymore. The anaerobic threshold increased from 700 mL/min (37% VO2 pred) to 1005 mL/min (61% pred).

DISCUSSION

Herein, we report the first liver transplantation in CDG, namely in a patient who has MPI-CDG. Transplantation was performed because of therapy resistance and repeated hemolytic episodes on mannose supplementation, and progressive liver fibrosis with pulmonary involvement. One year after transplantation her physical exercise tolerance, pulmonary functions, and metabolic parameters became fully restored.

The patient at the age of 28 years developed extreme exercise intolerance. Already during minimal exercise there was a plateau in the oxygen pulse. According to the Fick equation (VO2 = CO times C(a-v)O2) the oxygen pulse can be abnormal by a decreased stroke volume or a decreased peripheral extraction of oxygen. Because cardiac examination was completely normal, we speculated that there could be a severe depletion of oxygen availability at tissue level because of the defect in (glycosylation of) hemoglobin. The transplantation was very successful, because our patient changed from a young woman in a wheelchair using oxygen continuously to a young woman walking and swimming. Pulmonary evaluation after transplantation demonstrated that the oxygen pulse plot had been normalized and the anaerobic threshold increased to normal.

So far, liver transplantation has not been a therapy for patients who have CDG. The advantage of this treatment, in addition to organ function restitution, is causal metabolic therapy. Because thrombosis and bleeding diathesis are common severe symptoms in MPI-CDG, it led to an immediate hemostatic restitution in our patient. Interestingly, gastrointestinal symptoms also improved in our patient after transplantation. Glycosylation of non–liver-glycosylated proteins (IgG) is possibly related to ameliorated glycosylation of secretory and circulatory glycoproteins.

Cardiac transplantation has been performed in 3 patients who have Dolichol Kinase Deficiency-CDG with relatively benign outcome.[11] Hepatic cell and stem cell transplantation have not yet been reported in patients who have CDG. Based on the positive outcome in our patient, one might expect similar beneficial effects by using these cells in MPI-CDG. In the most common CDG form, PMM2-CDG stem cell transplantation should improve the liver function and restitute endocrine and coagulation defects as well, thus improving the quality of life for patients. However, liver cirrhosis is rare in patients who have PMM2-CDG and the congenital central nervous malformations are not susceptible for transplantation therapy. Our results in this patient plead for further research in liver and stem cell transplantation in patients who have CDG.

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