



**HAL**  
open science

# The clinical spectrum of phosphomannose isomerase deficiency, with an evaluation of mannose treatment for CDG-Ib

P. de Lonlay, N. Seta

► **To cite this version:**

P. de Lonlay, N. Seta. The clinical spectrum of phosphomannose isomerase deficiency, with an evaluation of mannose treatment for CDG-Ib. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, 2009, 1792 (9), pp.841. 10.1016/j.bbadis.2008.11.012 . hal-00517926

**HAL Id: hal-00517926**

**<https://hal.science/hal-00517926>**

Submitted on 16 Sep 2010

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Accepted Manuscript

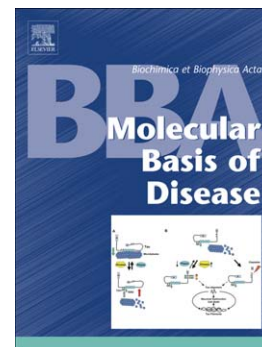
The clinical spectrum of phosphomannose isomerase deficiency, with an evaluation of mannose treatment for CDG-Ib

P. de Lonlay, N. Seta

PII: S0925-4439(08)00248-2  
DOI: doi:[10.1016/j.bbadis.2008.11.012](https://doi.org/10.1016/j.bbadis.2008.11.012)  
Reference: BBADIS 62900

To appear in: *BBA - Molecular Basis of Disease*

Received date: 17 September 2008  
Revised date: 15 November 2008  
Accepted date: 24 November 2008



Please cite this article as: P. de Lonlay, N. Seta, The clinical spectrum of phosphomannose isomerase deficiency, with an evaluation of mannose treatment for CDG-Ib, *BBA - Molecular Basis of Disease* (2008), doi:[10.1016/j.bbadis.2008.11.012](https://doi.org/10.1016/j.bbadis.2008.11.012)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The clinical spectrum of phosphomannose isomerase deficiency, with an evaluation of  
mannose treatment for CDG-Ib

P de Lonlay<sup>a,c</sup>, N Seta<sup>b,c</sup>

<sup>a</sup>AP-HP, Centre de références de maladies métaboliques, Hôpital Necker-Enfants

<sup>b</sup>Malades; AP-HP, Biochimie Métabolique et Cellulaire, Hôpital Bichat;

<sup>c</sup>Université Paris Descartes, Paris, France

**Corresponding author:**

Pr Pascale de Lonlay

Centre de références des maladies métaboliques

Département de Pédiatrie

Hôpital Ncker-Enfants Malades

149, rue de Sèvres

F - 75015 Paris

Tel: +33 1 44 49 52

Fax: +33 1 44 49 48 50

E-mail: pascale.delonlay@nck.aphp.fr

**Key words:** mannose supplementation, heparin therapy, Congenital Disorder of Glycosylation, hepatomegaly, PMI, phosphomannose isomerase

## Summary

Phosphomannose isomerase (PMI) deficiency or congenital disorders of glycosylation type Ib (CDG Ib) is the only CDG that can be treated. Despite variable severity leading to dramatically different prognoses, clinical presentation is relatively homogeneous with liver and digestive features associated with hyperinsulinism and inconstant thrombosis. A feature of CDG is that coagulation factors are decreased. In our experience, mannose given orally at least 4 times per day not only transformed lethal CDG Ib into a treatable disease, but also improved the general condition and digestive symptoms of all reported patients but one. Liver disease, however, still persisted. Heparin can be used as an alternative to mannose in certain patients, particularly in the treatment of enteropathy.

## Introduction

Congenital disorders of glycosylation (CDG) result from a defect in N-glycosylation (1), and phosphomannose isomerase (PMI; E.C 5.3.1.8) deficiency is the only CDG (CDG-Ib, OMIM 602579) that can be treated. This enzyme, located in the cytosol, catalyzes the isomerisation of fructose 6-phosphate to mannose 6-phosphate which can also originate from free mannose entering the cell via a specific transporter (1) (Fig 1). Consequently mannose supplementation is successfully used to treat PMI deficiency.

CDG Ib is a rare autosomal recessive disease, with only few patients (less than 50 cases) reported in comparison with CDG Ia patients. It should be pointed out, however, that CDG Ib is probably under-diagnosed.

## Clinical presentation

The first clinical description of CDG-Ib was made by Pedersen in 1980 (2). Pelletier et al. in 1986 also reported a lethal disease in 4 patients from the “Saguenay-Lac St-Jean” area in Quebec (3). All patients died, and diagnosis of CDG Ib was retrospective (4) as the metabolic error causing CDG Ib was described later (5).

Despite variable severity, clinical presentation is relatively homogeneous with liver

and digestive feature, associated with mild hyperinsulinism and inconstant thrombosis (2, 3, 5-13).

Digestive symptoms are vomiting, intractable diarrhoea and malnutrition due to protein-losing enteropathy, sometimes associated with mild villous atrophy (12). Duodenal biopsies can be normal (7). The most severe patients, with an onset of their disease in the first months of age, require parenteral nutrition.

Liver disease is revealed by hepatomegaly, sometimes associated with oedema or anasarca. The liver biopsy reveals a fibrosis very similar to that of congenital hepatic fibrosis (CHF), with biliary dystrophy and portal fibrosis (14). This fibrosis is reported in all patients but one (8) where liver biopsy was performed (3, 5, 6, 13, 15).

Hyperinsulinism is frequently associated with CDG Ib but probably under diagnosed because hypoglycaemia is moderate or frequently compensated in patients requiring parenteral nutrition for their digestive symptoms, including glucose infusion.

Thrombosis is not present in all patients, although frequent. It can be multiple in the same patient.

Since the first report (2), clinical heterogeneity in terms of clinical presentation and severity of symptoms has been described with variable prognoses even among siblings. Untreated patients manifesting their disease in the first year of age died in the first years of life. Other patients can present with only hepatomegaly and hyperinsulinism, or mild diarrhoea and transaminase cytolysis. Westphal et al (13) reported two siblings with the same mutation, with gut and liver disease. One died at 5 years of age with hepatic fibrosis while the other one, a girl, survived and is 33-year-old at the time of publication, with no further symptoms following childhood, and no treatment. This patient currently has a normal life with healthy children.

### **Biological presentation and diagnosis**

*Liver cytolysis.* Transaminases are usually mildly elevated (among 60 IU/l, normal values < 50; sometimes higher up to 1000 IU/l), while serum bilirubin and GGT levels are normal.

*Coagulation.* As a feature of CDG, factor XI, antithrombin III, proteins C and S are decreased, down to 5-33%. Prothrombin time is slightly decreased with a normal factor V level. Like in CDG Ia, thrombosis, more often than bleeding, can be observed, because of markedly low levels of several coagulation factors and/or oesophageal varices.

*Liver failure.* Hypoalbuminemia (<30 g/l) related to liver dysfunction is present in severe cases as well as hypocholesterolemia.

*Diagnosis.* To ascertain the diagnosis, biochemical and molecular investigations are necessary, including transferrin western blot and/or isoelectric focusing of patterns typical of CDG I. PMI deficiency is evidenced in patients' blood mononuclear cells and/or fibroblasts. The presence of mutations in the *MPI* gene evidenced by direct sequencing confirms the diagnosis.

*Differential diagnosis.* Interestingly, contrary to CDG Ia patients, no neurological symptom has been noted in CDG Ib patients. The lack of psychomotor retardation, cerebellar hypoplasia, strabismus or lipocutaneous abnormalities in CDG Ib might limit the diagnosis, as most CDG are presently associated with these clinical symptoms. Inversely, hyperinsulinism associated with thrombosis, digestive and hepatic failures can also be present in CDG Ia. Thus, a precise diagnosis with enzymatic and molecular investigation is required to confirm the diagnosis of CDG Ib and Ia.

### **Medical treatment by mannose and follow-up**

PMI enzyme defect leads to decreased mannose 6-phosphate that is synthesized from fructose 6-phosphate (Fig. 1). However, mannose 6-phosphate can also originate from free mannose entering the cell via a specific transporter (1), demonstrating that mannose supplementation can successfully treat PMI deficiency. Presently, CDG Ib is the only treatable CDG.

Niehues et al (8) successfully treated a 6 year old CDG Ib patient using oral mannose with an 11 month follow-up. Clinical response to mannose was observed within two weeks, although a slower improvement in glycosylation of glycoproteins was observed.

Studies have proved that mannose therapy improved the general condition and digestive symptoms in all reported patients (8, 10-12, 15-17) but one (18), whereas the first patients with severe clinical presentations who received no mannose treatment died. Mannose therapy normalized hypoglycaemia and vomiting after a few weeks, and the general status of patients dramatically improved. Biological abnormalities, including diarrhoea, were normalized in the first year. Only hepatomegaly persisted in certain cases.

Oral supplementation of mannose is recommended as it is well absorbed in the gut. Normal serum mannose level in fasting controls is from 46 – 65 mM (19). Blood mannose levels increase in a dose-dependent fashion with increasing oral doses of mannose. The clearance half-time of mannose is 4 hours (8) and a peak blood mannose concentration occurs at 1-2 hours following ingestion of mannose. Patients with CDG Ib have less than 10 mM of serum mannose before treatment (9,15). The mannose treatment in CDG Ib patients is given in order to achieve a plasma mannose concentration  $> 20 \mu\text{mol/l}$  before mannose administration ( $T_0$ ) and  $> 100 \mu\text{mol/l}$  one hour thereafter (19). The dose of mannose recommended in CDG Ib patients is 0.2 g /Kg / 4 hours at the beginning of the treatment (8). Following this, patients are treated with 4 uptakes of mannose. However, the mannose doses depend on plasma mannose measurement, and the frequency of mannose uptakes are crucial because of the short clearance half-time mannose. We recommend measuring plasma mannose at  $T_0$ , at 1 hour and 2 hours after mannose uptake. A reduction of the frequency and/or the dose of mannose administration (for example by increase of the weight of the patient) can be followed by a recurrence of diarrhoea and a decrease in the residual mannose level, reversible when mannose treatment is reintroduced.

Unbound mannose can be determined in blood samples collected on EDTA in an assay derived from the method of Etchison and Freeze (20) in specialized laboratories. We propose measuring the blood level of free mannose before and after mannose administration (21).

Oral mannose supplementation is well tolerated, while single mannose doses of  $> 200 \text{ mg/kg}$  body wt can induce osmotic diarrhoea. No side effects have been reported after 21 days of continue infusion (5.7 g/kg/day) in CDG I (22), or in the long-term

treatment of CDG Ib patients, followed-up over a 10 year period. To date, neurological development under mannose treatment has been normal.

Concerning liver disease, Hendriksz et al (16) observed 3 years of successful mannose treatment that achieved clinical and biological improvement, but persistent hepatomegaly. Our experience, as well as that of other teams, is that while liver disease persists in the most severe patients, their other symptoms disappear after several months (15). Hepatomegaly remains, with some patients having signs of chronic liver disease, splenomegaly, palmar erythema, persistently elevated transaminases, symptoms of portal hypertension, and at liver biopsy proliferating dystrophic and dilated bile ducts, and prominent portal fibrosis, akin to CHF. Neither inflammation, steatosis or cholestasis are observed. Thus, mannose does not seem to act effectively on the liver, even when administered in the first months of life. Liver improvement probably depends on the severity of the disease at diagnosis, as liver disease seems to evolve by itself. Abnormal glycosylated proteins in the liver could also interfere with the normal development of the liver, either by accumulation of an abnormal product, or more probably by loss of function. Finally, a link may exist between the progression of liver disease and long-term side effects of mannose supplementation (23): *Mpi* <sup>-/-</sup> mouse embryos died around E11.5 under mannose. Mannose supplementation hastened their death, caused by Man-6-P accumulation which inhibits glucose metabolism (glycolytic enzymes) and depletes intracellular ATP. Although Pannerselvam et al (24) showed that incubation with exogenous mannose transiently corrected altered N-glycosylation in fibroblasts from patients with CDG I and Alton et al (19) showed the feasibility and safety of orally ingested mannose, the toxicity of mannose remains questionable. Thus, an unsolved issue is the duration of mannose supplementation, particularly in patients with mild presentation (13), but also in more severe patients.

There is a possible negative relation between the severity of hepatic disease and the correction of transferrin profile, due to its synthesis in the liver. Indeed, CDG Ib patients without any clinical or biological liver disease (8, 16) or few liver symptoms (12) are those where complete correction of the glycosylation profile is observed using mannose therapy.



All other patients had incomplete normalization of the transferrin isoelectrofocusing profile (15).

Recently, Liem et al (18) reported an adult patient with CDG Ib who presented with edema, diarrhea, hypoalbuminemia and pancytopenia and had a history of congenital hepatic fibrosis, portal hypertension and esophageal varices. In the past she had had no positive response to mannose therapy because of associated diarrhoea and abdominal pain which increased on mannose supplementation. Because protein-losing enteropathy was observed, an alternative therapy was needed. Heparin has been previously used to treat protein-losing enteropathy, mainly in children using Fontan procedure (25). Indeed, mucosal injury and increased lymphatic pressure as the two mechanisms known to cause protein-losing enteropathy have been shown to be reversed by heparin sulfate in several models (26). Infusion of unfractionated heparin relayed by subcutaneous injections of unfractionated heparin twice a day was proposed as a solution, and found to improve the overall clinical condition. The dosage of heparin was monitored using heparin antifactor Xa levels, which remained well below the therapeutic range. Thus, heparin therapy could be an alternative (or be complementary) to mannose in some patients, particularly in the case of profuse enteropathy unresponsive to mannose therapy., Further studies are however necessary to confirm its efficacy on protein-losing enteropathy and to specify the characteristics of CDG Ib patients who could require this new therapy.

### **Conclusion**

Therapy with mannose has transformed lethal CDG Ib into a treatable disease, and the success achieved by oral administration of mannose makes diagnosing PMI deficiency all the more important. It should be pointed out, however, that in some patients this treatment cannot control post-natal liver disease, possibly a consequence of a disorder in foetal development. This will probably be a prognostic factor for the future of such CDG1b patients. Heparin therapy could be an alternative to mannose to treat protein-losing enteropathy of CDG Ib patients.

**Acknowledgments:**

This work was funded by Euroglycanet (FP6- Contract Nr. LSHM-CT2005-512131) and the Fondation Jérôme Lejeune.

1. Jaeken J, Carchon H. Congenital disorders of glycosylation: a booming chapter of pediatrics. *Curr Opin Pediatr* 2004;16(4):434-439.
2. Pedersen PS, Tygstrup I. Congenital hepatic fibrosis combined with protein-losing enteropathy and recurrent thrombosis. *Acta Paediatr Scand* 1980;69(4):571-574.
3. Pelletier VA, Galeano N, Brochu P, Morin CL, Weber AM, Roy CC. Secretory diarrhea with protein-losing enteropathy, enterocolitis cystica superficialis, intestinal lymphangiectasia, and congenital hepatic fibrosis: a new syndrome. *J Pediatr* 1986;108(1):61-65.
4. Vuillaumier-Barrot S, Le Bizec C, de Lonlay P, Barnier A, Mitchell G, Pelletier C, et al. Protein-losing enteropathy-hepatic fibrosis syndrome in Saguenay-Lac St-Jean, Québec is congenital disorder of glycosylation type Ib. *J Med Genet* 2002;39(11):849-851.
5. Jaeken J, Matthijs G, Saudubray JM, Dionisi-Vici C, Bertini E, de Lonlay P, et al. Phosphomannose isomerase deficiency: a carbohydrate-deficient glycoprotein syndrome with hepatic-intestinal presentation. *Am J Hum Genet* 1998;62(6):1535-1539.
6. de Koning TJ, Dorland L, van Diggelen OP, Boonman AM, de Jong GJ, van Noort WL, et al. A novel disorder of N-glycosylation due to phosphomannose isomerase deficiency. *Biochem Biophys Res Commun* 1998;245(1):38-42.
7. de Koning TJ, Nikkels PG, Dorland L, Bekhof J, De Schrijver JE, van Hattum J, et al. Congenital hepatic fibrosis in 3 siblings with phosphomannose isomerase deficiency. *Virchows Arch* 2000;437(1):101-105.
8. Niehues R, Hasilik M, Alton G, Korner C, Schiebe-Sukumar M, Koch HG, et al. Carbohydrate-deficient glycoprotein syndrome type Ib. Phosphomannose isomerase deficiency and mannose therapy. *J Clin Invest* 1998;101(7):1414-1420.
9. de Lonlay P, Cuer M, Vuillaumier-Barrot S, Beaune G, Castelnau P, Kretz M, et al. Hyperinsulinemic hypoglycemia as a presenting sign in phosphomannose isomerase deficiency: A new manifestation of carbohydrate-deficient glycoprotein syndrome treatable with mannose. *J Pediatr* 1999;135(3):379-383.
10. Penel-Capelle D, Dobbelaere D, Jaeken J, Klein A, Cartigny M, Weill J. Congenital disorder of glycosylation Ib (CDG-Ib) without gastrointestinal symptoms. *J Inherit Metab Dis* 2003;26(1):83-85.
11. Damen G, de Klerk H, Huijmans J, den Hollander J, Sinaasappel M. Gastrointestinal and other clinical manifestations in 17 children with congenital disorders of glycosylation type Ia, Ib, and Ic. *J Pediatr Gastroenterol Nutr* 2004;38(3):282-287.
12. Harms HK, Zimmer KP, Kurnik K, Bertele-Harms RM, Weidinger S, Reiter K. Oral mannose therapy persistently corrects the severe clinical symptoms and biochemical abnormalities of phosphomannose isomerase deficiency. *Acta Paediatr* 2002;91(10):1065-1072.
13. Westphal V, Kjaergaard S, Davis JA, Peterson SM, Skovby F, Freeze HH. Genetic and metabolic analysis of the first adult with congenital disorder of glycosylation type Ib: long-term outcome and effects of mannose supplementation. *Mol Genet Metab* 2001;73(1):77-85.

14. de Koning TJ, Dorland L, van Berge Henegouwen GP. Phosphomannose isomerase deficiency as a cause of congenital hepatic fibrosis and protein-losing enteropathy. *J Hepatol* 1999;31(3):557-560.
15. Mention K, Lacaille F, Valayannopoulos V, Romano S, Kuster A, Cretz M, et al. Development of liver disease despite mannose treatment in two patients with CDG-Ib. *Mol Genet Metab* 2008;93:40-43.
16. Hendriksz CJ, McClean P, Henderson MJ, Keir DG, Worthington VC, Imtiaz F, et al. Successful treatment of carbohydrate deficient glycoprotein syndrome type 1b with oral mannose. *Arch Dis Child* 2001;85(4):339-340.
17. Mayatepek E, Kohlmuller D. Mannose supplementation in carbohydrate-deficient glycoprotein syndrome type I and phosphomannomutase deficiency. *Eur J Pediatr* 1998;157(7):605-606.
18. Liem YS, Bode L, Freeze HH, Leebeek FW, Zandbergen AA, Paul Wilson J. Using heparin therapy to reverse protein-losing enteropathy in a patient with CDG-Ib. *Nat Clin Pract Gastroenterol Hepatol* 2008;5(4):220-224.
19. Alton G, Kjaergaard S, Etchison JR, Skovby F, Freeze HH. Oral ingestion of mannose elevates blood mannose levels: a first step toward a potential therapy for carbohydrate-deficient glycoprotein syndrome type I. *Biochem Mol Med* 1997;60(2):127-133.
20. Etchison JR, Freeze HH. Enzymatic assay of D-mannose in serum. *Clin Chem* 1997;43(3):533-538.
21. Freeze H. Human glycosylation disorders and sugar supplement therapy. *Biochem Biophys Res Commun* 1999;255:189-193.
22. Mayatepek E, Schroder M, Kohlmuller D, Bieger WP, Nutzenadel W. Continuous mannose infusion in carbohydrate-deficient glycoprotein syndrome type I. *Acta Paediatr* 1997;86(10):1138-1140.
23. DeRossi C, Bode L, Eklund EA, Zhang F, Davis JA, Westphal V, et al. Ablation of mouse phosphomannose isomerase (Mpi) causes mannose 6-phosphate accumulation, toxicity, and embryonic lethality. *J Biol Chem* 2006;281(9):5916-5927.
24. Panneerselvam K, Freeze HH. Mannose corrects altered N-glycosylation in carbohydrate-deficient glycoprotein syndrome fibroblasts. *J Clin Invest* 1996;97(6):1478-1487.
25. Bendayan I, Casaldaliga J, Castello F, Miro L. Heparin therapy and reversal of protein-losing enteropathy in a case with congenital heart disease. *Pediatr Cardiol* 2000;21:267-268.
26. Bode L, Salvestrini C, Park PW, Li JP, Esko J, Yamaguchi Y, Murch S, Freeze H. Heparan sulfate and syndecan-1 are essential in maintaining murine and intestinal epithelial barrier function. *J Clin Invest* 2008;118(1):229-238

## Figure legend

Figure 1: Biosynthesis of GDP-mannose from the glycolytic intermediate fructose 6-phosphate: phosphomannose isomerase (PMI), phosphomannomutase (PMM) and GDP-mannose pyrophosphorylase (GMPP). Synthesis of GDP-mannose from exogenous mannose requires hexokinase (HK) (or glucokinase in the liver) together with PMM and GMPP.

Figure

