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Oral mannose therapy persistently corrects the severe clinical symptoms and biochemical abnormalities of phosphomannose isomerase deficiency

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Phosphomannose isomerase (PMI) deficiency (CDG-Ib) is a newly recognized disorder of mannose and glycoprotein metabolism. PMI deficiency manifests itself mainly as a gastrointestinal disorder with protein-losing enteropathy and life-threatening intestinal bleeding. Hypoglycaemia is an additional prominent symptom. In contrast to phosphomannomutase deficiency (CDG-Ia), there are no neurological symptoms. PMI deficiency blocks the endogenous mannose formation from glucose. Exogenous oral mannose supply bypasses the enzymatic block and leads to the disappearance of all symptoms in the patient. The striking ultrastructural abnormalities of the rough endoplasmatic reticulum of the duodenal epithelial cells completely normalize and the hypoglycosylation disappears, as evidenced by the normal isoelectric focusing pattern of serum transferrin, the standard diagnostic procedure for recognition of CDG. This paper includes a detailed description of the clinical symptomatology of the first-ever diagnosed and treated patient with PMI deficiency and a 5-y follow-up study of mannose therapy.

Key words: *Gastrointestinal bleeding, hypoglycaemia, mannose therapy, phosphomannose isomerase deficiency (CDG-Ib), protein-losing enteropathy*

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In 1980 Jaeken et al. (1) described a new type of multisystem disorder, which has been termed carbohydrate-deficient glycoprotein syndrome (CDG) and, more recently, congenital disorders of glycosylation (CDG). The clinical picture comprises psychomotor retardation, cerebellar ataxia, lower-limb neuropathy, retinal degeneration, skeletal deformities, vomiting and diarrhoea with concomitant failure to thrive during infancy (2, 3).

In 1995 it was shown that in most patients the enzyme phosphomannomutase (PMM), which converts mannose 6-phosphate to mannose 1-phosphate, is deficient (4). This leads to an incomplete N-linked glycosylation of glycoproteins, an abnormal polypeptide folding in the endoplasmic reticulum and alterations in the physicochemical properties of the proteins. The most constant and characteristic biochemical finding in CDG is the presence of hypoglycosylated plasma glycoproteins. The hypoglycosylation is routinely determined by isoelectric focusing (IEF) of serum transferrin. Owing to partially missing carbohydrate side chains, the abnormal transferrins show a characteristic altered IEF pattern (type 1 pattern) (5–8).

Recently, a new type of CDG was described, with a deficiency of phosphomannose isomerase (PMI), which converts fructose 6-phosphate to mannose 6-phosphate (9). The IEF pattern of serum transferrin of this patient was identical to that observed in PMM-deficient patients. However, in contrast to PMM deficiency, the clinical phenotype of PMI deficiency was very different and consisted of gastrointestinal symptoms, whereas neurological abnormalities were absent.

This paper provides details on the clinical presentation and the results of 5 y of treatment with oral mannose in the first-ever diagnosed and treated child with PMI deficiency.

Patient report

The patient is the second son of non-consanguineous parents of Austrian and southern German origin. The father and the grandmother on the mother's side as well as two maternal uncles suffered from recurrent duodenal ulcers.

After an uneventful pregnancy, the patient was born

Table 1. Important clinical events in the PMI-deficient patient.

			Laboratory values*					
Event	Age	Symptoms, interventions	Hgb g/dl	WBC/ mm^3	Protein (P) or albumin (A) g/l	AT III %	Glucose mmol/L	Others
1	13 mo	Fever, vomiting, dark diarrhoeal stools, oedema, abdominal distension	8.8	41.600	28 (P)	/	2.33–3.27	ASAT 60 U, ALAT 58 U
2	4 y	Fever, vomiting, diarrhoea, severe pain in all extremities and in the temples, suggillations in both legs	10.7	47.300	58 (P)	17	/	Fibrinogen 130 mg /dl d-Dimers 146–192 μg/ml
3	4 y 9 mo	Severe bleeding from a duodenal ulcer (Ø 1 cm)	6.3	19.000	31 (A)	45	/	Transferrin 175 mg/dl CHE 2.682 U/L
4	5 y 3 mo	Severe abdominal pain, headache, temporal swelling	12.6	20.000	28–35 (A)	18–26	1.88	CHE 1369 U/l, Transferrin 150 mg/dl, α_1 AT 85 mg/dl
5	5 y 6 mo	Severe abdominal pain, right temporal swelling, vomiting, diarrhoea	10.8	25.700	28 (A)	7	0.44–1.99 HbA_1C 3.9%	Faecal α_1 AT 6 mg/g, Factor VII, XI, XII, prot. C and S, 28–68%
6	5 y 10 mo	Severe abdominal pain, → laparotomy; diffuse abacterial peritonitis, jejunal microthrombotic-like spots	10.1	20.000	21 (A)	8	3.82	ALAT 40 U, CHE 1705 U/L Fibrinogen 618 mg/dl CRP 8,3 mg/dl
7	5 y 11 mo	Massive bleeding from a small duodenal ulcer, stopped endoscopically by adrenalin and adhesive fibrin	6.8	13.800	19–28 (A)	54	2.22	/
8	6 y	Recurrence of a diffuse duodenal bleeding → ligation of the A. Gastroduodenalis	8.8	12.300	28 (A)	/	/	CHE 2222 U/L
9	6 y 9 mo	Severe gastric bleeding which could not be stopped (40 erythrocyte transfusions) → partial gastrectomy, factor XIII, octreotide	7.6	10.400	23 (A)	37	2.60	Fibrinogen 518 mg/dl

* Normal values: Total serum protein 61–79 g/L, albumin 34–50 g/L, antithrombin (AT) III 80–120%, Glucose 60–100 mg/dl = 3.3–5.5 mmol/L, HbA_1C 4.2–6.3%, ASAT $<$30 U/l, ALAT $<$23 U/L, cholinesterase (CHE) 3000–6000 U/L, transferrin 208–347 mg/dl, $\alpha_1$antitrypsin (AT) 147–245 mg/dl, fibrinogen 200–400 mg/dl, d-Dimers $<$0.5 μg/ml, faecal α_1AT $<$1 mg/g dried stool, CRP $<$1.0 mg/dl.

PMI: phosphomannomutase.

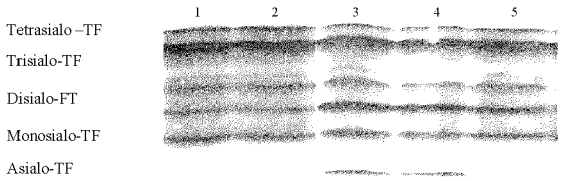

Fig. 1. Isoelectric focusing (IEF) of serum transferrin (TF). 1 + 2: controls; 3: PMM (phosphomannomutase) deficiency; 4: PMI deficiency before mannose; 5: PMI deficiency after 5 y on mannose.

with a birthweight of 3350 g and a hypospadias (degree I–II). He was breastfed exclusively for the first 7 mo and showed normal physical and psychomotor development during this period. After the introduction of solid food during the 8th mo of age, the patient suffered occasional vomiting episodes.

At the age of 13 mo in addition to vomiting, fever and diarrhoea occurred. Some of the stools were dark in colour so that, in retrospect, a gastrointestinal bleeding was suspected. The boy was undernourished and apathetic, and displayed oedema and abdominal distension. The most striking laboratory findings are listed in Table 1 (event 1). Although glucose was given intravenously, there was a tendency towards low blood glucose levels. After intravenous serum protein substitution and without any antibiotic treatment being given, the patient recovered rapidly but only temporarily. Diarrhoea and insufficient weight gain persisted and the total serum protein concentration remained low (30 g/L). When IgA and IgG gliadin antibodies became slightly elevated (66 and 36 Arbitrary Units, respectively, normal values $<$25 AU), a small intestine biopsy was performed revealing a subtotal villous atrophy, suggestive of coeliac disease. A gluten-free diet was not as successful as expected nor did an additional trial with a cow's-milk-free diet later on improve the clinical situation. After 2 mo on the diet a second small intestine biopsy again revealed a subtotal villous atrophy and the serum protein concentration continued to be low (40 g/L).

From the 4th y of life, several dramatic events made hospitalization imperative (Table 1). Clinically, these events were similar to the first one and were characterized by sudden onset, occasional fever, vomiting, severe abdominal pain and moderate enlargement of the liver, diarrhoea, painful temporal swellings and one-time painful suggillations on the legs (events 2, 4, 5).

At the age of 5 y 10 mo (event 6) a sudden fever with persistent severe abdominal pain occurred. The severe abdominal symptoms made a surgical intervention inevitable. Laparatomy revealed diffuse abacterial peritonitis. The jejunum showed many microthrombotic-like spots. However, an intestinal resection was avoided.

All the clinical events were accompanied by normocytic anaemia, excessive leucocytosis, low serum

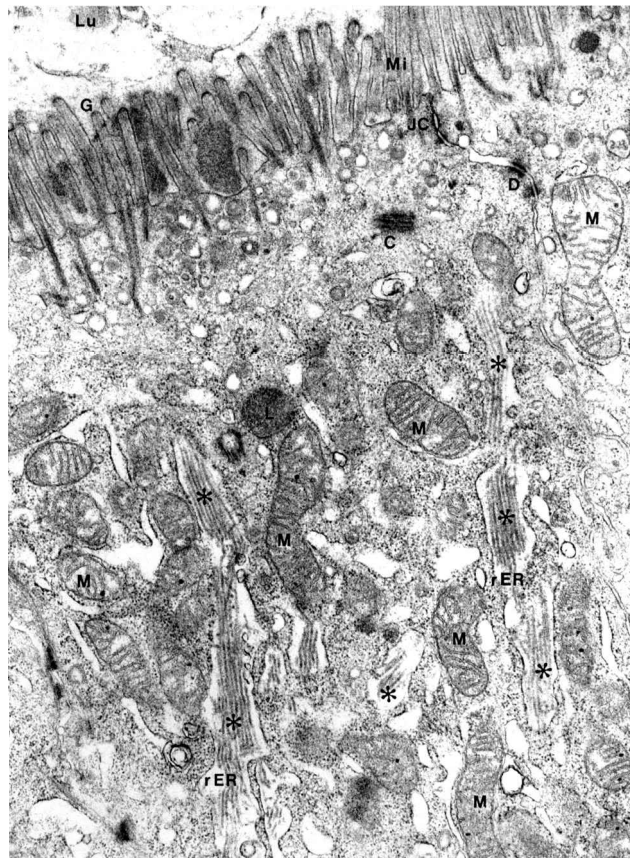

Fig. 2. Ultrastructure of enterocytes before mannose therapy. Epon section of the small intestinal biopsy specimen showing an enterocyte with tubular bundles within the rough endoplasmic reticulum (rER). These longitudinal and parallel structures are indicated with asterisks. The glycocalyx (G) appears to be reduced. Lu = lumen; Mi = microvilli; M = mitochondria; C = centriole; D = desmosome; L = lysosome. ×26000.

proteins, slightly elevated transaminases, low cholinesterase activity, hypoglycaemia and low AT III activity. Low AT III was first recognized at the age of 4 y (Table 1).

No proteinuria was found, but a protein-losing enteropathy was demonstrated by elevated faecal α_1-antitrypsin (event 5).

During hypoglycaemia of 48 mg/dl (event 5), insulin and C-peptide were found to be in the normal range at 20 μU/ml and 2.8 ng/ml, respectively (normal values for insulin 8–24 μU/ml and C-peptide 1.1–3.6 ng/ml). Furthermore, growth hormone, cortisol and IgF1 levels were normal.

During event 4 the low AT III levels, which were also seen when the patient was in good health, initiated CDG diagnostics. The IEF of serum transferrin, the standard diagnostic test for CDG, showed the characteristic hypoglycosylation pattern of PMM deficiency (Fig. 1). However, the patient did not show any signs of neurological or mental disorders and did not present

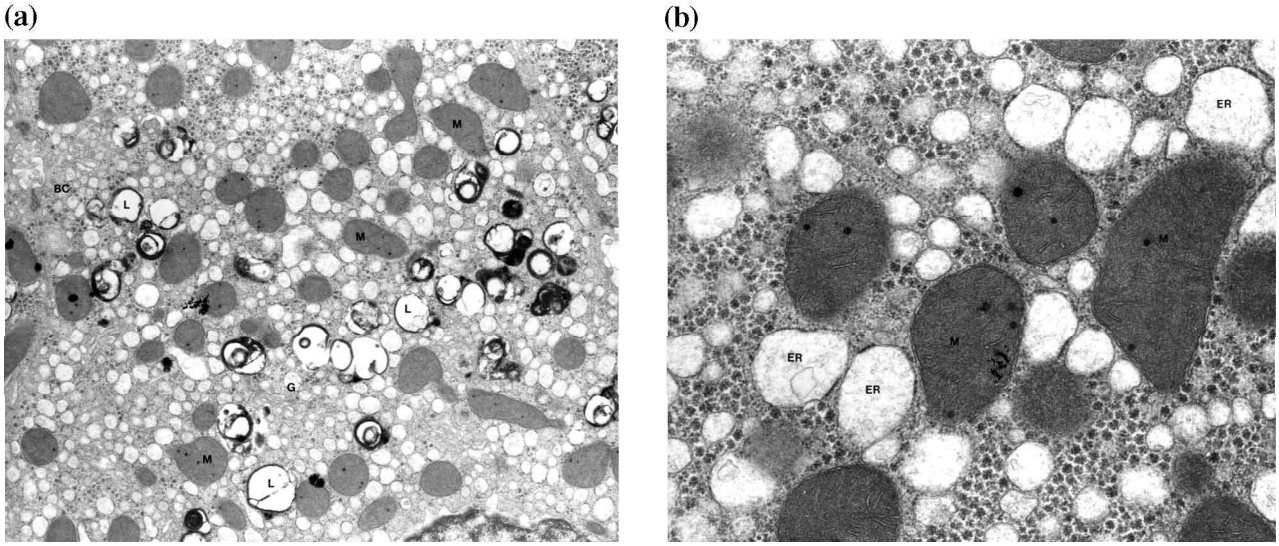

Fig. 3. Ultrastructure of hepatocytes before mannose therapy. a) Epon section of a hepatocyte showing many lysosomes (L) containing myelin-like structures. M = mitochondrium; G = Golgi apparatus; BC = Bile canaliculus. ×16 000. b) The lumen of the rough endoplasmic reticulum (ER), which can be identified by the widening of the ribosomes on the outside of this compartment. The lumen does not contain any paracrystalline structures; M = mitochondrium. ×45 000.

any skeletal deformities or lipodystrophy. Only chronic diarrhoea, failure to thrive and low AT III levels fit the description of PMM deficiency. Serum levels of LH, FSH, testosterone, TSH, T_3 and T_4 were normal. MRI of the brain was normal.

From the 5th y of life severe upper gastrointestinal bleeding became the dominant symptom. These bleeding episodes occurred when AT III was low (event 3, 7), but also when AT III was normal after weekly AT III infusions (event 8). Endoscopically, only a single small duodenal ulcer of barely 1 cm in diameter surrounded by multiple small erosions was seen on two occasions (events 3 and 7). The last and most severe bleeding (event 9) was localized to the gastric corpus, and was very diffuse, without visible mucosal defects.

Upon histological investigation, the duodenal mucosa merely showed a focal unspecific duodenitis, normal vessels and a normal villous architecture. Light microscopy of the resected gastric tissue (event 9) again showed only mucosal and submucosal bleedings and no thrombosis. Electron microscopy (EM) of the gastric mucosa was also normal. Gastric and duodenal mucosa was free of *Helicobacter pylori*.

Two months after the fifth event, when the patient was in good clinical condition, selective liver and small intestine biopsies were performed, which showed striking abnormalities on EM examination (Fig. 2, 3).

In general, the sudden severe attacks without bleeding (events 1, 2, 4, 5) quickly disappeared after AT III and albumin substitution, whereas the severe upper gastrointestinal bleeding could not be stopped endoscopically or with gastric acid blockers, antacids or the infusion of clotting factors. Even surgical interventions, including ligatures of the A. gastroduodenalis and A. gastrica sinistra as well as a partial gastrectomy had no lasting effects. Finally, the erythrocyte transfusions (event 9) led to a life-threatening hyperinfusion syndrome with pulmonary oedema, and the bleeding stopped only when the somatostatin analogue Octreotide® and factor XIII concentrate were given.

Mannose treatment

During the last bleeding episode, a paper by Panneerselvam et al. (10) described how the addition of mannose to cultures of PMM-deficient CDG fibroblasts corrected the incorporation of mannose into proteins and the size of lipid-linked oligosaccharide precursors.

Although PMM deficiency had already been excluded and we assumed the condition to be a new CDG type, the severe complications of our patient encouraged us to try oral mannose therapy. The fasting mannose levels of our patient, determined spectrometrically as well as by mass chromatography/mass spectrometry (11), ranged between 11 and 37 μM and were below the normal range of 45–65 μM (12). Blood levels were raised to 270–280 μM by treatment with 100 mg mannose/kg body weight and to 330–490 μM with 150 mg/kg after a maximum of 60 to 90 min of ingestion (9).

Oral mannose therapy was started with 3 × 2 g (0.1 g/kg body weight per dosis) in a 10% aqueous solution. After one month on mannose and 6 wk after the last AT III substitution, the first normal AT III value of 116% appeared (Fig. 4). Since then, AT III levels have been constantly within the normal range. Albumin slowly

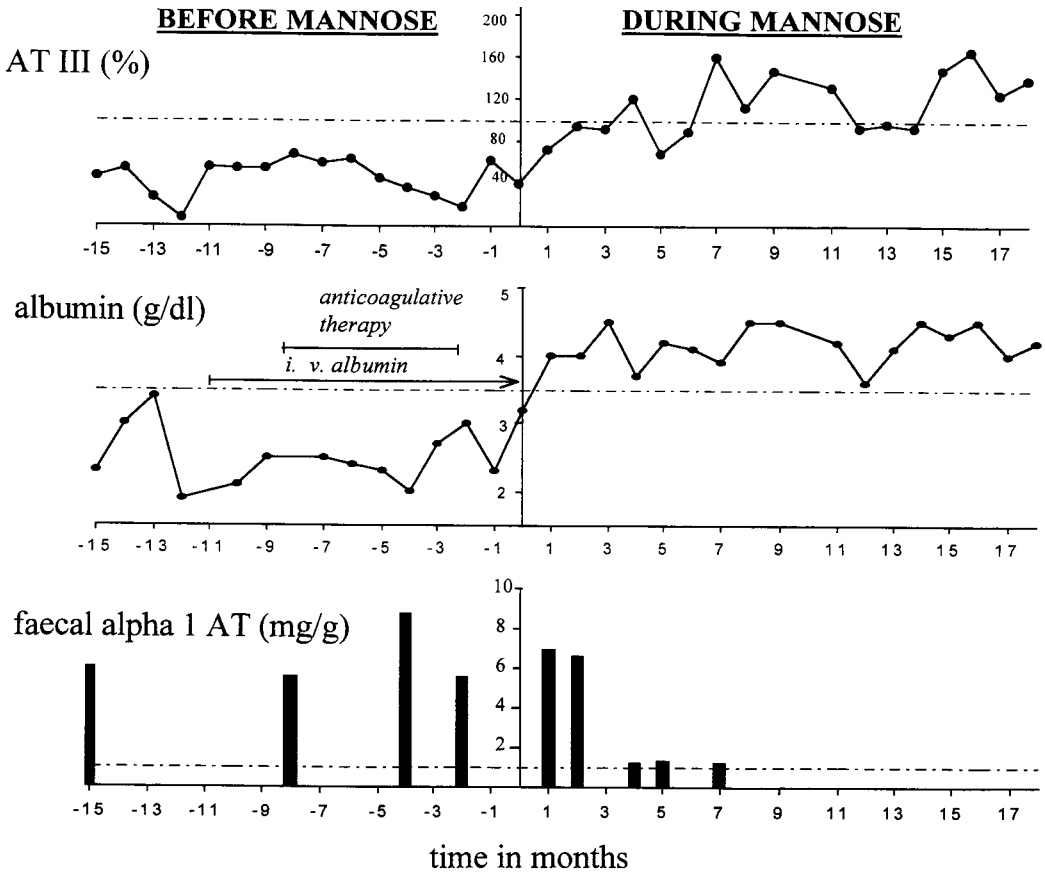

Fig. 4. The course of antithrombin III (AT III), serum albumin and faecal α_1 antitrypsin (AT) before and during mannose therapy. The dotted lines represent the low normal limits.

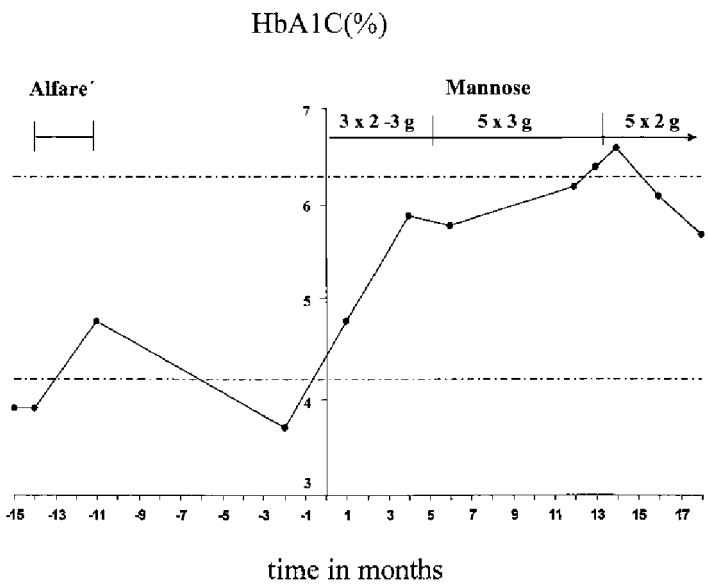

Fig. 5. The figure shows the course of the HbA_1C values before and during mannose therapy. The normal range is indicated by dotted lines; 750 ml of the hydrolysate Alfaré® in a high caloric density of 1 kcal/ml was given by nasogastric tube during a period of 3 mo.

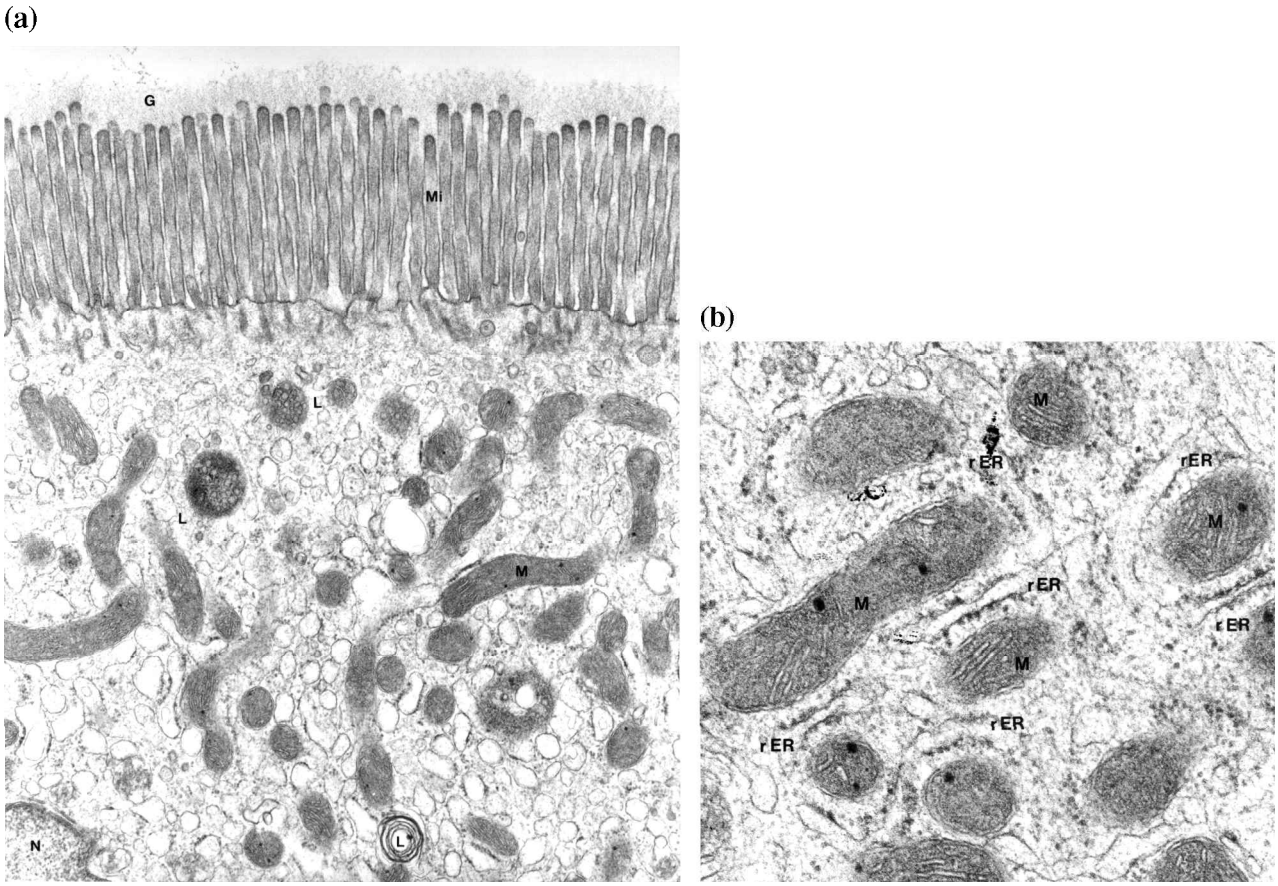

Fig. 6. Ultrastructure of enterocytes after 16 mo on mannose therapy. a) A few lysosomes (L) are still detectable within the enterocytes. The glycocalyx (G) is broader than that in Fig. 1a; N = nucleus; ×26 500. b) The rough endoplasmic reticulum (rER) is not widened and lacks any tubular structures that were detectable before start of the mannose therapy; M = mitochondrium. ×70 000.

increased from 32 g/L to 42 g/L within 2 mo. No further substitution was necessary. The faecal α_1-antitrypsin excretion became normal by the fourth month of therapy (Fig. 4). In parallel, stool consistency and frequency normalized.

After only 11 mo of therapy a definite shift from abnormal isoforms to a normal pattern of transferrin and other glycoproteins was observed. Today the isoelectric focusing of transferrin is indistinguishable from a normal control (Fig. 1). Both, the quality and the quantity of serum glycoproteins changed during mannose therapy. Transferrin increased from a mean of 180 mg/dl during the first year on mannose to a mean of 227 mg/dl during the second year. A similar behaviour pattern was found for α_1-antitrypsin and IgG with a mean of 133 mg/dl α_1-antitrypsin and 703 mg/dl IgG (normal 570–1500 mg/dl) during the first year and 143 mg/dl and 856 mg/dl, respectively, in the subsequent year of treatment.

Upon mannose treatment, hypoglycaemia disappeared, the fasting glucose levels became normal and HbA_1C levels rose to the normal range (Fig. 5). When mannose was further increased to 5 × 3 g, slightly loose stools and abdominal bloating appeared and HbA_1C increased above the normal limit (Fig. 5). The reduction of mannose to 5 × 2 g brought the HbA_1C level back into the normal range. Mannose administration merely induced normoglycaemia but no hyperglycaemia, since the glucose levels were 91 and 93 mg/dl one and a half hours after application of, respectively, 2 g and 3 g mannose.

Sixteen months after the initiation of mannose therapy, another small intestine biopsy was obtained. The paracrystalline structures in the endoplasmic reticulum of the epithelial cells were no longer visible and the glycocalix was now of normal thickness. (Fig. 6).

Excessive mannose doses may be toxic for the kidneys (13, 14). After 4 y on mannose, our patient showed a normal creatinine clearance and inconspicuous ultrasounds of the kidneys.

Today the patient is 11 y of age and attends the secondary school, with no problems. His height follows the 5th percentile and his weight the 25th percentile.

During the past five years he merely experienced some bouts of the common cold, which he recovered from without any complications.

Discussion

The patient described above plays a key role in the CDG group, since he was the first to be free of neurological and mental symptoms and the first whose severe symptoms disappeared completely and permanently with oral mannose therapy. About one year after the beginning of the successful mannose therapy, a deficiency of phosphomannose isomerase (PMI) proved to be the cause of the condition (9).

Meanwhile, the case studies of 12 additional PMI-deficient patients have been published, mostly as short communications and confirmations of the efficacy of mannose therapy (15–22).

The increasing number of known PMI-deficient patients and the unspecific symptomatology, at least in the beginning of the disease, suggest that the disease is more frequent than supposed and presumably underdiagnosed.

Usually the symptomatology of PMI deficiency starts with gastrointestinal problems, as in our patient, where the clinical picture was indistinguishable from coeliac disease. Only the slow response to a gluten-free diet and the persistent marked hypoproteinaemia were atypical for coeliac disease. At the age of 5 y, when the patient was still on a gluten-free diet, the villous architecture of the small intestinal mucosa was normal but revealed striking ultrastructural abnormalities of the epithelial cells. The tubular bundles enlarging the rough endoplasmic reticulum, may have represented hypoglycosylated misfolded and precipitated proteins. The glycocalix was small.

The persistent low albumin levels observed in our index patient were also seen in eight other PMI-deficient patients (16–18, 21), but the gastrointestinal protein loss was also proven in only three of them. However, the mechanism of the intestinal protein loss is difficult to explain by the ultrastructural changes of the epithelial cells only. A disturbed hepatic albumin synthesis may also contribute to hypoalbuminaemia, as shown in one patient (21, 23).

One of the most prominent symptoms in our patient, which was seen in only one other PMI-deficient patient (23), was the life-threatening upper gastrointestinal bleedings. These occurred in parallel with temporal and extremity swellings and elevated D-dimers, but also after optimizing the AT III levels or during anticoagulative therapy. The histology of resected material could not explain the bleedings. The underdeveloped glycocalix and a capillary leakage may have contributed to the mostly diffuse bleedings. Hypoglycaemia was found to be one of the most regular symptoms in PMI deficiency (16–20). In some patients, mild hyperinsulinism was found during several but not all hypoglycaemic episodes (17, 18), indicating that this might not be the only explanation for hypoglycaemia in this metabolic disorder.

In our patient liver disease did not seem to be as severe as that described in the other PMI-deficient patients (16–22). Liver enlargement and temporary slight changes of liver enzymes occurred only when our patient experienced sudden attacks of abdominal pain, vomiting, fever, etc. (Table 1). The histology of the liver revealed only a very slight fibrosis.

For as long as the underlying enzyme defect was unknown, the success of oral mannose therapy was thought to be a "miracle". All clinical and biochemical abnormalities became normal with 5×100 mg mannose kg^{-1} d^{-1} after 1–4 mo on treatment and the striking ultrastructural changes in the small intestine epithelial cells disappeared. The higher affinity for haemoglobin of mannose compared to glucose (24) may explain the good correlation of the HbA_1C levels with the amount of mannose given. Therefore regular HbA_1C monitoring may be helpful in preventing overdosage.

Obviously, a normal or gluten-free diet, as in our patient, did not provide enough mannose to compensate for the failure of its endogenous production, but the fact that our patient experienced a relatively mild phase of the disease from the second to the fourth year of his life, may point to better dietary mannose supplementation during this period. We found out that the gluten-free diet of the patient at this time included about 15 g/d of the cacao supplement CAROB®, which is made from locust beans. The concentration of free mannose was high and about 500 μmol in a solution with 37.5 mg Carob/ml.

Very little is known about the quantities of mannose in the human diet and its availability. A recent study of a 33-y-old PMI-deficient adult (21) who never received oral mannose supplementation and who was free of symptoms after childhood underlines the need for more research on dietary mannose.

PMI deficiency makes clear for the first time the relative importance of mannose generated by two metabolic pathways: the endogenous pathway (I) where fructose-6-phosphate is isomerized to mannose-6-phosphate by PMI or where mannose originates from the cellular glycoconjugate breakdown, and the exogenous pathway (II), where mannose comes from the diet. It became obvious that, under normal dietary conditions, the exogenous mannose provision is not enough to compensate for an endogenous metabolic block, whereas oral supplementation of higher amounts of mannose may bypass the endogenous blocking of mannose synthesis and fully correct its pathological consequences without major side effects during 5 y of therapy.

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