Dietary Mannose Supplementation in Phosphomannomutase 2 Deficiency (PMM2-CDG)

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Research

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Abstract

Background

PMM2-CDG (CDG-Ia) is the most frequent N-glycosylation disorder. While supplying mannose to PMM2-deficient fibroblasts corrects the altered N-glycosylation in vitro, short term therapeutic approaches with mannose supplementation in PMM2-CDG patients have been unsuccessful. Mannose found no further mention in the design of a potential therapy for PMM2-CDG in the past years, as it applies as ineffective. This retrospective study analyzes the first long term mannose supplementation in 20 PMM2-CDG patients. Mannose was given at a total of 1–2 g mannose/kg b.w./d divided into 5 single doses over a mean time of 60,7 months. Protein glycosylation, blood mannose concentration and clinical presentation were monitored in everyday clinical practice.

Results

After a mean time period of more than 1 year the majority of patients showed significant improvements in protein glycosylation.

Conclusion

Long-term dietary D-mannose supplementation shows biological effects in PMM2-CDG, an inherited disorder of mannose metabolism. It improves glycosylation in the majority of patients and could become the first cornerstone in the treatment of this disease.

1. Introduction

Congenital disorders of glycosylation (CDG) are a steadily growing group of inherited disorders caused by an impaired glycoprotein and -lipid production [1]. The most common type is the N-glycosylation defect caused by phosphomannomutase 2 (EC 5.4.2.8) deficiency (PMM2-CDG or CDG-Ia; OMIM 601785) [2]. Patients with PMM2-CDG have a broad and variable spectrum of clinical presentations with psychomotor retardation, muscular hypotonia, failure to thrive, ataxia, epilepsy, strabismus, cerebellar hypoplasia, liver dysfunction, coagulopathy, variable development delay, dysmorphic features, and inverted mammilles; in later stages there may be stroke-like episodes and retinitis pigmentosa, while nerve conduction velocity and tendon reflexes decrease with age [3–6].

In another CDG, MPI-deficiency (EC 5.3.1.8) (CDG-Ib, mannosephosphate isomerase deficiency; OMIM 154550), patients benefit from a dietary supplementation of mannose, a monosaccharide that bypasses the reduced endogenous Man-6-P (mannose-6-phosphate), production caused by the MPI defect [7] *(Fig. S1)*. In PMM2-CDG utilization of exogenous mannose or Man-6-P originating from Frc-6-P (fructose-6-phosphate) is impaired, due to the enzyme PMM2 being located downstream their entrance. [7–10]. Mannose supplementation in PMM2-CDG should be less or not effective *(Fig. S1)*. However, adding mannose to a culture of PMM2-deficient fibroblasts [11] led to a correction of the glycosylation defects in

CDG-fibroblasts [11, 12]. In addition, a hypomorphic PMM2 mouse model showed that mannose could overcome the embryonic lethality of PMM2 offsprings, proving the biological effect of mannose in a PMM2-deficient in vivo model [13]. Short term attempts of providing dietary mannose to improve the hypoglycosylation in PMM2-CDG patients failed to show improvements [3, 4, 14, 15]. Since profound correction of the abnormal isoform pattern took eleven months in MPI-CDG [7], a time frame much longer than the biological half-life of the marker protein transferrin (app. 2 weeks) [16], it could take even more time in PMM2-CDG. To date, mannose applies as utterly ineffective for PMM2-CDG and no causative treatment for this disease is found, yet. This retrospective analysis provides data of a positive biochemical effect of a long-term mannose supplementation in PMM2-CDG.

2. Patients And Methods

Patients

Dietary sugar supplementations are standard-of-care in disorders of glycan metabolism in our hospital. 20 patients (10 female, 10 male) with PMM2-CDG aged ≤ 1 year – 27 years, who were treated with oral mannose, were analyzed retrospectively *(Table S1)*.

Diagnosis of each patient had previously been confirmed by isoelectric focusing of transferrin [17], by Sanger sequencing of the PMM2 gene and in some patients additionally by measuring PMM2 activity [17][18]. Data analysis was approved by the local ethics committee (Ethikkommission der Ärztekammer Westfalen-Lippe, No. 2019-199-f-S). All data used in this study were generated from standard clinical follow up visits.

Mannose supplementation

Mannose supplementation was done orally or by tube feeding. D-mannose was obtained as a dietary supplement from Nutricia GmbH. Parents were advised to dissolve mannose in water and to give it to their child with or after meals in 5 doses per day. No other nutritional interventions were done. In order to prevent gastrointestinal side effects, mannose was gradually increased over a few weeks to the final dose. If well tolerated, patients had the option to raise the mannose supplementation to a dose higher than 1 g/kg bw/d. In case of loose stools or flatulence parents were advised to reduce or stop the mannose supplementation until clinical recovery and to raise the dosage again.

Mannose assay

D-Mannose serum concentrations were determined by gas chromatography/ mass spectrometry employing trimethylsilyl derivates as described before [19], using perseitol and trehalose as internal standards. Blood samples before and after mannose ingestion were taken at random time points in our out-patient clinic.

Glycoprotein analyses

Serum or capillary blood samples in heparinized Microvettes® were used for quantification of transferrin isoforms by high performance liquid chromatography (HPLC) using the “CDT in serum- HPLC” kit from Chromsystems (Gräfelfing, Germany) [20]. Plasma levels of ATIII, factor IX, protein C and S were determined by routine clinical chemistry. Isoelectric focusing (IEF) was performed as described before [21–23]. Reference values of Tf- HPLC are according to Gründahl et al. and Nolting et al. [20, 22]: asialo- Tf: below level of detection; monosialo- Tf: below level of detection; disialo- Tf: 1,1 ± 0,72%; trisialo- Tf: 3,76 ± 2,6%; tetrasialo- Tf: 89,84 ± 4,16%; pentasialo- Tf: 6,4 ± 3,8%.

Reference values of coagulation parameters:

AT III: 82–126%; Prot. C act.: 70–140%; Factor XI: >70%; Protein S: 60–140%.

Routine parameters and supervision

Transaminases, bilirubin, LDH, CK, potassium, sodium, glucose, alkaline phosphatase and HbA1c were routinely measured by clinical chemistry methods.

Clinical data collection

Medical data of the 20 patients described in this study were retrospectively obtained between 1998 and 2019 from medical reports as well as from caretakers’ reports. Data for motor skills, speech, reading, writing and counting for each patient were raised using different methods including Griffith- Test, MFED (Münchener funktionelle Entwicklungsdiagnostik), developmental steps after Clahsen, physical examination in our ambulance and pediatric neurology as well as from other medical professionals and the parents’ reports. Every patient received physiotherapy (Voijta, Bobath or Galileo) as well as logopedic treatment and ergotherapy.

3. Results

Mannose supplementation

Patients were treated for a mean time period of 60,7 months. At the time of data collection, 9 patients were still treated with mannose without a long-term interruption. 11 patients stopped or interrupted the mannose supplementation for different periods of time. Episodes of mild diarrhea and/or flatulence occurred as side effects of mannose ingestion. A positive response to mannose therapy was defined as increase of tetrasialo-transferrin in Tf-HPLC by 50% of pretreatment levels within 2–3 years of mannose therapy. Probands were divided in “Responders” (n = 12) and “Non-responders” (n = 8) *(Table S1)*.

3.2 Glycoprotein analyses

Before mannose therapy, all patients had an abnormal glycosylation pattern in isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC) of serum transferrin. Sialo-transferrin glycosylation improved considerably in 12 patients under mannose (Fig. 1C, S2*)*. Other glycoproteins such as

Antithrombin III, Protein C, Protein S and Factor XI as well as transaminases improved to the same extent as the transferrin- HPLC pattern *(*Fig. 1B, *not all data shown)*.

Two responders were still treated with mannose at the time the data was collected *(Fig. S2)*

Ten probands with a response to mannose supplementation stopped mannose supplementation after respectively different periods of time *(*Fig. 1C*)*. Four patients, who stopped mannose supplementation are still undergoing follow up for a mean period of 43,25 ± 3 months without mannose therapy. Six of these ten patients did not receive any CDG-specific treatment for a mean period of 14,2 ± 1 years. Interruption of mannose intake after this time resulted in the reoccurrence of deficient HPLC glycosylation patterns to pretreatment values *(*Fig. 1C*)*. No patient was able to maintain the reference range of transferrin glycosylation. No patient developed pathologically increased HbA1c values, as it was described for oral mannose therapy in MPI- CDG patients (mean: 4,43 ± 0,7%; reference: 4,2–6,1%) [9]. No toxic side effects [24, 25] were observed.

3.2 Mannose Assay

We were able to obtain follow up data of mannose concentrations 60 and 90 minutes after ingestion from 5 patients *(Fig. S3)*. There were obvious intraindividual and interindividual fluctuations of the blood mannose concentration even if collected at the same time with the same mannose dosage. The mean D-mannose concentration in our patients before ingestion of mannose was 29,5 ± 7,7 µmol/l (n = 11; literature values for PMM2-CDG: 5–40 µM). Mannose concentrations increased to the mean peak blood mannose concentration of 247,5 ± 124 µmol/l (n = 7) 60–90 min after mannose ingestion.

Clinical presentation and development

Table 1

Clinical findings in all patients and by group (responders vs. non-responders)

Table 2

Structure oriented to Schiff et al., 2018 [33]. Retrieved clinical follow up data was not uniformly distributed for every partial aspect of clinical characteristics as well as no control group was examined. Thus, it should be acknowledged, that the retrospective analysis of clinical characteristics is intended to only provide an impression of the clinical development of our patients. Interpretation of clinical data has to be done with caution. Responders in particular made considerable progress including three- word sentences before five years and more word sentences before ten years of age. Reading, writing and counting skills were predominant in the responders' group. Three patients who started their mannose therapy after the age of five learned to speak three or more-word sentences despite previous non-existent speech anddeveloped free sitting or walking by the hand during mannose therapy.

Characteristics (n = number of patients with available data)	All patients n = 20	Responder n = 12	Non-responder n = 8
Failure to thrive (n = 20)	20	12	8
Dysmorphic symptoms (n = 13)	12	9	3
Motor involvement (n = 20)	20	12	8
Axial hypotonia (n = 13)	13	10	3
Cerebellar hypoplasia (n = 10)	9	4	5
Ataxia (n = 12)	12	8	4
Stroke-like episodes (n = 5)	4	2	2
Epilepsia (n = 6)	5	4	1
Demyelinating neuropathy (n = 12)	0	0	0
Hydrocele (n = I)	1	1	0
Upper limb nerve conduction velocitiy reduced (n = 1)	1	1	0
Lower limb nerve conduction velocity reduced (n = 10)	10	8	2
No proprioceptive reflex (n = 17)	14	9	5
Positive Babinski sign (n = 12)	3	2	1
Cognitive issues (n = 5)	5	4	1
Reading before 10 years (n = 2)	2	2	0
Aquired (n = 1)	1	1	0
Able to decipher (n = 2)	2	2	0
Counting (n = 5)	5	3	2

Characteristics (n = number of patients with available data)	All patients n = 20	Responder n = 12	Non-responder n = 8
Writing (n = 5)	3	2	1
Aquired (n = 2)	1	0	1
Single words (n = 3)	3	2	1
Speaks words before 2 years (n = 1)	6	4	2
Speaks 3 word sentences before 5 years (n = 10)	9	7	2
Speaks sentences before 10 years ≥ 2 years (n = 4)	2	2	0
Adapted education in normal school or kindergarden (n = 7)	7	4	3
Special institution for disabled individuals (n = 7)	7	3	4
Free sitting before 2 years (n = 15)	7	6	1
Standing with help device /AID before 2 years (n = 13)	4	4	0
Standing without help in ≥ 2–10 years (n = 10)	8	5	3
Walking autonomously before 2 years (n = 16)	0	0	0
Walking with help device/AID before 2 years (n = 12)	1	1	0
Walking autonomously in ≥ 2–10 years (n = 7)	1	1	0
Walking with help device/aid before ≥ 2–5 years (n = 15)	12	8	4
Sensorineural deafness (n = 9)	0	0	0
Strabismus (n = 15)	14	9	5
Retinitis pigmentosa (n = 5)	1	0	1
Nystagmus (n = 6)	3	1	2

Characteristics (n = number of patients with available data)	All patients n = 20	Responder n = 12	Non-responder n = 8
Astigmatism (n = 4)	1	1	0
Myopia (n = 2)	2	1	1
Hyperopia (n = 4)	4	2	2
Kyphosis and scoliosis (n = 8)	4	3	1
Osteopenia (n = 3)	0	0	0
Thorax deformation (n = 5)	2	2	0

Nerve conduction velocity and proprioceptive reflexes follow up

Three responders with follow up data showed a normalization of their nerve conduction velocity (NCV) during mannose therapy (reference values: ulnar nerve: >49 m/s, Post. tibial nerve: > 40 m/s) *(*Fig. 2, *not all data shown)*. Four responders with no proprioceptive reflexes at first clinical examination developed distinctly redeemable proprioceptive reflexes (particularly knee jerk).

4. Discussion

Previous reviews illustrated the relevance of an increased flux of Man-6-P (mannose-6-phosphate) into the glycosylation pathway, promoting individual or combined approaches of several pharmaceutical perspectives and mannose [26]. Still, mannose found no further mention in the design of a potential therapy for PMM2-CDG in the past years. This first approach of a long-term mannose supplementation in PMM2-CDG provides valuable data, that mannose is not completely inert in PMM2-CDG and underscores, that the underrecognized role of mannose in PMM2-CDG should be reconsidered. Long-term oral mannose supplementation in PMM2-CDG was well tolerated and led to considerable biochemical improvements in the majority of patients and indicates possible clinical improvements. Mannose supplementation is currently the standard of care treatment for MPI-CDG resulting in favorable effects on the biochemistry and the clinical outcome [7, 9]. In PMM2-CDG patients, dietary supplementations with mannose at 100 mg/kg every 3 h over 9 days [4] or 0,17 g/kg every 3,5 h over a period of 6 months [15], as well as a continuous i.v. mannose infusion of 5,7 g/kg mannose in a PMM2 deficient patient over a period of 3 weeks [14], failed to show improvement in glycosylation patterns or clinical benefits. The most likely explanation for the failure of mannose therapy in vivo is, Man-6-P being catabolized by the fully operative MPI, transferring the surplus of mannose to glycolysis [8], as an unfavorable PMM2:MPI ratio does not favor flux into glycosylation pathways [8]. However, the glycosylation deficiency in PMM2 fibroblasts can be restored completely by supplementing more than 250 µmol/l mannose[12][15].

Assuming, that mutations in PMM2 are hypomorph and reduce enzyme affinity for Man-6-P [11], it is possible, that exogenous mannose supplementation in PMM2-CDG fibroblast cultures leads an increased intracellular Man-6-P concentration, that counters the increased K_m requirements of deficient PMM2. This may lead to higher levels of Man-1-P, increasing the deficient GDP-mannose pools and culminating in the normalization of glycosylation [3]. Another possibility may be cytosolic mannose being directly converted into Man-1-P by another enzyme or system (not detected yet) [11]. Mannose therapy needs a long time to show effects in PMM2-CDG patients. Even in MPI-CDG, the first partial corrections in IEF- and SDS-patterns of serum transferrin occurred not until the first 6 months after initiation of a mannose therapy with a dose of 100 mg/kg three times a day [7], which cannot be explained by the half-life period of transferrin (CDT = ~ 14d; Not-CDT = ~ 8d) and other glycoproteins (AT III: 3d; Protein C: 6–8 h) [27]. Effects on the IEF pattern would be expected not later than four weeks. Eleven months after initiation and increased mannose dosage, a funded decrease of the abnormal isoforms in MPI-CDG was observed [7]. Thus, a biochemical correction in PMM2-CDG under mannose therapy may take a longer time and higher dosage to show positive effects, in the light of countering the K_m- requirement of the attenuated PMM2. Ichikawa et al. found that the contribution of exogenous mannose is higher than previously thought and that other potential sources of mannose such as mannose salvaged from degraded glycoproteins, glycogen and gluconeogenesis do not make significant contributions to N-glycosylation [10]. In fibroblasts increased exogenous mannose (1 mM) can completely replace glucose-derived mannose and become the sole source of mannose in N-glycans and also contribute to galactose and N-acetylglucosamine in N-glycans [10, 28]. Explanations for the higher contribution of mannose to N-glycans may be specific mannose transporters (GLUT-like mannose transporter, SGLT-5 mannose specific transporter) [29, 30]. About one third of mannose found in N-glycans takes detours as it is first converted to Frc-6-P and reconverted to Man-6-P again. Since the transient Frc-6-P derived from Man-6-P does not equilibrate with the total cellular pool of Frc-6-P, another suggestion may be the presence of separate Frc-6-P-pools ($Frc\text{-}6\text{-}P^{GP}$/$Frc\text{-}6\text{-}P^{G}$) like check-points for glycosylation, glycolysis and gluconeogenesis, generated by the anomeric selectivity of Glc-6-P and Man-6-P metabolizing enzymes *(Fig. S1)* [10, 28]. A preferable ratio of a- and ß- Man-6-P as well as of MPI (ß-Man-6-P anomer specific) and PMM2 (a-Man-6-P anomer specific) might result in a higher efficiency of exogenous mannose use in glycosylation [10]. Substances enhancing the impact of check points of mannose flux to the glycosylation pathway may improve the effect of exogenous mannose supplementation. Which other undefined factors and check points of mannose metabolism [10] have an influence on the effect of mannose supplementation need to be further investigated.

It has to be considered, that the glycosylation of transferrin and other glycoproteins may improve in time, with age and the degree of liver involvement [31–33]. There are 2 major arguments against spontaneous improvement in this study. First, the patients in this study started their mannose therapy at very different ages from 1 year to 27 years *(Table S1)*. The majority of responders showed a similar improvement with similar kinetics after a similar lag-time, suggesting that mannose supplementation, not age, was responsible for glycosylation improvement. Secondly the significant correction of the hypoglycosylated serum transferrin returned to approximately pretreatment patterns after long-term interruption of

mannose supplementation *(*Fig. 1C*)*. This clearly indicates the biochemical effect of mannose on these patients' glycosylation and not an improvement with age. Crucial developmental steps during embryogenesis and infancy are negatively affected by hypoglycosylation. Thus, different organ manifestations of PMM2-CDG may have different responses to a mannose treatment [13].

Repetitive doses of orally ingested mannose at certain intervals can maintain elevated blood mannose levels in PMM2-CDG patients [34]. Our patients showed fluctuations in blood mannose concentrations even when maintained on the same dose (*Fig. S3)*. Healthy probands (40–80 µM baseline) reach and maintain blood-mannose levels of more than 200 µmol/l after 1 h by supplementing 0,2 g/kgBW of mannose. [29] [28]. It must be assumed that, even when supplying ≥ 1 g/kg b.w. mannose, the blood mannose levels could not be maintained properly over the daily period and night time and were lower on average than the concentration shown to correct abnormal glycosylation in fibroblasts (≥ 250 µM [15] [12]). Despite the positive responses in the majority of patients, these circumstances have certainly limited the effectiveness of mannose under clinical circumstances. Parenteral application, for instance by subcutaneous infusion, might be an approach to reach steady blood mannose levels during day and night time.

Since the collection of the clinical data in this study was done in everyday clinical practice without a specific protocol and without matching a control group, retrospective analysis necessarily introduces some bias, which affect the interpretation regarding the outcome and coherence negatively. Nonetheless, this study observed considerable data, that under mannose PMM2-CDG patients developed a normalization of their motor nerve conduction velocity and furthermore regained a redeemable knee jerk. In the literature peripheral neuropathy with reduced nerve conduction velocity as well as peripheral tendon reflexes stay stable or gradually deteriorate [17, 31, 35, 36]. These findings suggest a clinical effect of mannose therapy. For the respective patient, parents and caretakers uniformly reported improved reactivity, attention and better general state while supplementing mannose. Nonetheless, mannose therapy alone does not lead to the disappearance of the disease. There are crucial developmental steps during pregnancy and early childhood being disrupted and leading to evident, irreversible malformations and abnormalities (similar to MPI-patients with ductal plate malformations in the liver [37]). Therefore, prenatal application of mannose might be an issue to make a significant difference in improving these children's health condition. [25] Detailed clinical efficacy should be tested in a controlled, double blinded, randomized study.

5. Conclusion

This study supports future perspectives discussed earlier [8] and demonstrates mannose as one effective cornerstone in a therapeutic approach. In coherence with the previous findings in vitro [12] and with prenatal mannose supplementation in PMM2-mice, we demonstrated that mannose has a biochemical impact on a majority of PMM2- CDG patients. The degree of effectiveness of mannose in PMM2- CDG cannot be utterly understood from this study. Mannose alone does not restitute the symptoms of this disease, which leads us to the assumption that an effect foremost depending on PMM2:MPI ratio and the

anomeric preference of PMM2 and MPI [3, 10, 28] should call attention on co-administrations with pharmaceuticals, addressing crucial check points of mannose metabolism, such as PMM2-activators, MPI inhibitors, PMM2-replacement [3, 38], pharmacological chaperoning [39] or proteostasis regulators [40] and others, to reduce their toxicity and improve the metabolic flux of mannose into glycosylation. High mannose blood levels were well tolerated with no severe side effects even in long term supplementation. Production and acquisition of mannose are affordable, quick and practical. Possible confounding factors include impaired intestinal mannose absorption as well as a fluctuating and insufficient serum mannose concentration. Thus, this study should promote viable animal models together with controlled clinical approaches (especially double-blinded randomized trials) to further evaluate the therapeutic potential of mannose in PMM2-CDG and to further test simultaneous approaches with the aforementioned perspectives.

Declarations

Ethics approval

Approval of the local ethic committee was obtained (Ethikkommission der Ärztekammer Westfalen-Lippe, No. 2019-199-f-S). All samples and therapeutic approaches described were obtained with informed consent from either the patients themselves or the patients' parents.

Consent for publication

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Availability of data

Not applicable.

Author contributions

Conceptualization, Methodology, Investigation, Formal analysis, Resources

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Figures

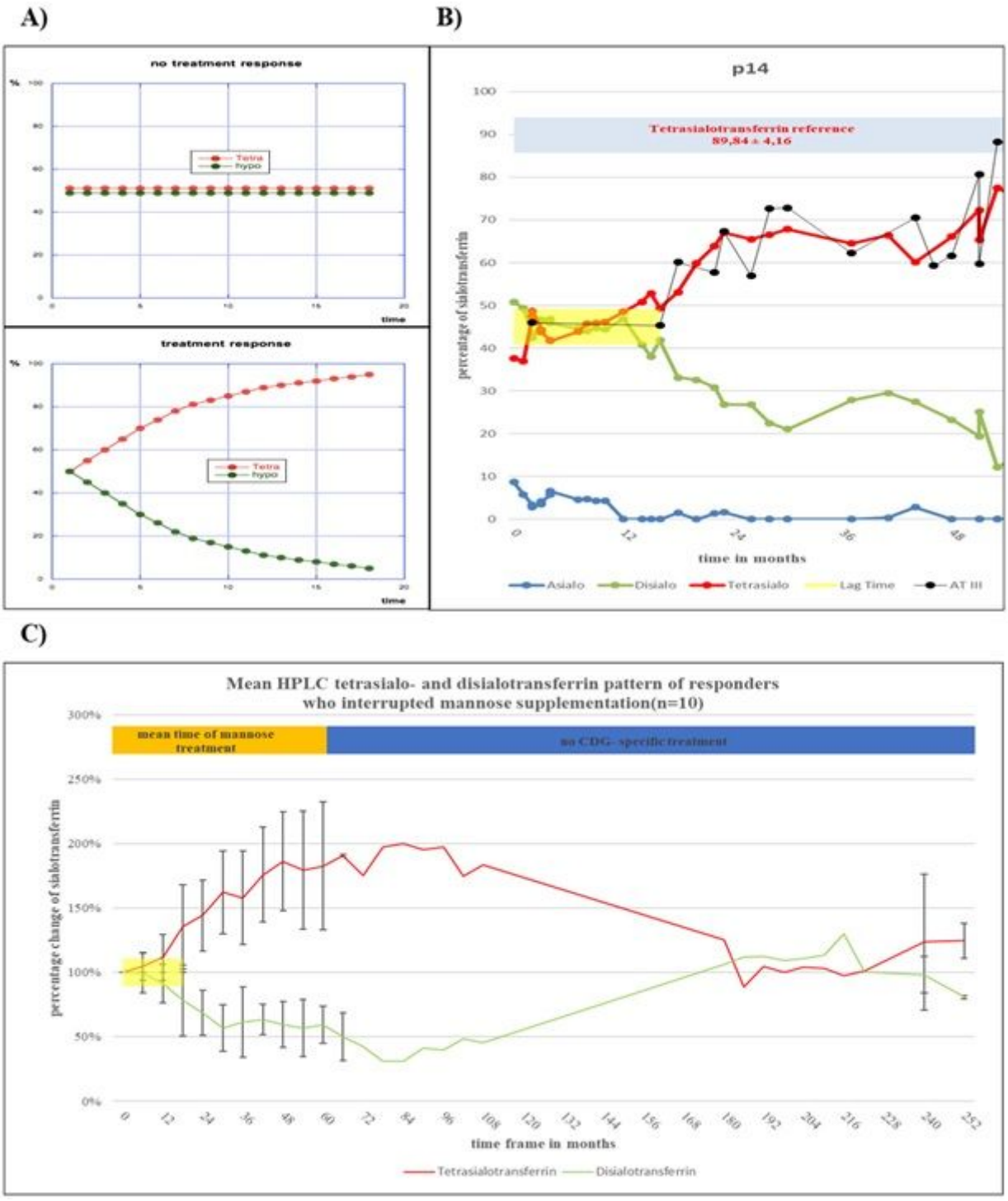

Figure 1

A) Scheme showing responding and non-responding sialo-transferrin patterns under mannose treatment. A response to therapy was a rather rapid increase in tetrasialo-transferrin with a simultaneous decrease in evenly hypoglycosylated sialo-transferrin proteins. Some responders presented a certain lag time of fluctuating sialo-transferrin values before response (mean 21±8 months). Non-responders showed fluctuating values around the pretreatment values of sialo-transferrrin. B) Example of lag time period in p14. This graph shows the sialo-transferrin-HPLC pattern during mannose supplementation. This patient showed only physiological fluctuations under mannose treatment for approximately 17 months, before hypoglycosylation improved. The example of AT III shows, that other glycoproteins like coagulation parameters reacted concordantly to the sialo-transferrin pattern. The blue area represents the physiological value of tetrasialo-transferrin. We observed similar periods of lag time (mean 21±8 months) in the other responders. C) Graph showing the percentage change of tetra- (red) and disialo-transferrin (green) quantified by HPLC of the responding patients. The initial pretreatment value was defined as 100%. The sialo-transferrin values measured during mannose supplementation were set in relation to the initial value. Under mannose therapy tetra- and disialo-transferrin values improved steadily to twice the initial value. After cessation of mannose treatment (orange mark), the sialo-transferrin rates declined to nearly pretreatment values (n=10).

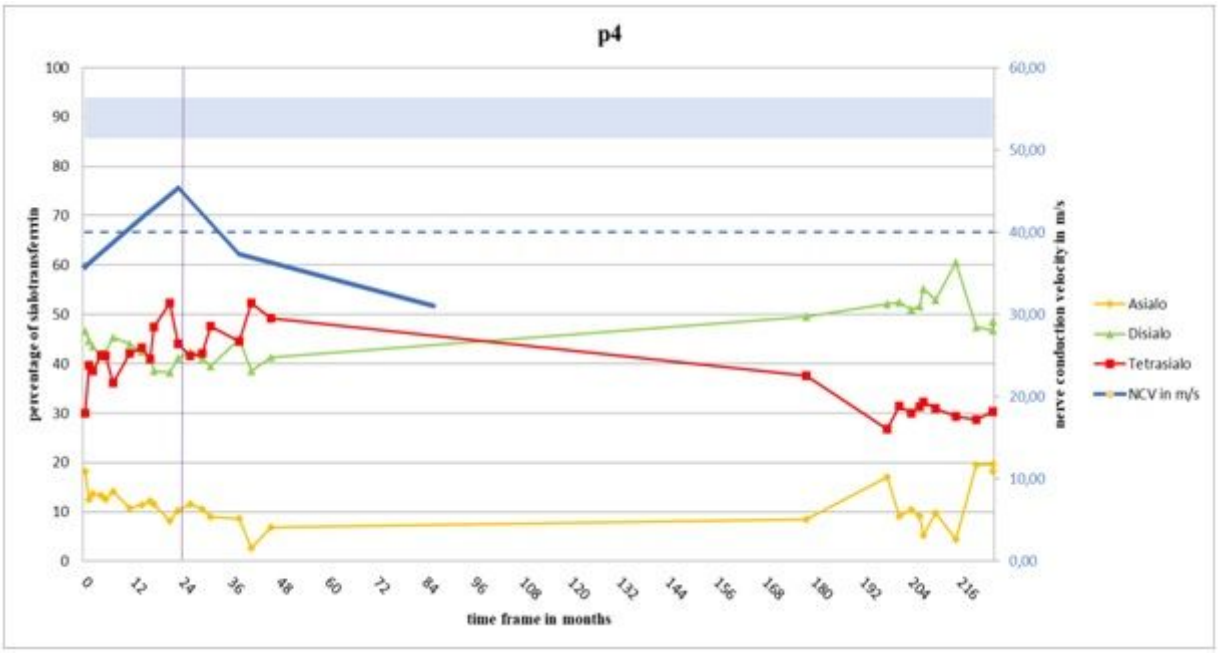

Figure 2

One patient`s pretreatment NCV (nerve conduction velocity) of the posterior tibial nerve improved and stayed stable within two years of mannose treatment (NCV reference of posterior tibial nerve > 40m/s; blue dashed line). Improvement of the sialo-transferrin pattern was concordant to NCV development (blue area= tetrasialo-transferrin reference). When mannose treatment was discontinued for this patient after 24 months (purple mark), the NCV of the posterior tibial nerve fell and stayed low for four more years without mannose.

Supplementary Files

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