Dysglycosylation pattern in SLC39A8-CDG: Mass spectrometry leads the way

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Introduction

Deleterious mutations in SLC39A8 lead to intracellular Mn2+ depletion by disrupting the ion channel ZIP8. In turn, impaired function of Mn2+-dependent glycosyltransferases leads to secondary dysglycosylation. In addition, a Leigh-like phenotype is seen in a subset of patients. Manganese-sulfate supplementation is a causative treatment.

Mn2+ toxicity necessitates careful monitoring of patients. In the past, measurement of blood manganese levels and glycosylation analysis of serum transferrin have been used.

We report on two patients with SLC39A8-CDG and normal transferrin glycosylation in addition to a Leigh-like phenotype. N-glycome profiling identified dysglycosylation and biomarkers for improved therapy monitoring.

Materials & Methods

Patients underwent exome sequencing in addition to glycosylation studies using high-performance liquid chromatography (HPLC) and isoelectric focusing (IEF).

N-glycome profiling using MALDI-TOF MS was performed to delineate subtle glycosylation abnormalities.

All procedures were approved by the relevant institutional IRBs (Shodair Children’s Hospital IRB00008287, PKU-016; University of Münster 2019-199f-s, Massachusetts General Hospital 2017P000115.)
Results
Case report

Patient 1 is a three-year-old girl of Turkish ancestry. She presented a complex phenotype with psychomotor retardation, dystonia, seizures, and dysmorphic features. cMRI identified bilateral T2 hyperintense lesions of the caudate and lentiform nuclei (Fig. 2).

Exome sequencing identified the homozygous variant c.608T>C [p.F203S] in SLC39A8. Blood manganese levels were severely reduced (1–3 ng/ml, reference: 7–11 ng/ml) while urinary manganese was undetectable. No abnormal pattern was seen in IEF of serum transferrin (Fig. 3).

Patient 2 is a two-year-old boy of Hutterite ancestry. He presented with infantile spasms and hypsarrythmia, accompanied by severe dystrophy and facial dysmorphisms. Bilateral T2 hyperintensities of the putamen and lentiform nucleus were noted on cMRI (Fig. 2).

The patient is homozygous for the previously described variant c.112G>C [p.G38R] in SLC39A8. Serum manganese was well below reference ranges (1.5 ng/ml, ref. 4–15 ng/ml). Transferrin glycosylation showed no abnormalities (Fig. 3).

Fig. 2 - Leigh-like T2-hyperintense bilateral lesions in the basal ganglia of patient 1 (A) as well as patient 2 (B,C).

Fig. 3 - Normal glycosylation pattern in IEF of serum transferrin both in patients 1 and 2 (P1, P2), as well as their respective parents (P1.1, P1.2 and P2.1, P2.2). + = SLC39A8-CDG positive control, - = negative control

![Fig. 2 image](image-url)

![Fig. 3 image](image-url)

N-glycome profiling by MALDI-TOF MS

Analysis of the entire N-glycome showed clear abnormalities in both patients not detected by conventional methods.

- **monosialo-monogalacto-biantennary glycan A2G1S1 m/z 2227 significantly increased** in P1 and P2 as well as other SLC39A8-CDG patients when compared to heterozygous carriers (p < .01) and wild-type controls (p < .005)
- **Bisected glycans** significantly reduced in SLC39A8-CDG vs heterozygous carriers (p < .05) and controls (p < .001)

![Fig. 4 image](image-url)

Discussion

- Transferrin glycosylation can be normal in SLC39A8-CDG
- N-glycome profiling by MALDI-TOF MS identifies a distinctive pattern of dysglycosylation, allowing detection of previously overlooked abnormalities
- Alterations in A2G1S1 and bisected glycans might serve as biomarkers in the context of therapy monitoring

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