Clinical History and Background

A 6-month-old male presented to the emergency department during the COVID-19 pandemic with 3-day history of fever, nasal congestion, cough, and decreased oral intake. He was not able to sit with support or roll over, and his growth parameters were severely reduced (<1st percentile). He tested negative for COVID-19, and had an unrevealing newborn screen. Severe failure to thrive (FTT) had been evident since his well-child visit at age 2 months. The family was instructed to increase his caloric intake. At the 6 months visit, he was found to have only gained 1 kg since birth and was febrile, prompting emergency department referral.

Initial workup was notable for increased aspartate aminotransferase [567 U/L, reference interval (RI): 20–64 U/L] and alanine aminotransferase (210 U/L, RI: 5–45 U/L), decreased normal total protein (5.6 g/dL, RI: 5.4–7.0 g/dL) and albumin (3.5 g/dL, RI: 3.1–4.2 g/dL), and low thyroid-stimulating hormone (0.22 μIU/ml, RI: 0.70–4.20 μIU/mL) and free thyroxine (0.5 ng/dl, RI: 1.0–1.8 ng/dL). His chest radiograph showed cardiomegaly, and echocardiogram identified a large globally distributed pericardial effusion associated with normal ventricular function.

Genetic and metabolism services were consulted for FTT and developmental delay. Hypotonia, poor head control, intermittent esotropia, inverted nipples, bilateral undescended testes, and suprapubic and lateral gluteal fat pads were noted, suggesting a congenital disorder of glycosylation (CDG). Carbohydrate-deficient transferrin analysis revealed a type-I pattern, with profoundly increased hypoglycosylated transferrin glycoforms (Fig. 1, A). Total plasma N-glycan analysis revealed remarkable undermannosylation, with increased mannose-deprived tetrasaccharide and Man<sub>0-5</sub>GlcNAc<sub>2</sub>, and reduced Man<sub>8-9</sub>GlcNAc<sub>2</sub> (Fig. 1, B). The biochemical and clinical findings were consistent with phosphomannomutase 2 congenital disorder of glycosylation (PMM2-CDG), confirmed by compound heterozygous pathogenic variants in PMM2: c.368G>A (p.Arg123Gln) and c.691G>A (p.Val231Met). Unfortunately, the patient’s clinical status deteriorated, and he died due to bleeding complications during attempts to surgically address his pericardial effusion.

Diagnosis and Summary

PMM2-CDG is the most common CDG. It is an autosomal recessive condition caused by deficient phosphomannomutase-2 conversion of mannose-6-phosphate to mannose-1-phosphate, precursor for GDP-mannose. As a building block for glycan assembly, the deficiency of GDP-mannose leads to underglycosylation and undermannosylation (Fig. 2). Clinically, PMM2-CDG is associated with variable phenotypes, from severe antenatal presentation with multisystem involvement and high mortality rate to adulthood presentation limited to minor neurological involvement (1).

With emerging new therapies, early diagnosis may improve the survival of PMM2-CDG patients. A functional diagnosis of PMM2-CDG by plasma carbohydrate-deficient transferrin and N-glycan tests can be achieved within 24 h using mass spectrometry-based testing (2, 3). Thus, it is important to recognize the early clinical signs for PMM2-CDG, among which FTT is frequently noted. Hydrops fetalis, cerebellar atrophy, inverted nipples, peculiar fat pads, dysmorphism,
cryptorchidism, strabismus, and hypothyroidism (detectable by newborn screen) are also early features that can be detected perinatally. Other signs including hypotonia, seizure, pericardial effusion, ascites, and liver failure usually develop during the infantile period (1). The presence of any subsets of these findings should raise the suspicion for PMM2-CDG. Prenatal evidence for pericardial effusion was previously reported in late gestation at 34 weeks in a PMM2-CDG patient (4). In our case, a fetal echo performed at 21 weeks’ gestation was normal.

Because FTT was evident at 2 months in this child, this case represented a lost opportunity for early diagnosis and management of PMM2-CDG during the COVID-19 pandemic. Several common factors may be attributable to the delay in diagnosis, including an overall reduction in outpatient visits to reduce the risk of transmitting SARS-CoV-2, the limitations of telemedicine in identifying and

**Fig. 1.** Comparison of carbohydrate-deficient transferrin and N-glycan results for the proband and a normal control. (A) In the proband, α-glycosylated/di-glycosylated and mono-glycosylated/di-glycosylated transferrin ratios were 0.30 (reference <0.05) and 1.46 (reference <0.05), respectively. (B) In the normal control, the ratios were 0.02 and 0.01 respectively. (C) In total plasma N-glycan profiling, the proband displayed a profound undermannosylation profile with increases in mannose-deprived tetrasaccharide and Man$_5$GlcNAc$_2$, along with reduction of Man$_9$GlcNAc$_2$; of these findings, the most notable were the increases of mannose-deprived tetrasaccharide and Man$_7$GlcNAc$_2$. 
managing infants with FTT and developmental delay, and also a general lack of awareness of rare genetic and metabolic conditions, which could have prompted earlier referral.

Nonstandard Abbreviations: RI, reference interval; FTT, failure to thrive; CDG, congenital disorders of glycosylation; PMM2, phosphomannomutase 2.

Human Genes: PMM2.

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Fig. 2. Proposed noncanonical pathway in PMM2-CDG resulting in increase of mannose-deprived tetrasaccharide and Man$_3$GlcNAc$_2$.

The biosynthesis of GDP-mannose is disturbed in PMM2-CDG, leading to accumulation of GlcNAc$_2$ (Man0) and Man$_3$GlcNAc$_2$ (Man3) in endoplasmic reticulum. Man3 is excreted into circulation. Mannose-deprived tetrasaccharide (NeuAc$_1$Gal$_1$GlcNAc$_2$) is produced by further modifications of Man0 in Golgi, with addition of galactose and sialic acid by corresponding glycosyltransferases before secretion.