

## CASE REPORT

# PMM2-CDG and nephrotic syndrome: A case report

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**Abstract**

Congenital disorders of glycosylation (CDG) are a group of rare metabolic diseases, characterized by a defect in the protein glycosylation process. Enzymes involved in this metabolic mechanism have ubiquitous distribution; thus, their alteration can cause systemic involvement and considerable phenotypic variability. Nephrotic syndrome (NS) is a clinical condition characterized by edema, hypoalbuminemia, hyperlipidemia, and proteinuria. We hereby report the case of a girl with central hypotonia, epilepsy, and severe psychomotor delay diagnosed with phosphomannomutase 2 deficiency (PMM2-CDG) after presenting with nephrotic syndrome at age 4 years.

**KEYWORDS**

CDG, congenital disorders of glycosylation, nephrotic syndrome, phosphomannomutase 2 deficiency, PMM2-CDG, renal involvement

## 1 | INTRODUCTION

PMM2-CDG is the most frequent CDG with more than 900 reported patients. It is a multisystem disease with variable phenotype.<sup>1</sup> Renal involvement is described in only 6% affected patients<sup>2</sup> with only a few describing nephrotic syndrome (NS).<sup>3–6</sup>

## 2 | CASE

We report the case of a now aged 13-year-old girl who manifested with hypotonia, alternating strabismus and hypokinesia during her first months of life. First words and walking with support were at 24 months; thus, development was delayed. Metabolic (without serum transferrin IEF) and genetic investigations were normal (Table 1). Brain MRI showed incomplete myelination, cardiac US an atrial septal defect and auditory evoked potentials a maturation delay.

At 2 years, she was admitted for lethargy. CT scan and cerebral MRI angiography showed venous sinus thrombosis with widespread damage of hypothalamus, thalamus, and basal ganglia with cerebellar atrophy. She subsequently developed a predominantly left quadriplegia with ataxia, intentional tremor, and seizures partially responding to treatment. She has no relevant family history.

Until 3 years old, she was frequently admitted for recurrent episodes of both upper and lower airway infections. There was hypertransaminasemia (AST-ALT: 564–571 U/L) but no clotting abnormalities.

At 4 years, she presented a status epilepticus and was admitted to our department. Pneumonia and NS (urine P/C ratio: 3.6 mg/mg, n.v. <0.2 mg/mg) were diagnosed, with oliguria, edema, hypertension, and hypoalbuminemia (2.4 g/L; n.v.30–50). Steroids were started (prednisone 60 mg/m<sup>2</sup>/day for 6 weeks, then 40 mg/m<sup>2</sup>/day for other 6 weeks) with progressive clinical remission (P/C ratio 0.1 mg/mg after 10 weeks of treatment with normal

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TABLE 1 Diagnostic workup done establishing the diagnosis

Metabolic investigations
Disorders of purine metabolism
Disorders of tryptophane metabolism
Disorders of ketogenesis
Disorders of lipid metabolism
Disorders of glycolysis
Disorders of tricarboxylic acid cycl
Disorders of carnitine metabolism
Disorders of fatty acid metabolism
Genetic investigations
Karyotype
SNP-array CGH
X fragile syndrome diagnostics

values of urea and creatinine). Clotting factors were altered (PT 15.6 s, ratio 1.41; INR 1.39; aPTT 35.3 s; INR 1.22; ATIII 8%, n.v. 70–120%); 1 month after the acute episode protein S, protein C and AT III were 46% (n.v. 65–128%), 44% (72–142%), and 30% (70–120%), respectively. A CDG was suspected for the neurological picture and the NS episode: Serum transferrin IEF confirmed a type 1 pattern with increase of di- and asialotransferrin and decrease in tetrasialotransferrin. PMM2 activity in leukocytes was 0.19 mU/mg protein (n.v. 3–5), and 2 PMM2 variants were described at the molecular analysis, c.422G>A (p.R141H) and c.95TA>GC (p.L32R). She now shows large and dysplastic ears, no other dysmorphism. She walks with support and presents a normal growth, though she still shows alternating strabismus and frequent seizures under several antiepileptics. There was no retinitis pigmentosa. No other thrombotic episodes nor renal relapses have been reported. Serum transaminases have normalized. Her sister was found to be only a carrier when assessed for PMM2 on a molecular basis and to date have not been reported to show any kind of clinical sign related to CDGs.

### 3 | DISCUSSION

PMM2-CDG can present as a multisystemic disease with a wide variety from a mild-to-severe degree of clinical organ dysfunction and dysmorphism.

In a literature review on 933 patients with molecularly and/or enzymatically confirmed PMM2-CDG, renal abnormalities seem to be reported in 56 patients (6%). Among these, only 4 patients had nephrotic syndrome (NS), which include many different underlying causes, both acquired and genetic.<sup>3</sup>

<sup>4-7</sup> In the Hutchesson et al patient,<sup>4</sup> NS started at age 8 weeks old. Urinary protein was 1377 mg/mmol of creatinine (n.v. <20) and serum albumin 22 g/L (n.v. 30–50). He died at 106 days from respiratory failure. Van der Knaap et al.<sup>5</sup> reported on a boy with congenital NS. In the first 2–3 weeks, he developed generalized edema and ascites with progressive severe proteinuria (1113 mg/mmol creatinine) and hypoalbuminemia (9 g/L). Renal biopsy showed diffuse mesangial sclerosis. He died at 2 months for sepsis and meningitis. Some lysosomal enzymes were increased, leading to the CDG suspicion and the PMM2-CDG diagnosis. Because all attention was focused on the NS, this diagnosis was initially missed. Jamroz et al.<sup>6</sup> reported on a girl with cardiorespiratory insufficiency on her first day. CMV infection was diagnosed with pneumonia, endocarditis, and NS. At 4 months, she was admitted with a typical PMM2-CDG phenotype, confirmed by enzymatic and molecular analysis. She showed progressive deterioration with pericardial effusion and ascites and died at 5 months due to heart tamponade. In a review on 96 French patients with PMM2-CDG, Schiff et al.<sup>7</sup> mentioned 2 patients with NS without providing any other details. A mild-to-moderate proteinuria has already been reported in 1991 in 29 patients with the carbohydrate-deficient glycoprotein syndrome,<sup>8</sup> subsequently diagnosed as PMM2-CDG (though this is a tubular proteinuria, while the NS proteinuria is glomerular).

Our reported case suggests not only to have PMM2-CDG patients undergo routinary blood chemistry, urinary, and instrumental examinations to evaluate kidneys trend, but also and most important to consider such possible diagnosis when assessing patients with renal involvement without an established diagnosis or cause, mostly if presenting with proteinuria and tubular proteinuria (whether in the nephrotic range or not) and with positive history of neurological involvement. Although renal involvement has been reported to date only in a minor percentage of CDG patients, it should always be ruled out among patients in order to avoid possible dangerous consequences and chronic damage.

What caused our patient NS is still not clear (CDG itself? The pneumonia? A combination of both or else?). There has been no relapse anyhow, and her actual (at 13 years) urinary protein level is 61 mg/mmol creatinine.

In conclusion, NS evidence in the context of a multisystem disorder with neurological involvement should be reminiscent of PMM2-CDG.

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None.

#### CONFLICT OF INTEREST

The author(s) declare that they have no conflict of interest.

## AUTHOR CONTRIBUTIONS

All authors contributed equally to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

## ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## CONSENT

Informed consent was obtained from the participant involved in the study.

## DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

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