PMM2-CDG and nephrotic syndrome: a case report.

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Abstract

CDG are a group of diseases altering the glycosylation process. Enzymes involved have ubiquitous distribution with systemic involvement and high phenotypic variability. We 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.

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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 oedema, 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.

Congenital disorders of glycosylation; CDG; phosphomannomutase 2 deficiency; PMM2-CDG; nephrotic syndrome; renal involvement.

Introduction.

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

Methods.

The case of a now 13 yo female diagnosed with PMM2-CDG was retrospectively reviewed as she is one of the few patients presenting with renal involvement.

Results.

We report the case of a now aged 13 yo female who manifested with hypotonia, alternating strabismus and hypokinesia during her first months of life. First words and walking with support were at 24 mo, thus development was delayed. Metabolic (without serum transferrin IEF) and genetic investigations were normal. 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.

Until 3 yo 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 protein/creatinine ratio: 3.6 mg/mg, n.v. <0.2mg/mg) were diagnosed, with oliguria, oedema, hypertension and hypoalbuminemia (2.4 g/l; n.v.30-50). Steroids were started (prednisone 60 mg/m2/day for 6 weeks, then 40 mg/m2/day for other 6 weeks) with progressive clinical remission. Clotting factors were altered (PT 15.6 sec, ratio 1.41; INR 1.39; aPTT 35.3 sec; 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 of 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. No retinitis pigmentosa. No other thrombotic episodes nor renal relapses have been reported. Serum transaminases have normalized.

Discussion.

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

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 [3].

[4-7]. In the Hutchesson et al patient [4], NS started at age 8 wo. 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. [5] reported on a boy with congenital NS. In the first 2–3 weeks he developed generalized

oedema 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. [6] 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. [7] 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 [8], 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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