CASE REPORT

Congenital disorders of glycosylation with neonatal presentation

Catarina Resende,[1] Carmen Carvalho,[1] Artur Alegria,[1] Dulce Oliveira,[1] Dulce Quelhas,[2] Anabela Bandeira,[3] Elisa Proença[1]

[1]NICU, Júlio Dinis Maternity, Oporto Medical Center, Oporto, Portugal
[2]Genetic Center, Oporto, Portugal
[3]Pediatrics Department (Metabolic Diseases), Oporto Medical Center, Oporto, Portugal

Correspondence to
Dr Catarina Resende, resende_cat@hotmail.com

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SUMMARY

Congenital disorders of glycosylation (CDG) are a group of hereditary diseases characterised by deficiency of enzymes involved in proteins glycosylation. We describe the clinical case of a neonate with CDG type 1a, nowadays designated phosphomannomutase 2 (PMM2)-CDG. Physical examination showed an abnormal facies, axial hypotonia, abnormal fat distribution, inverted nipples, non-palpable testicles and arachnodactyly. Progressive multiple system organ involvement and worsening of hypertrophic cardiomyopathy occurred. Metabolic study revealed a CDG disturbance, which was confirmed by genetic study. The following mutations were identified: c.193G>T; p.D65Y and c.470T>C; p.F157S. Clinical deterioration was inevitable with multisystemic failure and death. CDG represents a challenge for physicians due to multiple organ involvement, and heterogeneous clinical manifestations. The neonatal form is usually associated with the worst prognosis.

BACKGROUND

Congenital disorders of glycosylation (CDG) are characterised by changes in the N-linked pathway or in the synthesis of the oligosaccharides.[1–3] The PMM2-CDG (CDG-1a)—(OMIM) 601785 is the most predominant disorder. It is caused by a deficit in the phosphomannomutase 2, an enzyme encoded by the PMM2 gene, situated in the 16p13 chromosome.[1 3]

The clinical spectrum is vast, with a wide variety of phenotypes. The nervous system is affected in all patients and many other organs can be involved.[2 4] PMM2-CDG (CDG-1a) is divided into three stages (infantile multisystem stage, late-infantile disability or childhood ataxia-intellectual disability stage and adult stable disability stage) with highly variable clinical presentation; from infants who die within the first year of life to adults with discrete involvement.[1 2]

In the present article, we describe the clinical case of a PMM2-CDG with neonatal diagnosis and serious multiple system involvement.

CASE PRESENTATION

A newborn male, second child of non-consanguineous young parents, with irrelevant heredofamilial background. Prenatal ultrasounds were inconclusive. Were performed a nuclear MR and a karyotype with normal results. A caesarean section was performed at 38 weeks; birth weight was 2560 g and Apgar score was 8/9. Physical examination showed abnormal facies, dysplastic ears, oedema, abnormal fat distribution (sacral region), inverted nipples, non-palpable testes, arachnodactyly (figure 1) and a systolic murmur cardiac auscultation.

INVESTIGATIONS

On the second day of life, an echocardiogram was performed that revealed biventricular hypertrophy of septal predominance and a small pericardial effusion (figure 2). Serial echocardiograms revealed severe hypertrophic cardiomyopathy, and propranolol was prescribed on the 36th day of life.

Renal ultrasound revealed bilateral parenchymal hyperechogenicity, with normal renal function.

A metabolic study was performed and serum quantification of carbohydrate deficient transferrin was abnormal, compatible with CDG.

An isolated clinical seizure occurred the on 56th day, and phenobarbital was started. Cerebral ultrasounds and EEG were normal. Cerebral MRI showed hypoplasia/atrophy of the cerebellum, involving hemispheres and the cerebellar vermis, with a pons of small dimension, compatible with the hypothesis of CDG (figure 2).

The study of gene regions PMM2 covering the coding regions and their flanking regions in genomic DNA extracted from peripheral blood revealed the mutations: c.193G>T; p.D65Y and c.470T>C; p.F157S, confirming the diagnosis of PMM2-CDG.

DIFFERENTIAL DIAGNOSIS

The neonate presented with multiple congenital malformation syndrome with peculiar facies and musculoskeletal changes. However, with progressive hypertrophic cardiomyopathy and multisystem involvement, the hypothesis of a metabolic disease seemed to be more plausible and the diagnostic study was expanded.

OUTCOME AND FOLLOW-UP

The patient evidenced feeding problems with uncoordinated suction, diarrhoea and failure to thrive. Transient thrombocytopenia was present with spontaneous recovery. The glucose status was always stable.

After the second month of life there was a continuous deterioration of the clinical condition, progressive hypertrophic cardiomyopathy of the left ventricle and worsening of the associated mitral insufficiency. At 6 months he developed anasarca. The patient's clinical condition, with a progressive multisystem organ failure, led to his death a few days later.

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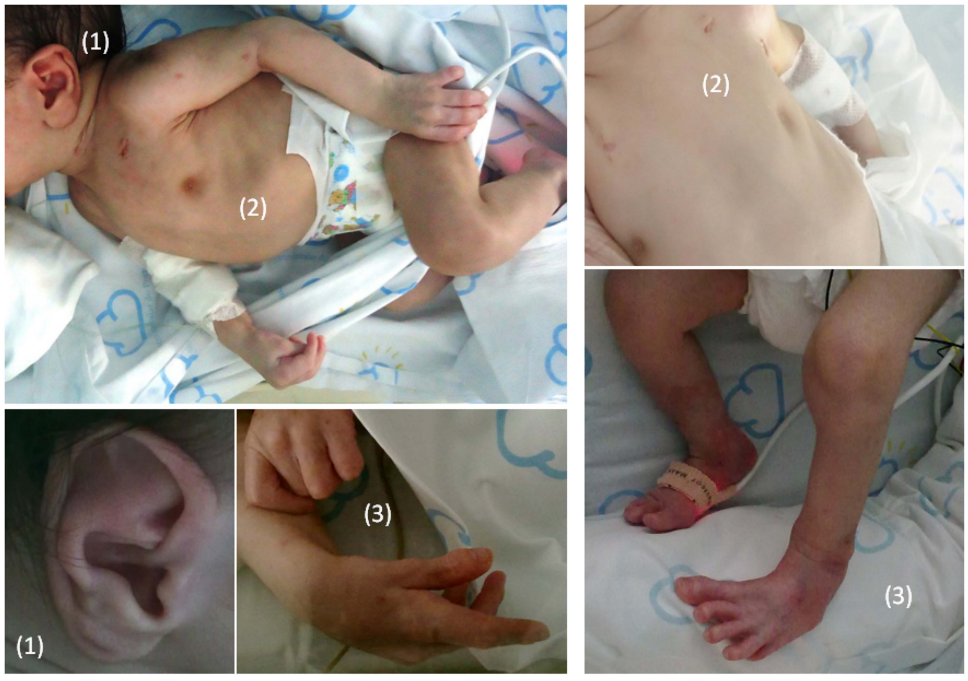

Figure 1 The patient. (1) Dysplasica ear. (2) Inverted nipples. (3) Arachnodactyly and leg joint contractures.

DISCUSSION

In PMM2-CDG (CDG-1a) infantile multisystem stage patients present axial hypotonia, hyperreflexia, esotropia and development delay.[1] Problems such as vomiting and diarrhoea are frequent and cause failure to thrive. Infants present an abnormal facies with high nasal bridge, prominent jaw and large ears.[1 2 4] Within this stage, two different clinical presentations can be identified: a neurological form that is usually non-fatal and a multivisceral neurological form with early signs and the involvement of almost all organs. Around 20% of the infants die in the first year. In the infantile catastrophic phase, the clinical course is complicated by infections, seizures and hypoalbuminaemia that may progress to anasarca and death, like in our case report.[1 4]

The implication of heart with biventricular hypertrophy is rare, but one of the factors of prognosis.[5] Orthopaedic changes are common, with long fingers, arthrogryposis, muscular contractions, kyphosis/scoliosis and restriction of hips and knee joints.[2]

Diagnosis of PMM2-CDG is based on clinical manifestations, neuroimaging and transferrin isoforms analysis. A positive test

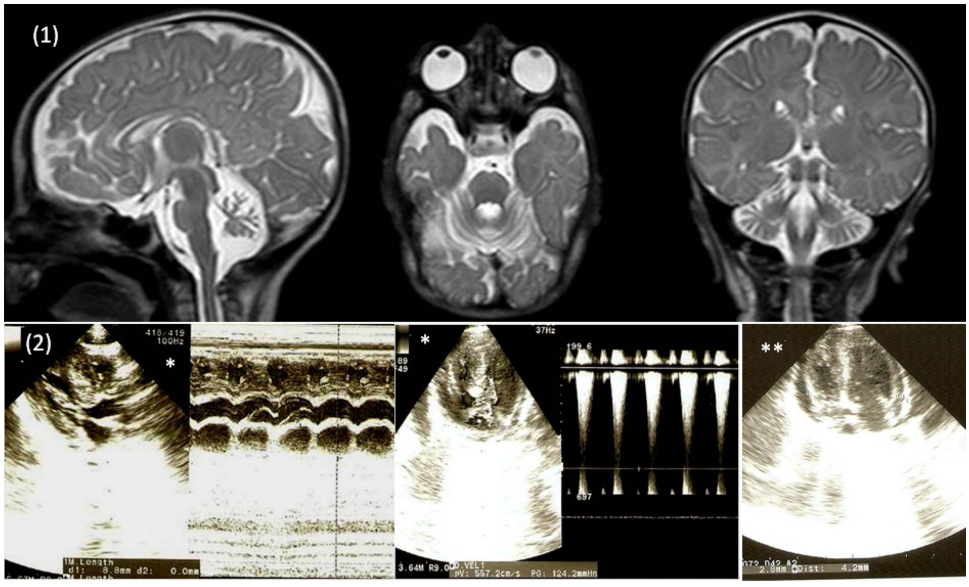

Figure 2 (1) NMR: hypoplasia/atrophy of the cerebellum, involving both hemispheres and vermis cerebellar, and a pons of small dimension. (2) Echocardiogram: *biventricular hypertrophy of septal predominance; **perdicaldial effusion.

must be confirmed by an enzyme or molecular test, showing a decreased activity of PMM2 in the leucocytes or in the fibroblasts.[2]

The p.D65Y mutation is presented only in Portuguese and Spanish families (Iberian Peninsula) and seems to have no relation with clinical severity.[3] However, mutation p.F157S in heterozygous seems to be associated with the neonatal presentation with more serious clinical manifestations and worst prognosis.[3 4]

The PMM2-CDG (CDG-1a), has no specific therapeutics. Nevertheless, studies are being developed in order to find therapeutics, namely supplements with mannose together with phosphomannose isomerase inhibitors.[6]

Parents' genetic counselling is essential as well as psychosocial support, considering the clinical severity and the lack of efficient therapeutic options.

Learning points

- The possibility of congenital disorders of glycosylation (CDG) must be considered in patients with an unexplainable neurological condition, especially in those who show psychomotor retardation, hypotonia and abnormal subcutaneous fat distribution.
- The clinical spectrum is wide, with a multiple systemic involvement and only symptomatic treatment.
- In phosphomannomutase 2 (CDG-1a) multiple system infantile stage there is an increased mortality in the first years of life due to vital organs involvement and serious infections.
- The hypertrophic cardiopathy is rare but one of the conditioning factors for a poor prognosis.

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Competing interests None.

Patient consent Obtained.

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