# Severe Hepatitis: An Unusual Presentation of Phosphomannomutase 2 Deficiency

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Port J Pediatr 2021;52:313-6
DOI: https://doi.org/10.25754/pjp.2021.21564

## Abstract

Phosphomannomutase 2 deficiency congenital disorder of glycosylation, the most prevalent N-glycosylation disease, is a multi-organ disease with marked clinical heterogeneity. Severe liver involvement is not a common finding in these patients. A 6-month-old girl was referred to the emergency department due to severe cytolysis without coagulopathy, found during the investigation of a pyelonephritis. A physical examination revealed hypotonia, erratic ocular movements, and an unusual distribution of subcutaneous fat. Thrombocytosis, high plasma lactate and ferritin levels, in addition to severe cytolysis, were found. An abdominal ultrasound showed normal dimensioned but hyperechogenic liver and kidney cortex. Echocardiogram revealed discrete pericardium effusion. At the time of diagnosis, severe cytolysis and liver steatosis were the main issues, but the presence of psychomotor development delay, hypotonia, and subcutaneous fat pads were the clues for a congenital disorder of glycosylation suspicion. The patient is now 4 years old. A liver biopsy shows incomplete septal fibrosis, mild steatosis, and micronodules rich in glycogen.

**Keywords:** Congenital Disorders of Glycosylation/diagnosis; Congenital Disorders of Glycosylation/genetics; Hepatitis/etiology; Infant; Phosphotransferases (Phosphomutases)/deficiency

## Introduction

Congenital disorders of glycosylation (CDG) are a growing group of genetic diseases caused by abnormal protein and/or lipid glycosylation. Nearly 100 types of congenital disorders of glycosylation have been identified, but phosphomannomutase 2 deficiency (PMM2-CDG) is by far the most common defect, affecting at least 900 patients worldwide.[1,2] It is a disorder of N-glycosylation caused by mutations in the *PMM2* gene and inherited as an autosomal recessive trait. It causes hypoglycosylation of several transport proteins, hormones, coagulation and thrombotic factors, lysosomal enzymes, and enzyme inhibitors. As the defect occurs in the cytosol, it can be identified by a type I pattern on the isoelectric focusing of serum transferrin.[3] Clinical spectrum varies widely and almost any organ system can be affected. Neurological involvement is always present, and only the nervous system can be affected. The most typical features are muscular hypotonia, developmental delay, feeding difficulties, inverted nipples, and unusual subcutaneous fat pads presented in the neonatal period, after an uneventful pregnancy.[4] Among the abnormalities, liver involvement is mostly mild, with recurrent increased plasma transaminases and hepatomegaly detected during intercurrent illnesses.[2,4] At present, the first line screening test is the isoelectric focusing of transferrin, a N-glycosylated plasma protein, which presents a type I pattern characteristic of the localization of the defect in the cytoplasm or the endoplasmatic reticulum.[5] In the presence of a type I pattern, a whole exome sequencing using a filter for *CDG-I* genes or targeted sequencing of a *CDG-I* gene panel is performed.[4] There is no specific treatment, although different therapeutic approaches under development have been proposed for PMM2-CDG, such as gene therapy, enzyme enhancement/replacement, and substrate supplementation.[5] Twenty percent of PMM2-CDG patients die within the first year of life, often due to multiorgan failure.[4] We report a case of PMM2-CDG presenting with predominant liver involvement.

## Case Report

We report a 4-year-old girl, born at 41 weeks via cesarian section, with no reported complications and

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Received: 24/11/2020 | Accepted: 06/05/2021 | Published online: 03/10/2021 | Published: 03/10/2021

with an Apgar index of 9/10/10. She was the first child of non-consanguineous young parents, with an irrelevant medical history. Birth weight and length were in the 25th percentile for gestational age. A cerebral ultrasound showing hyperechogenic foci was performed soon after birth, due to suture diastasis and a large posterior fontanelle. Within the first five months of life, she was reported to have a mild psychomotor development delay. Growth evolution for weight and length was around the third percentile, in spite of some feeding difficulties. Inability to follow objects led to ophthalmologic observation at the age of 3 months and was attributed to the immaturity of the optical pathways. Cerebral ultrasound was repeated at that time and showed abnormalities suggestive of lenticulostriate vasculopathy.

By the age of 6 months, she was evaluated in the context of an infection. She presented at the emergency department with a history of fever for three days, with a maximum temperature of 39.6ºC every six hours, food refusal and prostration. Physical examination revealed abnormal fat distribution (Fig. 1), a frontal cavernous angioma, hypotonia, erratic eye movements, and palmar erythema. The liver was enlarged, palpable 2 cm below the costal grid. Laboratory investigations disclosed thrombocytosis (895,000 cells/µL, reference values 200,000-400,000 cells/µL), with normal erythrocyte and leukocyte parameters. C reactive protein, blood glucose, ammonia, urea and creatinine levels, and blood gas analysis were normal. Plasma alanine aminotransferase of 1,220 U/L (reference values 5-45 U/L) and aspartate aminotransferase of 1,439 U/L (reference values 5-90 U/L), with normal creatine, alkaline phosphatase, gamma glutamyl transferase, and bilirubin levels. Alpha-fetoprotein levels were increased (80 ng/mL, reference values 0.6-8 ng/mL), plasma lactate was elevated (3.3 mmol/L, reference values 0.7-2.1 mmol/L) as well as ferritin levels 679 ng/mL (reference values 24-328 ng/mL). She presented normal albumin, coagulation tests, cholesterol, and triglycerides levels. An aseptic urine sample was collected, and it was suggestive of urinary infection. Abdominal ultrasound revealed normal dimensioned but hyperechogenic liver and diffuse increase in the reflectivity of the kidney cortex with the dilatation of the renal pelvis. Diagnostic hypothesis included various metabolic diseases – glycogen storage disease, mitochondrial disease, congenital disorders of glycosylation, urea cycle disorder –, exacerbated in the context of an intercurrent disease, a febrile urinary tract infection. She was admitted for diagnostic workup and intravenous cefuroxime.

A cardiovascular exam unveiled insignificant pericardium effusion. Urine organic acids, blood acylcarnitine profile, and pyruvate levels were normal. Thyroid function tests were normal. Urine culture revealed an *Escherichia coli* resistant to ampicillin.

Increased carbohydrate-deficient transferrin (36%, reference values 0%-2.6%) with a type I pattern in isoelectric focusing showing markedly increased disialotransferrin and decreased tetrasialotransferrin bands, was consistent with the hypothesis of congenital disorders of glycosylation. Molecular analysis of the *PMM2* gene disclosed compound heterozygosity for c.470T> C (p.F157S) e c.710C> T (p.T237M) pathogenic

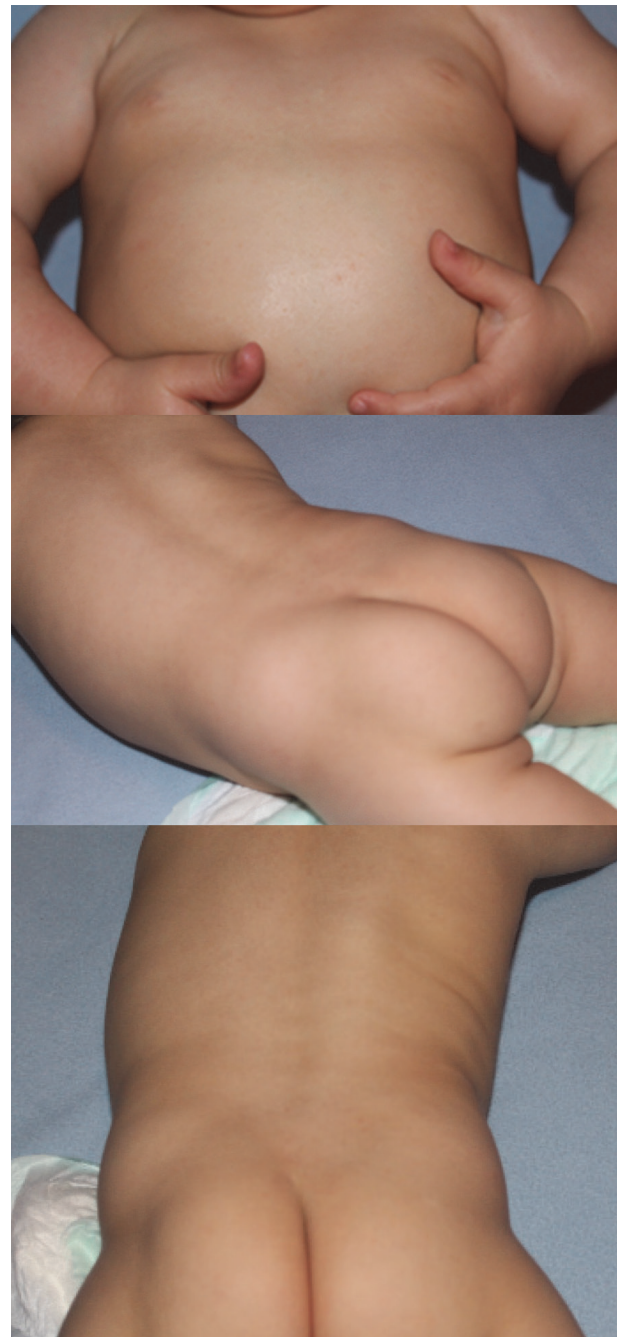

**Figure 1.** Abnormal fat pads distribution and inverted nipples.

variants. Both parents are heterozygous for the mutations c.710C>T (p.T237M) (mother), c.470T>C (p.F157S) (father).

The patient is now 4 years old, has a multidisciplinary follow-up and is under multiple therapies. Growth is around the 15th-50th percentiles for weight and the 3rd-15th percentiles for length. She has made some progress in psychomotor development. Her development quotient was 46 at 3 years of age (Ruth Griffiths scale). A globous liver and a hyperechogenicity of the hepatic parenchyma persist, with preserved synthetic liver function and fluctuating increased transaminases with a tendency to normalization (alanine aminotransferase of 69 U/L and aspartate aminotransferase of 76 U/L). Liver biopsy, performed at the age of 4-years-old, showed incomplete septal fibrosis, mild macrovacuolar steatosis, and micronodules rich in glycogen (Fig. 2). Apart from cortical hyperechogenicity, there are no other kidney abnormalities. A recent cardiac evaluation was normal. Cerebral magnetic resonance will soon be performed.

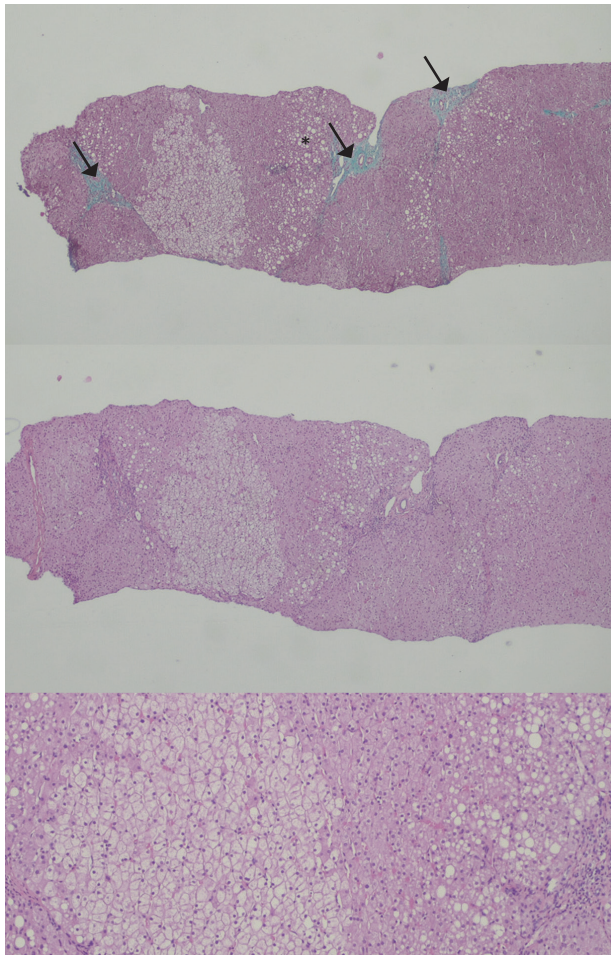

**Figure 2.** Biopsy of the liver showing incomplete septal fibrosis (arrow), mild macrovacuolar steatosis (*) and micronodules rich in glycogen.

## Discussion

The liver is a major site of glycosylation in the body, producing most of the glycosylated serum proteins. Nevertheless, liver involvement is present in only 20%-30% of congenital disorders of glycosylation types.[1,6] In this respect, congenital disorders of glycosylation can be divided into two groups: one with predominant or isolated liver involvement and the other with associated liver disease but not as a predominant feature. Phosphomannomutase 2 deficiency is included in the latter.[1,7] In fact, in PMM2-CDG patients, the presenting signs are mostly neurological (hypotonia, intellectual disability, and cerebellar syndrome).[4,5,7]

In the reported patient, severe cytolysis and liver steatosis were the main issues at the age of 6 months, leading to further investigation. In spite of liver disease rarely being the predominant feature in PMM2-CDG, the presence of abnormal subcutaneous fat distribution associated with psychomotor development delay and hypotonia was the clue for diagnosis.

Hepatopathy in PMM2-CDG is an unexplored field of investigation and its description is mostly vague.[2] Hepatomegaly and elevated transaminases are frequently reported, more often during intercurrent illnesses.[1,2,4] Liver failure has also been reported but often in the setting of multiorgan failure, frequently associated with pericardial effusions.[2] Liver biopsy, which is rarely performed in these patients, usually shows steatosis, fibrosis, and lysosomal inclusions in the hepatocytes, such as what we have observed in our patient.[1,2] The evolution of this alteration is unknown and the regression of liver fibrosis in other congenital disorders of glycosylation has been reported.[8]

In this case, liver involvement was detected during an intercurrent illness, and hepatitis was the main presentation. Transaminases remained increased but at low levels. Hopefully, they will normalize over time. In fact, some authors report that they seem to decrease with age, reaching normal values in the second decade of life.[2]

Pediatricians should be aware of this condition and liver workup (function tests and ultrasound) should always be performed in congenital disorders of glycosylation patients. Liver biopsy will help to characterize liver lesions such as steatosis, inflammation, and fibrosis.

Regarding the multiple possible presentations of PMM2-CDG, this differential diagnosis should be considered in any child presenting with unexplained symptoms, namely hepatitis, in particular in the setting of some typical features such as inverted nipples, abnormal subcutaneous fat distribution, and cerebellar atrophy.[4]

Although at present there is no effective treatment for

PMM2-CDG, it is of utmost importance to correctly diagnose patients, not only for family counseling, but also for defining the natural history of the disease and preparing future clinical trials.

**WHAT THIS CASE REPORT ADDS**

- Although neurological involvement is always present in phosphomannomutase 2 deficiency and only the nervous system can be affected, this report highlights an unusual feature of this disease: liver involvement.
- The most typical features are muscular hypotonia, developmental delay, feeding difficulties, inverted nipples, and unusual subcutaneous fat pads presented in the neonatal period, after an uneventful pregnancy. Erratic eye movements also constitute a frequent feature of phosphomannomutase 2 deficiency, and if present in a patient, they should lead to etiological study or very close surveillance.
- Although there is no effective treatment for phosphomannomutase 2 deficiency yet, it is of utmost importance to correctly diagnose patients, not only for family counseling, but also for future clinical trials.
- There is still the need to explain the effect of hypoglycosylation resulting in such a plethora of symptoms seen in phosphomannomutase 2 deficiency.

## Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.


## Funding Sources

There were no external funding sources for the realization of this paper.


## Provenance and peer review

Not commissioned; externally peer reviewed

## Consent for publication

Consent for publication was obtained.

## Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.


## Acknowledgements

The authors gratefully acknowledge the family enrolled in this case report for their kindness.


## Awards and presentations

This case report was presented in XV Curso básico de Doenças Hereditárias do Metabolismo, held in Coimbra, Portugal.

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**Hepatite Grave: Uma Apresentação Rara de Deficiência de Fosfomanomutase 2**


**Resumo:**

A doença congénita de glicosilação por deficiência de fosfomanomutase 2 é a doença de N-glicosilação mais prevalente. Trata-se de uma doença multiorgânica com uma marcada heterogeneidade clínica. Um compromisso hepático grave não é comum nestes doentes. Uma menina de 6 meses foi referenciada para o serviço de urgência por citólise grave sem coagulopatia, detetada durante a investigação de uma pielonefrite. O exame físico revelou hipotonia, movimentos oculares erráticos e uma distribuição pouco comum da gordura subcutânea. Identificaram-se trombocitose, níveis plasmáticos aumentados de lactato e ferritina, além de citólise grave. A ecografia abdominal revelou um córtex renal e hepático de dimensões normais, mas hiperecogénicos. O ecocardiograma revelou um derrame pericárdico discreto. Na altura do diagnóstico, os principais problemas eram citólise grave e esteatose hepática, mas a presença de atraso do desenvolvimento psicomotor, hipotonia e acumulações de tecido adiposo subcutâneo foram as pistas para a suspeita de uma doença congénita da glicosilação. A doente tem agora 4 anos. A biópsia hepática mostra uma fibrose septal incompleta, esteatose ligeira e micronódulos ricos em glicogénio.



**Palavras-Chave:** Defeitos Congénitos da Glicosilação/diagnóstico; Defeitos Congênitos da Glicosilação/genética; Fosfotransferases (Fosfomutases)/deficiência; Hepatite/etiologia; Lactente