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Pulmonary hypertension as a sign of onset of multiple mitochondrial dysfunction syndrome☆

Hipertensión pulmonar como forma de inicio del síndrome de disfunción mitocondrial múltiple

Dear Editor:

A pulmonary artery pressure of 25 mmHg or above at rest is rare and severe. Pulmonary hypertension is a feature of various conditions, including metabolic disorders such as multiple mitochondrial dysfunctions syndrome (MMDS, OMIM #605711) or pyruvate dehydrogenase lipoic acid synthetase deficiency (PDHLD, OMIM #614462), which affect mitochondrial oxidative decarboxylation. This disease is associated with leukoencephalopathy, pulmonary hypertension and hyperglycinaemia without ketosis, thus sharing the characteristics of nonketotic hyperglycinaemia (NKH, OMIM #605899), an autosomal recessive disorder of glycine (Gly) metabolism that manifests with an elevation of Gly in the absence of ketoacidosis.

In the context of these metabolic disorders, MMDS is a recently described syndrome. The term refers to a group of rare inborn errors of energy metabolism caused by deficiencies in the formation or attachment of iron-sulphur (Fe-S) clusters, leading to abnormal function of enzymes dependent on lipoic acid and other proteins involved in intermediate metabolism and oxidative phosphorylation that participate in electron transport chain reactions and the function of complexes I, II and III. This explains the multiple mitochondrial dysfunctions associated with NFU1 (OMIM *608100), BOLA3 (OMIM *613183), LIAS (OMIM *607031), ISCU (OMIM *611911), IBA57 (OMIM *615316) and LIPT1 (OMIM *610284). Multiple mitochondrial dysfunctions syndrome is a severe autosomal recessive disorder of systemic energy metabolism with onset in infancy characterised by lack of neurologic development, hypotonia, respiratory failure, lactic acidosis and early death.

We present the cases of 2 patients with PH that received a diagnosis of PDHLD, one of which has been described previously.[1]

Case 1

Boy aged 2 months. Onset with heart failure associated with metabolic acidosis, hyperlactataemia and cardiomegaly. The echocardiographic examination revealed suprasystemic PH, type III ventricular septal defect and dilatation and hypertrophy of the right ventricle. A computed tomography (CT) angiogram ruled out pulmonary embolism. Treatment was initiated with milrinone, sildenafil and bosentan. The initial response was poor, with progression to septic shock

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Table 1 Summary of clinical and biochemical characteristics of the 2 patients with PDHLD.

	Case 1	Case 2
Presentation at admission	Acute heart failure	Cardiogenic shock
Echocardiography	Suprasystemic PH, RV dilatation and hypertrophy	Infrasystemic PH, RV hypertrophy and adequate ventricular function
Treatment at admission	Milrinone, sildenafil and bosentan	Epinephrine, milrinone and iNO
Serum lactate	11 mmol/L (NR: $\leq$ 2.1 mmol/L)	6,7 mmol/L (NR: $\leq$ 2.1 mmol/L)
Glycine	→Plasma glycine 808 μmol/L (NR: 220 ± 64) →Urinary glycine 2.381 mmol/mol creat. (NR: →380 ± 179) → CSF glycine 72 μmol/L (7 ± 3) CSF:plasma Gly = 0.08	→ Plasma glycine 563 μmol/L (NR: 220 ± 64) → Urinary glycine 4.652 mmol/mol creat. (NR: 380 ± 179) → CSF glycine 20 μmol/L (7 ± 3) → CSF:plasma Gly = 0,03
Muscle biopsy	Increased lipid deposition in muscle fibres	
NFU1 gene testing	Homozygous c.622 G > T variant in exon 7 of *NFU1*: p.Gly208Cys	Homozygous c.622 G > T variant in *NFU1*: p.Gly208Cys
Treatment initiated for suspected NKH	Sodium benzoate, dextromethorphan, L-carnitine and vitamin B_6	Dextromethorphan, sodium benzoate and B-complex vitamins
Outcome	Septic shock and multiple organ failure → refractory hypoxemia and death	Discharge to ward → readmission due to pulmonary oedema, neurologic impairment with progressive hypotonia → refractory hypoxemia and death
Neurologic features	Central apnoeic episodes, sucking movements, athetosis in upper extremities, clonus in lower extremities, hypotonia	Feeding refusal, irritability and progressive hypotonia
Head MRI	Supratentorial ventricular enlargement and deepening of sulci possibly related to initial atrophy. Mild myelinization delay and very mild rolandic seizures	Not performed

CSF, cerebrospinal fluid; Gly: glycine; iNO, inhaled nitric oxide; MRI, magnetic resonance imaging; NKH, nonketotic hyperglycinaemia; NR, normal range; PDHLD, pyruvate dehydrogenase lipoic acid synthetase deficiency; PH, pulmonary hypertension; RV, right ventricle.

and multiple organ failure, and subsequent improvement. Following extubation, the patient developed episodes of choreoathetosis, sucking, tongue fasciculations, hypotonia and breathing difficulty that required reintubation. The electroencephalogram showed background slowing with focal temporal activity. A magnetic resonance imaging (MRI) scan revealed bifrontal cerebral atrophy, white matter changes and delayed myelinization. Chemistry tests detected elevation of Gly in plasma, urine and cerebrospinal fluid (CSF), a pathological CSF-to-plasma glycine ratio and elevated levels of organic acids in urine (Table 1). Nonketotic hyperglycinaemia was suspected, so treatment was initiated with sodium benzoate, dextromethorphan, L-carnitine and vitamina-B_6. Examination of a muscle biopsy revealed an increase in lipids in muscle fibres. Genetic testing identified a change in the *NFU1* gene in homozygosis. The parents carried the variant in heterozygosis and were asymptomatic. The patient died at 40 days from refractory hypoxaemia.

Case 2

Boy aged 3 months with no relevant history transported to the hospital with cardiogenic shock. The echocardiography and cardiac catheterization revealed severe precapillary PH, while the findings of the angiogram were normal. Treatment was initiated with epinephrine, milrinone and inhaled nitric oxide and then switched to sildenafil and bosentan. The patient exhibited progressive respiratory symptoms and hypotonia that required intubation, hyperlactataemia and progression of PH with diastolic right ventricular failure.

Testing revealed elevation of organic acids and Gly in plasma and urine compatible with PDHLD, leading to initiation of dextromethorphan, sodium benzoate and B-complex vitamins. Molecular testing of the *NFU1* and a skin biopsy for fibroblast cell culture were ordered. The progressive worsening of the patient led to the decision to withdraw life support, and the patient died after 27 days.

The association between NKH and PH was known in the past, but a group of diseases that may develop in association with PDHLD has been recently described under the term SDMM.[2]

Lipoic acid (LA) is a cofactor in multienzyme complexes that play essential roles in mitochondrial energy metabolism: 2-oxoacid dehydrogenase, α-ketoglutarate dehydrogenase and branched-chain α-ketoacid-dehydrogenase complexes and H-protein in the

glycine cleavage system.[3] It is synthesised in the mitochondria through a reaction catalysed by LA synthetase that requires an iron-sulphur (Fe-S) cluster as a cofactor and is assembled in a complex pathway involving proteins such as NFU1, ISCU, BOLA3 or IBA57.[4]

Following the initial description of MMDS, there have been reports of cases produced by changes in the genes encoding proteins involved in the Fe-S cluster biogenesis, such as *NFU1*, *BOLA3*, *IBA57* or *ISCA2* (OMIM*615317) or in LA synthesis.[5] Onset usually occurs in the neonatal period or infancy with neurologic manifestations (hypotonia, leukoencephalopathy, psychomotor retardation) and non-CNS symptoms such as pulmonary hypertension. The biochemical manifestations include lactic acidosis, Gly elevation and abnormalities in mitochondrial respiratory chain complexes.[6]

Pyruvate dehydrogenase lipoic acid synthetase deficiency shares some features of classic NKH, such as encephalopathy, early death, white matter changes, PH and hyperglycinaemia. However, Gly levels tend to be lower compared NKH and is associated with lactic acidosis and elevation of 2-ketoglutaric or 2-ketoadipic acid in urine.

These patients had a c.622 G > T mutation in exon 7 of the *NFU1* gene, which encodes a protein involved in the synthesis of Fe-S clusters, which results in the substitution of glycine at position 208 by cysteine (p.Gly208Cys). It is one of the most frequent variants, especially in southern Europe, which is suggestive of a founder effect.[5]

Pulmonary hypertension is a frequent feature in patients with this variant. In the series published by Navarro Sastre et al., a lung biopsy was performed in 2 patients, revealing obstructive vasculopathy with involvement of proximal and acinar arteries.[5] Different hypotheses have been proposed to explain this association (increased oxidative stress due to decreased synthesis of LA or decreased synthesis of the haem group), although none have been proven. Supplementation with LA has shown no benefits, and the treatment is symptomatic.

In conclusion, the presence of PH associated with hyperlactataemia should raise suspicion of mitochondrial disorders. In addition, patients with elevation of glycine in both serum and cerebrospinal fluid associated with lactic acidosis should be monitored for the development of PH.

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