Primary Pulmonary Hypertension Associated with Asymptomatic Methylmalonic Aciduria in a Child

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ABSTRACT
Methylmalonic acidemia or aciduria (MMA) is an inborn error of metabolism that results in the accumulation of methylmalonic acid in blood with an increased excretion in urine. MMA usually presents in early infancy and its effects vary from mild to life-threatening. The clinical symptoms mainly include vomiting, dehydration, hypotonia, developmental delay, and failure to thrive. An association between pulmonary arterial hypertension (PAH) and MMA has been rarely reported. In the present work, the authors report a 16-month boy, who was admitted to the Pediatric Department for cyanosis and fever. He had a family history of primary pulmonary hypertension in a sister. The echocardiography showed a mild pericardial effusion and PAH. The metabolic screening led to the diagnosis of MMA. The condition of the baby worsened rapidly and he died a few days later. Physicians should be aware about this atypical presentation of the disease, which can be fatal if not diagnosed and managed promptly.

Key Words: Metabolic disease, Methylmalonic aciduria, Pulmonary arterial hypertension.

INTRODUCTION
Pulmonary hypertension is a progressive and fatal disease. It may be due to pulmonary arterial hyper-tension (PAH), pulmonary venous hypertension, respiratory disorders and/or hypoxemia, thromboembolic diseases and disorders affecting directly the pulmonary vasculature.\(^1\) An association with metabolic diseases was reported with Gaucher disease, type I, glycogen storage disease or pulmonary interstitial glycogenosis, nonketotic hyper-glycinemia, mitochondrial disease and Cobalamin C defect, but rarely with methylmalonic acidemia (MMA). We report a new case of PAH associated with MMA in a child.

CASE REPORT
A 16-month boy, born at full-term, with weight 2.750 kgs, to first-degree relative parents, presented with a history of four episodes of bronchiolitis-like illness. The boy had a family history of an 18-month sister, who died of primary PAH. The echocardiography showed a mild pericardial effusion and PAH. The metabolic screening led to the diagnosis of MMA. The condition of the baby worsened rapidly and he died a few days later. Physicians should be aware about this atypical presentation of the disease, which can be fatal if not diagnosed and managed promptly.

PO2: 14.6 kpa, base excess (BE) -4.6, HCO\(_3\): 17.8) and blood glucose level were normal. Electrocardiogram showed sinus rhythm without any abnormalities of conduction. White blood count was 19,700/mm\(^3\), haemoglobin (Hb) 12 g/dl, platelets 362,000/mm\(^3\) and C-reactive protein was 2.5 mg/l. The echocardiography showed a mild pericardial effusion and PAH. The baby was started on digoxin, captopril, and furosemid for PAH and aspirin for the treatment of pericarditis. The viral serologies for coxackie, adeno-virus, influenza, echo-virus and infectious mononucleosis were negative. To investigate the PAH, a metabolic screening was performed that showed on gas chromato-graphy mass spectroscopy (GC/MS) analysis of urine, the presence of markedly elevated levels of methyl-malonic acid (1,580 \(\mu\)mol/mmol creatinine) and methyl citrate. Homocystein level was normal.

DISCUSSION
PAH was clearly established in our patient. The diagnosis was made by a right-sided cardiac catheterisation, which is considered the gold standard confirmatory test.\(^1\) This PAH seemed to be familial, as the patient's sister died at the age of 18 months of primary PAH.
This patient showed methylmalonic aciduria and apparently did not present with any of symptoms suggestive of the disease. However, the recurrent bronchiolitis-like episodes might be related to relapses of dyspnea secondary to metabolic acidosis. This finding was intriguing. Nevertheless, Leadly et al. reported asymptomatic children aged between 18 months and 13 years with methylmalonate accumulations in blood and urine and mutase deficiency was evidenced in all of them.\(^2\)

An association between PAH and methylmalonic aciduria was first reported in a newborn in 2014.\(^3\) More recently, a 35-year female with MMA developed PAH 20 years after her first hemodialysis. However, although PAH may complicate regular hemodialysis, it was considered to be a complication of MMA, because it was responsive to medical treatment and reversible.\(^4\) Other patients developed late-onset lung disease and PAH revealing Cobalamin C deficiency.\(^5\) The relationship between these two conditions is unclear, MMA could be a trigger enhancing PAH in cases of genetic or familial predisposition to PAH. PAH experts estimate that only 10% to 20% of the family members, that carry the gene, are responsible for PAH at risk to express the disease.\(^1\)

In this patient, it could be a pathogenic or a coincidental association between two distinct and rare diseases. PAH is associated with a number of other diseases or may develop after exposure to specific toxins and drugs; and MMA metabolites could be a trigger or a potential factor for the development of PAH in cases of genetic or familial predisposition to PAH.\(^1\)

Cullinane et al. reported pulmonary arterial media hyperplasia in two siblings with pulmonary hypertension and severe metabolic acidosis.\(^6\) Wideman et al. showed, by experimental studies on broilers, the influence of acute metabolic acidosis on pulmonary vascular resistance.\(^7\) These reports could suggest a pathogenic association between MMA and PAH. Brandstetter et al. reported pulmonary vascular complications of MMA when associated with homocystinuria.\(^8\) Liu et al. speculated that pulmonary microangiopathy, secondary to combined MMA and homocysteinemia, was the primary cause of diffuse lung disease with or without PAH.\(^5\) However, in all described MMA cases, such a complication has been rarely presented. This patient did not have such abnormalities and the clinical manifestations were different.

Sildenafil oral therapy was successfully tried in the treatment of PAH.\(^9\) In this case, it was proved efficient during right-side cardiac catheterisation. The fatal outcome of this patient in an anasarca decompensation remains unexplained.

Taking into consideration our patient, we think that it is judicious, in case of primary PAH, to search for MMA with or without homocysteinemia even when the patient has no suggestive signs. On the other hand, in case of “benign” MMA or classic MMA with cardio respiratory manifestations, arterial pulmonary pressure should be checked.

**REFERENCES**


