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# Persistent pulmonary hypertension of the newborn due to methylmalonic acidemia: a case report and review of the literature

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## Abstract

**Background** Persistent pulmonary hypertension of the newborn manifesting with refractory and severe cyanosis is the consequence of high pulmonary vascular resistance causing extrapulmonary right-to-left shunt. Acidosis and hypoxemia produce pulmonary vasoconstriction. Persistent pulmonary hypertension of the newborn occurs due to numerous disorders and has been rarely reported as a manifestation of methylmalonic acidemia. We report a newborn with methylmalonic acidemia who presented with persistent pulmonary hypertension of the newborn.

**Case presentation** A 1-day-old Iranian girl presented with respiratory distress and refractory metabolic acidosis. She was born at 39 + 5 weeks gestational age with Apgar scores of 8 and 9 in the 1st and 5th minutes, respectively, and was in good condition up to 10 hours of life. After that, she presented with cyanosis, tachypnea, retraction, and hypotonia. Despite receiving oxygen, she had low oxygen saturation. Echocardiography revealed severe pulmonary hypertension and right-to-left shunt through patent ductus arteriosus and foramen ovale. Her acidosis worsened despite receiving full support and medical therapy. So, she was started on peritoneal dialysis. Unfortunately, she did not respond to treatment, and after she had died, biochemical tests confirmed methylmalonic acidemia.

**Conclusion** Persistent pulmonary hypertension of the newborn is a very rare manifestation of methylmalonic acidemia. Severe inborn errors of metabolism may cause irreversible damage with adverse lifelong morbidity, and early diagnosis may help to prevent such complications. Furthermore, diagnosis of these disorders aids in prenatal diagnosis through the use of cultured amniocytes or chorionic villi to detect gene mutations, as well as biochemical analyses of amniotic fluid for subsequent pregnancies.

**Keywords** Methylmalonic acidemia, Persistent pulmonary hypertension of the newborn, Inborn errors of metabolism, Organic acidemias, Metabolic acidosis, Persistent fetal circulation, Newborn, Case report

## Background

Methylmalonic acidemia (MMA), the most common form of organic acidemia [1], is the result of methylmalonyl COA mutase (MCM) enzyme deficiency or defect in synthesis or transport of its coenzyme, adenosylcobalamin (AdoCbl), or deficiency of methylmalonyl-CoA epimerase enzyme [2, 3]. Acute clinical presentation of MMA is sepsis-like, and nonspecific symptoms such as vomiting, poor feeding, lethargy, respiratory distress, decreased level of consciousness, hypo-/hypertonia, seizure, and temperature instability may develop [4]. Cardiomyopathy, arrhythmias and sudden death were also reported without clear pathogenesis [5, 6]. Laboratory findings include severe and persistent metabolic acidosis, hypoglycemia or hyperglycemia,

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**Table 1** Review of the articles (cases reported with isolated MMA and cardiac manifestations)

| Authors and references | Age at MMA diagnosis | Age at cardiac disease diagnosis | Sex | Manifestations of MMA | Cardiovascular manifestations | Outcome |
|---|---|---|---|---|---|---|
| Prada *et al.* [5] | 4 months | 22 years | F | Developmental delay<br>Chronic tubulointerstitial nephropathy<br>ESRD | Pericardial effusion<br>LV hypertrophy<br>Cardiomegaly<br>EF: 18% | Died |
| Prada *et al.* [5] | 2 days | 7 months | M | Tachypnea<br>Hyperglycemia<br>Vomiting | Cardiomyopathy<br>Aortic stenosis<br>EF: 20–42% | Died |
| Prada *et al.* [5] | Neonate | 4 years | F | Kusmal respiration<br>Metabolic acidosis<br>Hyperammonemia<br>Renal tubular acidosis | Supraventricular tachycardia<br>Dilated cardiomyopathy<br>EF: 20–25% | Died |
| Chioukh *et al.* [15] | 16 months | 16 months | M | Fever<br>Cough<br>Tachypnea<br>Cyanosis | Mild pericardial effusion<br>PAH<br>Enlarged right ventricle | Died |
| Agarwal *et al.* [14] | Neonate | Neonate | F | Respiratory distress<br>Acidosis | PPHN | Died |
| Kido *et al.* [16] | 3 months | 35 years | F | Vomiting<br>Lethargy<br>Tachypnea<br>Renal failure | PAH | Survived |

EF, ejection fraction; ESRD, end-stage renal disease; F, female; LV, left ventricle; M, male; PAH, pulmonary arterial hypertension; PPHN, persistent pulmonary hypertension of the newborn

neonatal period. Chioukh *et al.* [15] reported the case of a 16-month-old male infant admitted with PAH and biochemical-test-confirmed MMA. The patient died despite treatment. Kido *et al.* [16] reported the case of a woman known to have had MMA at the age of 3 months, which was complicated with PAH at a 36 years of age. Their patient was treated successfully. Most case reports of MMA with cardiovascular diseases have combined MMA and homocystinuria such as eight cases reported by Liu *et al.* [6]. The mechanism has not been elucidated, but it may be due to vasculopathy and thrombosis [17]. In a cohort study of 301 Chinese patients with isolated MMA, six patients had cardiomyopathy and two of them developed PAH [2]. Other case reports with isolated MMA and cardiovascular manifestations are presented in Table 1. Although our patient had normal brain sonography on the first day of life, she developed IVH (Intra-Ventricular Hemorrhage) grade 3 on her last day of her life. Cerebral hemorrhage has been reported as a rare manifestation that could be due to correction of acidosis [18].

Our limitations in diagnosis and treatment include lack of prenatal diagnosis and delay in test results such as ammonia and biochemical tests. Furthermore, due to the short lifespan of the patient, some tests were not repeated. Regarding treatment, inhaled nitric oxide, the first line of PPHN treatment, was not available in our country, so other drugs were used to control PPHN. The patient's family received genetic counseling. However, they did not undergo genetic tests due to economic problems.

Severe IEM may cause irreversible damage with adverse lifelong morbidity, and early diagnosis may help to prevent such complications. Furthermore, diagnosis of these disorders helps prenatal intervention for subsequent pregnancies. Knowledge of the association between PPHN and IEM can help to consider underlying IEM and its management in some cases of idiopathic PPHN.

**Abbreviations**

| | |
|---|---|
| ABG | Arterial blood gas |
| IEM | Inborn errors of metabolism |
| MMA | Methylmalonic acidemia |
| PAH | Pulmonary arterial hypertension |
| PDA | Patent ductus arteriosus |
| PPHN | Persistent pulmonary hypertension of the newborn |
| PVR | Pulmonary vascular resistance |
| TTN | Transient tachypnea of neonate |
| MCM | Methylmalonyl COA mutase |
| AdoCbl | Adenosylcobalamin |
| NICU | Neonatal intensive care unit |
| CBC | Complete blood count |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| INR | International normalized ratio |

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