Abrupt onset of pulmonary hypertension and atypical haemolytic-uremic syndrome in a young child; diagnosis and successful treatment of rare metabolic disorder.

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Case Description

The primary subject matter of this case concerns: paediatric cardiology, pulmonary hypertension. Secondary issues examined include: Cobalamin C deficiency, thrombotic microangiopathy. The case has a difficulty level of seven: appropriate for doctoral students. The case is designed to be taught in two class hours and is expected to require four hours of outside preparation by students.

Case Synopsis

The enclosed case report exemplifies the problem of differential diagnosis while managing pulmonary hypertension in children. In the present case, the concomitant development of pulmonary hypertension and atypical haemolytic uremic syndrome suggested the diagnosis of underlying metabolic disorder, i.e. methylmalonic acidemia and homocystinuria due to Cobalamin C deficiency. Early identification of a treatable cause of pulmonary hypertension is mandatory, as to ensure the optimal final outcome and long-term survival to affected patients.

Case Report

A healthy 2-years boy was admitted to our hospital due to severe respiratory distress, with tachypnea (RR >60/min) and desaturation (blood oxygen saturation <85%). Within few hours from admission, severe systemic hypertension and anasarca appeared, requiring anti-hypertensive and diuretic treatment. Cardiologic evaluation excluded congenital heart diseases, whereas it revealed concentric left ventricular hypertrophy and signs of severe Pulmonary Artery Hypertension (PAH), with peak tricuspid regurgitation velocity >5 m/s. Mechanical respiratory support and phosphodiesterase-5 inhibitor treatment were promptly started, with initial stabilization of clinical parameters. Laboratory work-up documented mild anaemia, thrombocytopenia, increased blood creatinine level, reduced C3 and C4 complement fractions and positive haemolytic tests, suggesting the diagnosis of Haemolytic Uremic Syndrome (HUS) (Table 1).

Table 1. *Laboratory data of reported patient ad admission and at last available follow-up.*

	ONSET	LAST FOLLOW-UP	NORMAL VALUES
WBC (x103 /microL)	12	12,8	5-15
RBC (x106 /microL)	3,22	4,56	4,10-5,5
Hb (g/dl)	8,9	13,4	12-14
MCV (fl)	87,3	85,6	75-85
RDW (%)	23,1	12,7	11,6-16,5
PLT (x103 /microL)	61	347	130-400
Creatinine (mg/dl)	0,93	0,35	0,1-0,36
Blood urea (mg/dl)	91	16	9-22
Calcium (mg/dl)	9,1	9,6	9,2-10,3
LDH (UI/L)	1390	292	192-321
Aptoglobine (mg/dl)	<7,75	62	30-200
Total bilirubin (mg/dl)	0,9	0,05	0,05-0,4
Total protein (g/dl)	5,1	7,4	6,1-7,5
Albumin (serum) (g/dl)	3	3,9	3,5-4,5
Proteinuria (mg /24h)	202,6	75,8	<150
Total urinary proteinuria (mg/L)	3247	94	<100
Albumin (urine) (mg/L)	2510	31,8	<25
IgG (Urine) (mg/L)	112	4,6	<5
A1 microalbumin	47,3	<7,81	<10
C3c (mg/dl)	81	107	90-180
C4 (mg/dl)	19	26	10-40
IgG (mg/dl)	223	949	432-1100

IgA (mg/dl)	<7,83	55,9	30-125
IgM (mg/dl)	72	52	40-120
Vitamin B12 (pg/ml)	605	>6000	160-800
Folate (ng/ml)	4,5	132	3-15
Total cholesterol (md/dl)	247	177	45-210
Triglycerides (mg/dl)	282	121	53-258
ADAMTS-13 activity (%)	80	-	50-150
ADAMTS-13 Inhibitors (U/ml)	1	-	0-15
Homocysteine (micromol/L)	74	8,7	<15
Propyonilcarnitine (C3 micromol/L)	5,64	0,89	<0,86
Metylmalonic acid (serum) (micromol/L)	138	1,9	<1
Metylmalonic acid (urine) (mM/mol)	919	2	<2

Given the negative history of fever and gastrointestinal symptoms, investigations for atypical HUS were considered. Extended metabolic screening revealed increased levels of plasmatic Homocysteine, Propyonilcarnitine (C3), blood and urinary Metylmalonic acid. Folic acid and vitamin B12 value resulted within normal range (Table 1). Peripheral blood smear highlighted hypersegmented neutrophils and schistocytes; the results lead to the diagnosis of methylmalonic acidemia and homocystinuria due to Cobalamin C deficiency (MMACblC), further confirmed at genetic test. The child underwent metabolic treatment, with rapid clinical improvement. Cardiologic evaluation confirmed progressive normalization of right pressure overload, even after sildenafil discontinuation. Systemic blood pressure gradually normalized, and anti-hypertensive therapy was discontinued within 6 months. At last available follow-up, after 2 years from discharge, the child showed regular growth and neurologic development. Echocardiography confirmed normal wall thickness, right chamber dimension and interventricular septum shape (Figure 1); no tricuspid regurgitation could be documented.

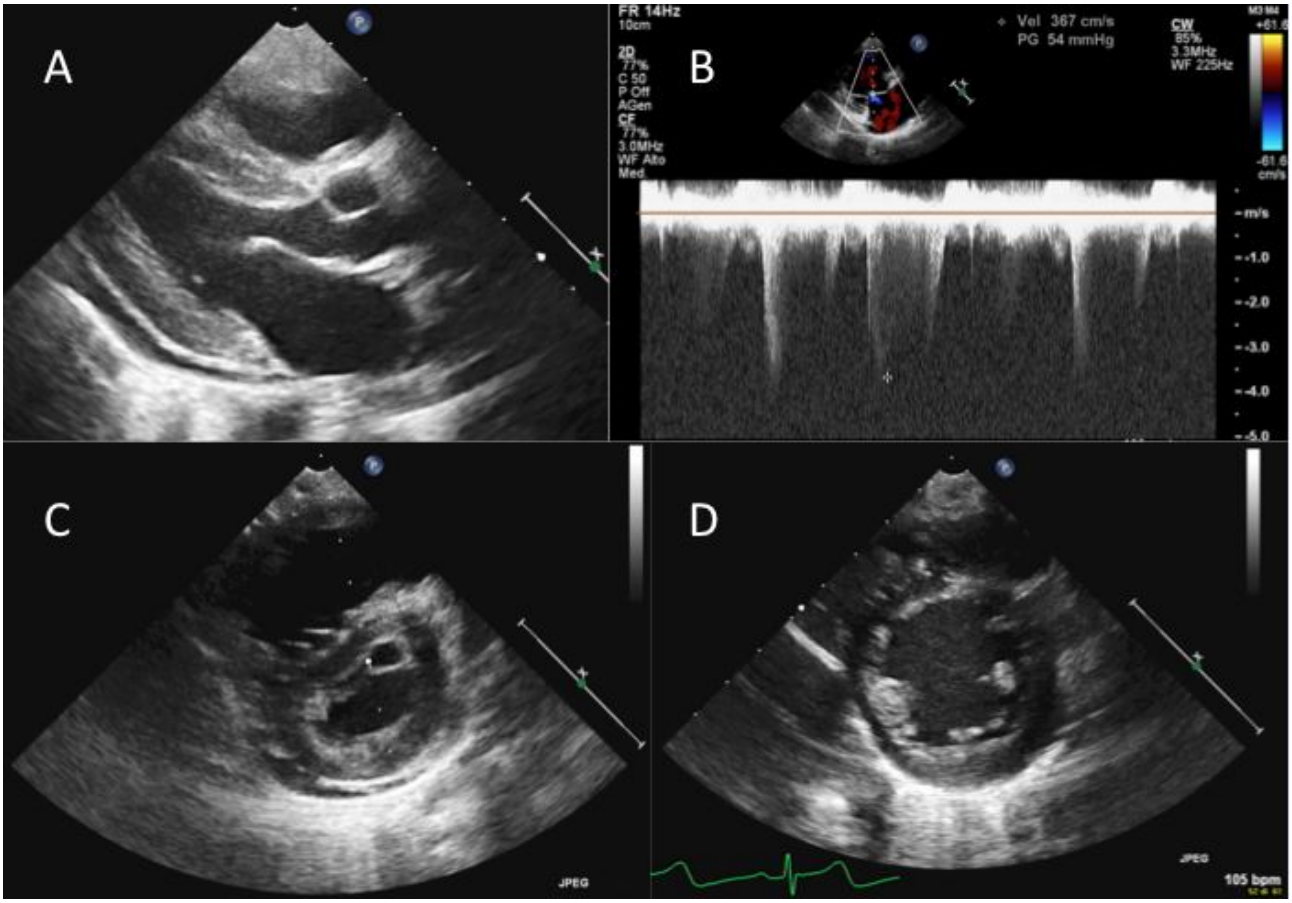

Figure 1. *On admission, mild left ventricular hypertrophy associated with pericardial effusion was documented (Panel A). Increased peak tricuspid regurgitation velocity (Panel B) and septal "D-shape" (Panel C) suggested increased pulmonary pressure. At last available follow-up, normalization of septal shape was confirmed (Panel D).*

Discussion

Pulmonary hypertension (PH) is a rare condition in paediatric population, defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization. PH may be primitive (either idiopathic or due to genetic mutation) as well as associated with multiple conditions as thromboembolism, hypoxia, congenital or

acquired left and right heart diseases, septal defects, valvular disorders, connective tissue disorders, infections (HIV, schistosomiasis, hydatidosis), endocrinopathies, hematologic conditions and drug/toxin exposure [1] (Table 2). According to recent ESC guidelines, persistent PAH in the newborn has been classified as a distinct condition, given its unique pathophysiology [1]. Concerning metabolic disorders, glycogen storage disease [2] Gaucher disease [3] and primary mitochondrial disorders [4,5] have been reported as possibly associated with PAH, even if the underlying mechanism remains unclear.

Tabel 2. *Differential diagnosis of pulmonary artery hypertension (from Simonneau G, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.*

1) Pulmonary arterial hypertension	
Idiopathic	
Heritable	BMPR2 mutation Other mutations
Drugs and toxins induced	
Associated with	Connective tissue disease Human immunodeficiency virus (HIV) infection Portal hypertension Congenital heart disease Schistosomiasis
Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	
Idiopathic	
Heritable	EIF2AK4 mutation Other mutations
Drugs, toxins and radiation induced	
Associated with:	Connective tissue disease HIV infection
Persistent pulmonary hypertension of the newborn	
2) Pulmonary hypertension due to left heart disease	
Left ventricular systolic/diastolic dysfunction	
Valvular disease	
Congenital or acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	
Congenital /acquired pulmonary veins stenosis	
3) Pulmonary hypertension due to lung diseases and/or hypoxia	
Chronic obstructive pulmonary disease	
Interstitial lung disease	
Other pulmonary diseases with mixed restrictive and obstructive pattern	
Sleep-disordered breathing	
Alveolar hypoventilation disorders	
Chronic exposure to high altitude	
Developmental lung diseases	
4) Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions	
Chronic thromboembolic pulmonary hypertension	
Other pulmonary artery obstructions	Angiosarcoma/ intravascular tumors Arteritis

	Congenital pulmonary arteries stenoses Parasites (hydatidosis)
5) Pulmonary hypertension with unclear and/or multifactorial mechanisms	
Haematological disorders	chronic haemolytic anaemia myeloproliferative disorders splenectomy
Systemic disorders	sarcoidosis pulmonary histiocytosis lymphangioleiomyomatosis neurofibromatosis
Metabolic disorders	glycogen storage disease Gaucher disease thyroid disorders
Others	pulmonary tumoral thrombothic microangiopathy fibrosing mediastinitis chronic renal failure (with/without dialysis) segmental pulmonary hypertension

Whether primitive or secondary to another disease, the prognosis of PAH is frequently unfavourable, with a 3-years mortality rate of 25% [6].

Cobalamin C deficiency is a rare inborn error of cobalamin metabolism, commonly presenting with neurological, ocular, hematologic, renal and gastrointestinal symptoms. Even rare, association between MMACblC and atypical HUS is well known [7]. Conversely, secondary PAH has been described only in few paediatric cases, exiting in death in at least half of them [8-13]. The pathogenesis of renal and pulmonary damage is presumably due to arteriolar and capillary thrombosis with consequent micro-vascular dysfunction distinctive of Thrombotic Microangiopathy (TMA) [12,13]. TMA is a pathological process of micro-vascular thrombosis, consumptive thrombocytopenia and haemolytic anaemia, leading to multi-organ failure. Multiple conditions may present with TMA; gastro-intestinal or systemic infections (*Escherichia coli*, *Shigella dysenteriae*, *Streptococcus pneumonia*) are the most common in children, mainly occurring with renal and cerebral dysfunction (classical Haemolytic-uremic syndrome). Other less common causes comprise genetic mutations (ADAMTS13 protease deficiency), pregnancy, malignant hypertension, autoimmune disorders, drug exposure and transplantation (renal, hematopoietic stem cell transplant) [14-16]. Irrespective of the triggering cause, final step is abnormal complement activation, endothelial damage and platelet activation.

In the reported case, the concomitant presence of renal failure, thrombocytopenia, haemolytic anaemia and pulmonary artery hypertension, along with the exclusion of common causes of classical HUS, suggested the diagnosis of underlying metabolic disorder. The early diagnosis allowed a prompt administration of specific treatment, leading to a long-term positive outcome.

Conclusion

We reported a dramatic improvement after the beginning of metabolic treatment in a patient presenting with MMACblC complicated with both PAH and aHUS.

Complete and stable resolution of PAH was confirmed after 24-months follow-up; this may be due to an early diagnosis with prompt treatment administration. We therefore suggest considering MMACblC in paediatric patients presenting with PAH, after other more common causes have been already excluded, since early administration of specific treatment could completely change the patient's outcome.

Conflict of Interest

Authors have no conflicts of interest to declare.

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