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Exceptional Case

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Renal thrombotic microangiopathy and pulmonary arterial hypertension in a patient with late-onset cobalamin C deficiency

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Abstract

Cobalamin C (cblC) deficiency is the most commonly inherited inborn error of vitamin B12 metabolism. It is characterized by multisystem involvement with severe neurological, hematological, renal and cardiopulmonary manifestations. Disease is most commonly diagnosed early in the first decade of life. We report a case of a 20-year-old woman who developed severe pulmonary arterial hypertension while under nephrologic follow-up for chronic kidney disease. She had initially presented at 14 years of age with visual disturbance and acute renal failure and been diagnosed with thrombotic thrombocytopenic purpura on the basis of kidney biopsy findings of thrombotic microangiopathy and compatible ADAMTS13 (a disentegrin and metalloproteinase with a thrombospondin type 1 motif member 13). When cblC deficiency was eventually diagnosed, remarkable improvement in cardiopulmonary function was evident upon initiation of treatment. This case highlights the importance of a timely diagnosis and initiation of treatment for cblC deficiency. Clinical diagnosis may be challenged by asynchronous organ symptom presentation and by misleading laboratory tests, in this case: an initial low ADAMTS13. A simple test of plasma homocysteine level should be encouraged in cases of thrombotic microangiopathy and/or pulmonary artery hypertension.

Key words: ADAMTS13 activity, cobalamin C deficiency, end-stage renal disease, pulmonary arterial hypertension, renal thrombotic microangiopathy

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Introduction

Combined methylmalonic aciduria with homocystinuria, cobalamin C (cblC) complementation type, is the most commonly inherited inborn error of intracellular cobalamin (vitamin B12) metabolism. It is caused by an autosomal recessive defect in the *MMACHC* gene located on chromosome 1p34 leading to impaired conversion of vitamin B12 into its two metabolically active forms: methylcobalamin and adenosylcobalamin [1]. Methylcobalamin is a cofactor for methionine synthase, which is responsible for the remethylation of homocysteine to methionine [2]. Adenosylcobalamin is a cofactor for methylmalonyl-CoA, which is responsible for the degradation of methylmalonic acid (MMA) [2]. Deficiency in these cofactors leads to elevated plasma levels of homocysteine (vasculopathy and thrombosis), elevated plasma and urine MMA (neurological toxicity) and low plasma levels of methionine (demyelination) [3].

The clinical presentation of patients with cblC deficiency is closely related to age of onset. Presentation is usually most severe and progressive in those with early-onset cblC deficiency. Prenatal manifestations can include dysmorphic features, intrauterine growth retardation, microcephaly, hydrocephalus or congenital heart disease [4–6]. Infants and toddlers often demonstrate failure to thrive, global developmental delay and neurological sequelae such as hypotonia and seizures. In addition, some individuals may present with cytopenias or progressive retinopathy. Renal thrombotic microangiopathy (rTMA) and pulmonary artery hypertension (PAH) are rare, but severe complications have been reported in a small number of cases [7]. In contrast to early-onset cblC deficiency, individuals with late-onset cblC deficiency presenting in adolescent or adulthood stage typically have less severe manifestations limited to progressive cognitive decline, neuropsychiatric symptoms and subacute combined degeneration of the spinal cord [8–10]. Renal manifestations also present in an age-specific pattern: hemolytic uremic syndrome (HUS) generally presents in infants and young children with median age of 6 years as seen in a review by Huemer *et al.* [11]. Conversely, more adults present with renal damage in the form of chronic thrombotic microangiopathic glomerulonephropathies [11, 12].

We report a case of late-onset cblC deficiency presenting with rTMA and PAH.

Case description

A previously healthy 14-year-old woman of Jewish descent presented to hospital in April 2010 with sudden bilateral vision loss. She had an uneventful family history, no siblings and no evidence of consanguinity. She was a lifetime non-smoker and denied use of alcohol and drugs. Her past medical history included an unremarkable childhood with no developmental problems. She was known to have hypothyroidism and ovarian cysts.

Upon admission, she was found to be severely hypertensive and fundoscopy showed hypertensive retinopathy with retinal hemorrhages and bilateral retinal detachment. A cranial magnetic resonance imaging was done, which showed normal findings. Laboratory studies showed acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia. Serum complement levels were normal. Although the ADAMTS13 (a disentegrin and metalloproteinase with a thrombospondin type 1 motif member 13) level was <5%, no antibodies were detected and genetic studies confirmed no mutation. Genetic testing for atypical HUS was also negative. She was screened for membranoproliferative glomerulonephritis, but there was no disease-causing mutation found in the *C3*, *APLN* or *THBD* gene. A renal biopsy showed severe thrombotic microangiopathy with 3 out of 24 glomeruli globally sclerosed with moderate interstitial fibrosis and tubular atrophy (Figure 1).

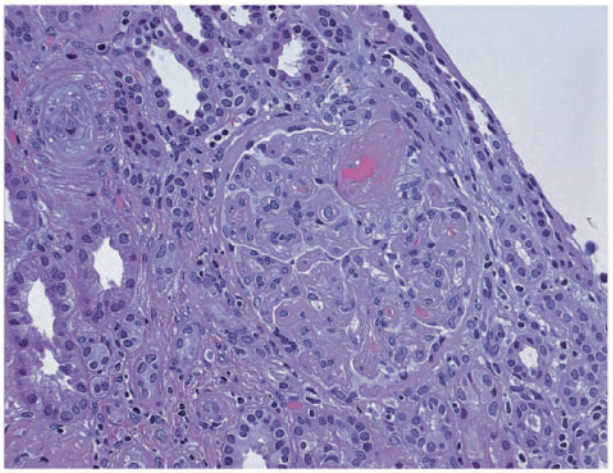

Fig. 1. Renal biopsy: this specimen consists of one core of renal cortex and medulla containing up to 24 glomeruli, 3 of which are globally sclerosed. Several glomeruli are ischemically shrunken with wrinkled capillary walls. There is mild-to-moderate (25%) interstitial fibrosis and tubular atrophy. Several arterioles and arteries show mural fibrinoid change with focal mucoid intimal thickening and fibrin/platelet thrombi.

Given these findings, she was treated for suspected thrombotic thrombocytopenic purpura (TTP) with a course of steroids and 12 sessions of plasmapheresis. She initiated hemodialysis, which was discontinued after 6 months as she recovered some renal function. Four months later she was thought to have a relapse of TTP and again was treated with steroids and plasmapheresis for a few days. Of note, a repeat ADAMTS13 level done at that time was normal.

In 2013, she remained stable with Stage 4 chronic kidney disease (CKD). Her vision returned to normal with a normal eye examination that showed resolution of her retinal hemorrhages. An abdominal ultrasound showed increased echogenicity of the renal cortical tissue of the right and left kidneys, which measured 8.7 and 9.9 cm, respectively. A transthoracic echocardiogram (TTE) showed normal left ventricular size and function with a left ventricle ejection fraction (LVEF) >55%, normal right ventricle size and systolic function, mild-to-moderate mitral regurgitation and no evidence of pulmonary hypertension based on the right ventricular systolic pressure (RVSP).

Over the next 2 years, she developed worsening dyspnea on exertion until November 2015 at which point she was admitted to hospital with New York Heart Association (NYHA) Class 3 symptoms, peripheral edema, abdominal distension and weight gain. A repeat TTE at that time showed significant changes with mildly decreased left ventricular (LV) systolic function (LVEF 50%) and findings suggestive of right ventricular pressure and volume overload, specifically a RVSP of 65 mmHg, moderate pulmonary regurgitation, severe tricuspid regurgitation, severely enlarged and thickened right ventricle and a 14-mm pericardial effusion (Figure 2).

She underwent extensive work up for idiopathic PAH. A ventilation–perfusion scan showed a low probability for pulmonary embolism. Right heart catheterization showed severe pulmonary hypertension (Table 1). On pulmonary function testing she had an FEV1/FVC ratio of 78%, a decreased FVC and FEV1 at 2.5

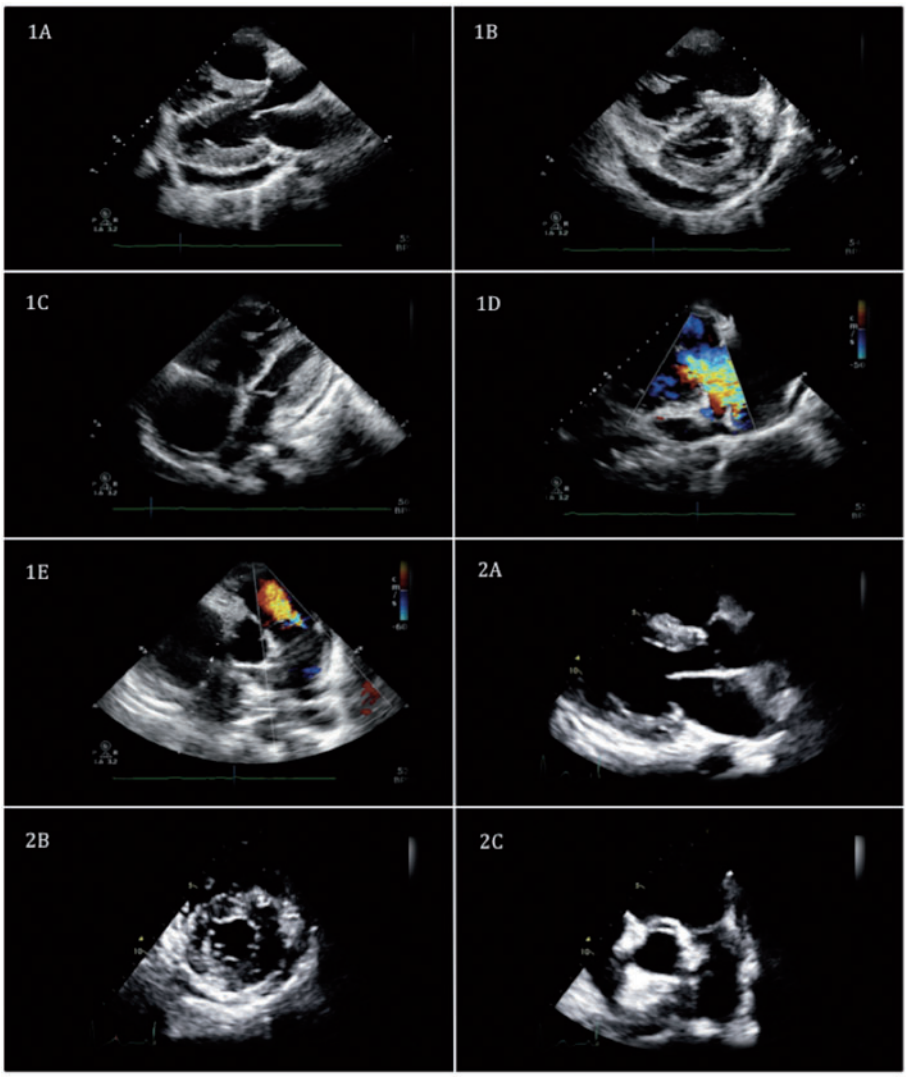

Fig. 2. 1. TTE 2015: (1A) parasternal long axis showing moderate pericardial effusion, (1B) parasternal short axis showing D-shaped septum in diastole, (1C) apical view showing massive RV, (1D) Tricuspid regurgitation, (1E) Pulmonary regurgitation 2. TTE 2017: (2A) parasternal long axis normal, (2B) normal in short axis, (2C) apical view normal.

and 2, respectively, a decreased total lung capacity at 4.2 and a diffusing capacity for carbon monoxide of only 6.7 (32% of predicted). Computed tomography thorax identified an enlarged pulmonary artery at 42 mm, a moderately sized pericardial effusion, extensive centrilobular ground glass nodules throughout both lungs and some interlobular septal thickening in the right lower lobe.

On this presentation, she was commenced on bosentan for idiopathic PAH. Despite this, she experienced further decompensation and was started on sildenafil. She continued to show no improvement in her symptoms and she progressed to requiring home oxygen. During this period, at age 20 years, she progressed to end-stage renal disease and was commenced on dialysis. Unfortunately, her RVSP did not improve following initiation of dialysis (Table 1).

It was considered that her PAH could represent extra-renal manifestations of thrombotic microangiopathy (TMA). As a result, she was considered for treatment with an anti-complement C5 monoclonal antibody, eculizumab. In the process of her work up, she was investigated for cblC deficiency, by measuring plasma homocysteine levels and MMA levels. Laboratory testing revealed a considerably elevated homocysteine level (124 nmol/L) and an elevated MMA level that was 100-fold over the expected level for patients with renal failure (80.15 μmol/L) (Table 1). She was noted to have normal folate and vitamin B12 levels. Molecular genetic analysis of the *MMACHC* gene revealed that she was positive for two heterozygous pathogenic variants confirming a diagnosis of cblC deficiency. These variants were c.271dupA, p.Arg91Lysfs14, heterozygous (autosomal recessive condition) and c.276G>T, p.Glu92Asp, heterozygous (autosomal recessive condition).

Treatment with 1 mg IM hydroxycobalamin, 3 g PO TID betaine, 5 mg PO OD folic acid and 660 mg PO TID carnitine was initiated. She subsequently reported significant improvement in her dyspnea to NYHA Class 1 and no longer required supplemental oxygen. A repeat TTE showed normal LV size and function with a markedly improved right ventricular (RV) size and function (Figure 2). A repeat right heart catheterization also showed significant improvement (Table 1). Overall, she demonstrated an excellent response to treatment with a significantly improved hemodynamic profile and resolution of her PAH.

Renal function also improved. After 15 months on hemodialysis the patient regained enough renal function so as to stop

Table 1. Clinical, biochemical and hemodynamic trends

Characteristic	Initial 2015/11	After diuresis[a] 2015/12	After PAH TX/intermittent hemodialysis[b] 2016/3–6	After cblC TX[c] 2017/1
Echocardiogram				
Left ventricular ejection fraction (%)	53	—	67	59
Right ventricular systolic pressure (mmHg)	65	—	122	33
Cardiac catheterization				
Pulmonary arterial pressure (mmHg)	72/34 (49)	69/28 (46)	60/20 (44)	50/18 (32)
Pulmonary capillary wedge pressure (mmHg)	20	9	12	13
Mixed venous O_2 (%)	51			70
Transpulmonary pressure gradient (mmHg)	30		32	8
Cardiac output (L/min)	3.58	3.6	—	6.8
Biochemical markers				
MMA (nmol/L)	—	—	80.15	2.31
Homocysteine (μmol/L)	—	—	124	37.7
Clinical features				
NYHA Class	3	3	3	1

[a]Following aggressive diuresis.
[b]Following treatment with sildenafil and bosentan and initiation of hemodialysis.
[c]Following treatment with hydroxycobalamin, betaine, folic acid and carnitine.

dialysis. At the time of writing she has been off dialysis for 6 months with an estimated glomerular filtration rate of 12 mL/min (CKD-EPI).

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this *Journal*.

Discussion

We report a case of a 20-year-old female with cblC deficiency who presented with rTMA and PAH. In the absence of newborn screening, cblC deficiency is difficult to recognize due to the wide variety of clinical manifestations. In most cases, those with severe multisystem involvement tend to present in early childhood. Individuals with a late-onset form typically present with a milder phenotype limited to neurological disturbances. Those with late-onset cblC deficiency may be missed on newborn screening, as the biochemical abnormalities at 48–72 h of life will be too mild for identification. As a result, physicians need to consider this condition despite the presence of negative newborn screening.

The association of rTMA with PAH in cblC deficiency is rare and has only been described in a few cases [13]. The majority of these cases occur with early-onset cblC deficiency presenting in childhood [13]. As a result, a unique feature of our case was the patient's age at the onset of her clinical manifestations. To our knowledge, only two other cases of late-onset cblC deficiency presenting with rTMA and PAH have been reported. Grangé *et al*. reported a case of an 18-year-old male who presented with renal failure, PAH, hemolytic anemia and thrombocytopenia [14]. Losito *et al*. reported a case of a 14-year-old male who presented with hypertension and was found to have rTMA and nephromegaly [13, 15]. He subsequently developed PAH 5 years later and was diagnosed with cblC deficiency 18 years after initial presentation [13, 15]. As in our case, both of these cases presented a considerable diagnostic challenge leading to a delayed diagnosis and initiation of treatment. To allow for a timely diagnosis, it is evident that screening for cblC deficiency through evaluation of homocysteine and MMA levels needs to be included in the investigation of rTMA regardless of the age at presentation [16].

Another interesting clinical fact is that the patient initially presented with low ADAMTS13 levels. One of the possible explanations could be the association of low ADAMTS13 with severe cblC deficiency [17]. Though no mechanism has been discovered, a low ADAMTS13 may potentially be falsely low in patients with cblC deficiency.

Other renal presentations well documented in the pediatric nephrology literature include presentation with renal tubular acidosis, tubulointerstitial nephritis and acute renal failure from thrombotic microangiopathy [18].

Endothelial dysfunction has been shown to play a pivotal role in the pathogenesis of both rTMA and PAH [19]. In the case reported by Losito *et al*., the patient experienced improvement in both his renal function and PAH following treatment with bosentan, an oral endothelin receptor antagonist [13, 15]. This, however, was not true for the patient in our case. In contrast, our patient experienced dramatic resolution of her PAH following treatment of her cblC deficiency with initiation of the treatment regimen used in this condition (hydroxycobalamin, betaine, folate and carnitine) [13, 15]. Based on this, the potential therapeutic value of bosentan and hydroxycobalamin/betaine/carnitine/folate in patients with cblC deficiency requires further investigation.

The patient in our case was found to be positive for two heterozygous pathogenic variants in the *MMACHC* gene: c.271dupA, p.Arg91Lysfs14, heterozygous and c.276G>T, p.Glu92Asp, heterozygous. The first variant is the duplication of an adenine at nucleotide position 271, which is predicted to result in a change from an arginine to a lysine at amino acid position 91 and a shift in the reading frame thereafter. A termination codon is predicted 13 codons beyond this change. This variant is a common pathogenic variant in patients with methylmalonic acuduria and homocystinuria and has been associated with early-onset cblC disease. In a case series by Kömhoff *et al*., five cases of combined PAH and rTMA in cblC deficiency are reported. In addition to our patient, four of these cases were positive for heterozygous mutations at nucleotide 276 in the *MMACHC* gene (c.276G>T or c.276G>A) [13]. Based on this, it can be speculated that mutations at nucleotide 276 may be associated with the presence of combined PAH and rTMA in cblC deficiency. Furthermore, two of these cases had the same two heterozygous mutations

as our patient, but in contrast, presented with early-onset disease.

Overall, the combined presence of rTMA and PAH in cblC deficiency is rare, but is heterogeneous with regards to age of onset, presentation and response to treatment. The prognosis for these patients is variable, but mortality rates approach 100% in untreated patients [20, 21]. As a result, a timely diagnosis is important to allow for early initiation of treatment with hydroxocobalamin, betaine, folinic acid and carnitine [18].

Conclusions

We have described a unique case of late-onset cblC deficiency presenting with rTMA and PAH. Determining the etiology of these conditions is necessary to evaluate the severity of disease, devise a management plan and assess prognosis. When considering a differential diagnosis for these patients, a careful metabolic screen should be included to ensure timely diagnosis and treatment of cblC deficiency [16].

Conflict of interest statement

None declared.

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