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CLINICAL QUIZ

A child presenting with severe hypertension and circulatory failure—a diagnostic conundrum: Answers

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Answers

Question 1

The differential diagnostic options we considered:

– Thrombotic microangiopathy (TMA) [atypical hemolytic uremic syndrome (HUS), cobalamin deficiency-associated HUS, non-Shiga toxin-infectious HUS, ADAMTS13 deficiency]
– Systemic lupus erythematosus
– Polyarteritis nodosa
– Neuroblastoma/pheochromocytoma
– Tumor lysis syndrome secondary to leukemia
– Sepsis with acute kidney injury (AKI)
– Acute disseminated encephalomyelitis
– Hyperthyroidism (adenoma, auto immune)

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– Other causes of glomerulonephritis, e.g. C3 glomerulonephritis/post-infectious glomerulonephritis.

Question 2

Complement levels of component 3 (C3; 0.7 g/L, reference level 0.9–1.8 g/L) were low, while C4 levels were at the lower limit (0.1 g/L, reference 0.1–0.4 g/L) of the normal range. Plasma renin levels were strongly elevated (1609 pg/mL, reference <35.7 pg/mL) with concomitant high aldosterone levels (>132 ng/dL, reference 3.7–43.2 dL). Cortisol levels were elevated (31.8 μg/dL, reference 2.69–10.4 μg/dL). Thyroid hormones were low [thyroid stimulating hormone 0.64 mU/L, reference 0.7–6.0; free thyroxine (FT4) 0.6 ng/dL, reference 1.0–1.8 ng/dL]. Autoimmune testing was negative for anti-nuclear antibodies, anti-cytoplasmatic antibodies and anti-double-stranded DNA antibodies. Repeated blood and urine cultures and intensive work-up for viral infections (including Epstein-Barr virus, cytomegalovirus, varicella, herpes simplex virus) was negative. A nasal swab was positive for adenovirus and corona virus.

Repeated abdominal ultrasound scans were negative for neuroblastoma and feochromocytoma, but neuron-specific enolase (a tumor marker for neuroblastoma) was moderately elevated (46.5 μg/L, reference 0–12.5 μg/L). Tests for catecholamines in urine were negative. Metabolic screening demonstrated sky high homocysteine levels (131.5 μmol/L, reference 3.3–8.3 μmol/L) with normal methionine levels (20 μmol/L, reference 11–76 μmol/L) while the remaining plasma amino acid profile was normal. Elevated plasma levels of vitamin B12 (1420 ng/L, reference 197–866 μmol/L), vitamin B6 (292 nmol/L, reference 26–102 nmol/L) and folate (14.4 μg/L, reference 2.0–9.1 μg/L) were noted, and the diagnosis of cobalamin deficiency-associated HUS was strongly

suspected. However, urine tested negative for organic acids including methylmalonic acid.

Question 3

The blood pressure (BP) was >99th percentile (BP 99th percentile 116/77 mmHg) according to age, height and sex, with associated end organ damage, and hypertension was classified as a hypertensive emergency. Current recommendations are to reduce mean arterial pressure by no more than 25% within the first 8–12 h and then gradually normalize it within the next 48–72 h [1, 2]. However, there were also signs of left ventricular failure for which milrinone (inotropic action, pulmonary vasodilatation) had been given by the intensivist. Antihypertensive treatment was initiated with continuous intravenous (IV) administration of nicardipine (0.5–4 µg/kg body weight/min), and the IV administration of furosemide was added in light of pulmonary edema and oliguria.

Case follow-up

Treatment was initiated with intramuscular hydroxocobalamin 1 mg/day (vitamin B12), IV levofolinic acid 30 mg/day and betaine 2 × 1 g/day 36 h after admission. Homocysteine levels gradually decreased (settling around 13.6–23.6 µmol/L, reference 3.3–8.3 µmol/L), but the clinical course was complicated by deep venous thrombosis of the left external iliac artery, for which low-molecular-weight heparin (subcutaneous enoxaparin 20 mg/day for 6 weeks) was prescribed.

In the first 48 h after admission, renal function deteriorated with rising creatinine (maximum 1.24 mg/dL), blood urea nitrogen (maximum 96 mg/dL) and oliguria. However, gradual improvement followed with normalization of diuresis and lowering of serum creatinine, and dialysis was unnecessary. The BP came down gradually, and in light of restored left ventricular function and tachycardia, IV nicardipine was exchanged for IV labetalol. Later this was switched to oral labetalol, amlodipine and lisinopril.

Antibiotic (cephotaxime) and antiviral (acyclovir) treatments were initially started but discontinued (after 72 h) in light of negative cultures/serology. Shortly after the start of mechanical ventilation, a left-sided pneumothorax developed for which a chest drain was temporarily inserted. Pulmonary edema gradually decreased and the pneumothorax resolved. A first attempt at extubation (6 days post admission) failed after the patient developed bilateral pleural effusions with respiratory distress, requiring reintubation (8 days post admission). Successful extubation was performed 15 days post admission. Neurologically she recovered well, but follow-up was deemed necessary in light of memory and speech deficits. Opthalmologic follow-up was planned due to retinal abnormalities, but vision was preserved at time of discharge.

Renal function improved and the creatinine level normalized, but low-level proteinuria and hypertension persisted (even months after the initial event). The ultrasound image of the kidneys also improved, with disappearance of cortical hyperechogenecity and normalization of corticomedullary differentiation (Fig. 1).

The patient was discharged from the pediatric intensive care unit in good clinical condition 21 days after initial admission. Molecular analysis (on isolated fibroblasts and blood) came back positive for two mutations (one frameshift mutation and one deletion) in the *MMACHC* gene on chromosome 1p34, corresponding with cobalamin C (Cbl C) disease. Genetic testing of the parents their carrier status. Testing for mutations in the *MTHFR* gene, associated with homocysteinemia related to impaired conversion of homocysteine to methionine [3], came back negative.

Discussion

Cobalamin C disease is one of the rarest causes of HUS. It is caused by mutations in the *MMACHC* gene with an autosomal recessive pattern of inheritance [4, 5]. Children usually present in the neonatal period with vomiting, poor sucking, failure to thrive, lethargy, hypotonia, thrombocytopenia, microangiopathic hemolytic anemia and AKI [4, 6].

Onset later in childhood has been described [7], and isolated cases of adult onset [8, 9] have also been reported. Neurologic symptoms are usually prominent at presentation and can include cognitive impairment, ataxia, and psychosis [10, 11]. Severe respiratory distress and liver failure at presentation have also been reported [11]. Intracellular cobalamin is derived from ingested exogenous cobalamin (vitamin B12) available in several food types (e.g. fish, red meat, fortified
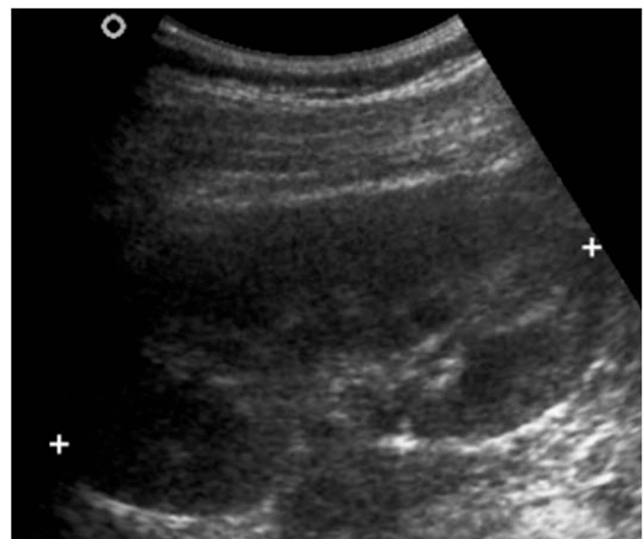

Fig. 1 Longitudinal view of left kidney: normal corticomedullary differentiation and cortical echogenicity can be seen

cereals, low fat milk, eggs and cheese). It plays an important role in cellular DNA synthesis and deficiencies, especially affecting rapidly dividing cells [11, 12]. After its uptake by cells, exogenous cobalamin is converted into two active coenzyme derivatives: methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl). MeCbl is essential for the conversion of homocystine to methionine by the cytoplasmic enzyme methionine synthase [9, 12]. AdoCbl is a cofactor of the mitochondrial enzyme methylmalonyl coenzyme A (CoA) mutase, which converts L-methyl-malonyl-CoA to succinyl-CoA. When a homozygous mutation in the *MMACHC* gene is present, MeCbl will not metabolize homocysteine to methionine and AdoCbl will not metabolize L-methylmalonyl-CoA to succinyl-CoA [10, 12]. In Cbl C disease, this deficiency leads to elevated levels of homocysteine (and L-methylmalonyl-CoA) which is suspected as being responsible for the endothelial damage and TMA [10, 12]. As a result of cobalamin metabolism abnormalities, the most common biological hallmarks of Cbl C disease, in addition to hyperhomocysteinemia, are low blood methionine levels and methylmalonic aciduria [10, 12].

The metabolism of homocysteine takes place via three pathways [3]:

(1) Via re-methylation of homocysteine to form methionine by methionine synthase in a vitamin B_{12}- and folate-dependent reaction. Mutations in the *MTHFR* or *MMACHC* genes can disrupt this pathway.

(2) The transsulfuration pathway, by which, after the addition of a serine group, homocysteine is converted to cystathionine by cystathionine β-synthase in certain organs (e.g. kidney and liver). Disruption of this pathway leads to classical homocysteinuria.

(3) Through re-methylation of homocysteine to methionine via betaine: homocysteine methyltransferase. High homocysteine levels can cause depletion of betaine [13].

For treatment of Cbl C disease, parenteral hydroxocobalamin (1 mg/daily or alternate day) combined with oral folinic acid (5–15 mg/day) and betaine (150–250 mg/kg/day) are recommended [11, 14, 15]. Prognosis is variable, but high mortality rates are reported [16, 17]. Timely treatment can improve outcome with better growth, hematological improvement and preservation of renal function [11]. However, developmental delay due to neurological involvement and visual complications may persist and/or worsen [11]. The case reported here presented a considerable diagnostic challenge. Our patient presented with severe neurological and circulatory involvement, and initially the origin of the problem was unclear. Renin-mediated hypertension inducing encephalopathy secondary to posterior reversible encephalopathy syndrome (PRES) and left ventricular dysfunction secondary to increased preload was at the core of this clinical conundrum. In retrospect, initial fluid therapy most likely increased the preload of the left ventricle, worsening left ventricular failure and pulmonary edema and thereby adding to circulatory and respiratory failure. The suspicion of underlying renal dysfunction as the primary cause arose when ultrasound images were reviewed. The detected increased corticomedullary differentiation, typically associated with vasculitis [18–20], was crucial in directing the additional diagnostic workup. Increased fragmentocytes in the blood smear also pointed towards TMA, leading to the workup for atypical HUS. Low albumin and thyroid hormone levels were secondary to significant proteinuria. Plasma homocysteine levels were rapidly assessed, which enabled quick confirmation of this condition and treatment. Low methionine levels and methylmalonic aciduria are also usually seen in Cbl C disease [11], but these were absent in this case. This atypical phenotype could possibly be explained by the compound heterozygous mutations of the *MMACHC* gene found, consisting of two different mutations in the paternal and maternal alleles instead of the usual homozygous pattern of inheritance.

Treatment of the hypertensive emergency also provided a challenge. The IV administration of beta blockers, which are first line agents, were contraindicated in light of left ventricular failure [21], and we decided to initiate treatment with a continuous IV infusion of an calcium channel antagonist (nicardipine) which allowed for gradual reduction of BP and the possibility to quickly adjust dosages. Other alternatives under consideration were hydralizine (vasodilator), fenoldopam (dopamine receptor agonist) and diazoxide (direct vasodilator) [21]. In treating malignant hypertension it is important to adhere to guidelines, as mentioned earlier, in order to prevent cerebral ischemia [21]. This case illustrates the importance of early ultrasound imaging in suspected AKI. Renal ultrasound traditionally performed to exclude obstructive causes can provide crucial information in discerning parenchymal causes of AKI, as illustrated in this case. Cbl C disease needs to be included in any workup of TMA regardless of the age at presentation. Early treatment of this condition can be effective, but long-term neurological and retinal sequelae may persist.

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