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BRIEF REPORT

Neurological involvement in a child with atypical hemolytic uremic syndrome

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Abstract We report the case of a 4-year-old boy, diagnosed with atypical hemolytic uremic syndrome (HUS) due to a hybrid factor H. He progressed to end-stage renal failure despite plasmatherapy and underwent bilateral nephrectomy because of uncontrolled hypertension. Three days after, he had partial complex seizures with normal blood pressure, normal blood count and normal magnetic resonance imaging (MRI), which recurred 1 month later. Eight months later, he had a third episode of seizures, with hemoglobin of 10 g/dl without schizocytes, low haptoglobin of 0.18 g/l, and moderate thrombocytopenia (platelets 98 × 10^9/l). He remained hypertensive and deeply confused for 2 days. The third MRI showed bilateral symmetrical hyperintensities of the cerebral pedunculas, caudate nuclei, putamens, thalami, hippocampi, and insulae suggesting thrombotic microangiopathy secondary to a relapse of HUS rather than reversible posterior leukoencephalopathy syndrome (RPLS), usually occipital and asymmetrical. Plasmatherapy led to a complete neurological recovery within 2 days although hypertension had remained uncontrolled. The fourth MRI 10 weeks after, on maintenance plasmatherapy, was normal and clinical examination remained normal, except for high blood pressure. In conclusion, brain MRI allows differentiating thrombotic microangiopathy lesions from RPLS in atypical HUS, which is crucial since lesions may be reversible with plasmatherapy.

Keywords Atypical hemolytic uremic syndrome · Cerebral thrombotic microangiopathy · Reversible posterior leukoencephalopathy syndrome · Magnetic resonance imaging

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Introduction

Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. In children, atypical HUS is often secondary to genetic abnormalities of the complement alternative pathway proteins. Among extra-renal complications, central nervous system manifestations are observed in 20% to 50% of cases and are responsible for increased morbidity and mortality [1].

Case report

We report the case of a previously healthy 4-year-old boy, first admitted because of a 3-week history of asthenia and

vomiting, without diarrhea. On admission, he was anuric, his blood pressure was 120/88 mmHg, and physical examination was remarkable only for peripheral and palpebral edema. The first laboratory tests revealed: hemolytic anemia (hemoglobin 5.1 g/dl with schizocytes, haptoglobin 0.06 g/l), thrombocytopenia (platelets 108 × 10^9/l), renal insufficiency (plasma creatinine 594 μmol/l, urea 42.6 mmol/l), and nephrotic syndrome (plasma albumin 23.5 g/l, proteinuria 23.4 g/l). Stool culture, polymerase chain reaction (PCR) of Shiga-toxin (Stx) in stools and detection of serum antibodies against lipopolysaccharides (LPS) were negative. CH50, C3, C4, complement factor H (CFH) antigen, factor I antigen, CD46 expression, and von Willebrandt factor (vWF) protease activity were normal. Genetic analysis of complement protein genes was negative at that time but a *CFH* hybrid gene was subsequently identified.

He was started on peritoneal dialysis and plasmatherapy. After three plasma infusions and seven plasma exchange sessions, urine output gradually increased and plasma creatinine progressively decreased to 117 μmol/l. He remained severely hypertensive. Two weeks later, a first relapse was treated with seven plasma exchanges, which improved hematological parameters, but renal function worsened. Hematological remission persisted, but despite plasma exchanges twice a week for 4 months followed by plasma infusions twice a week for 2 months, he progressed to end-stage renal failure. Eight months after the onset, he was started on chronic hemodialysis. One month later, he underwent bilateral nephrectomy because of uncontrolled hypertension despite five anti-hypertensive drugs. Three days after nephrectomy, he presented partial complex epileptic seizures of unclear etiology, without hemolysis or thrombopenia. The blood pressure, controlled by antihypertensive treatment of IV nicardipine followed by oral labetalol and nifedipine, was at that time stable and normal. Brain magnetic resonance imaging (MRI) 3 days after seizures was normal. The electroencephalogram (EEG) showed a posterior basic rhythm disrupted by many slow and monomorphic theta and delta waves.

One month later, he had a recurrence of generalized seizures without hemolysis (hemoglobin 9.4 g/dl without schizocytes, platelet 220 × 10^9/l) or severe hypertension. The second brain MRI, 6 days after admission, was normal. EEG was similar to the previous one, with posterior abnormalities that could be consistent with reversible posterior leukoencephalopathy syndrome (RPLS). He received antiepileptic medication (Levetiracetam).

Eight months later, he had a third episode of seizures, with decreased hemoglobin level (10 g/dl) without schizocytes, low but detectable haptoglobin of 0.18 g/l, and moderate thrombocytopenia (platelets 98 × 10^9/l). High blood pressure persisted, despite bilateral nephrectomy, hemodialysis, and antihypertensive treatment. He presented neurological symptoms for 2 days, including deep confusion and violent agitation. The clinical and biological symptoms were more suggestive of hypertensive encephalopathy than a HUS relapse, and a third MRI was performed 2 days after the seizures (Fig. 1). On FLAIR and T2 sequences, this brain MRI showed bilateral symmetrical hyperintensities on the cerebral pedunculas, caudate nuclei, putamens, thalami, hippocampi, and insulae. Diffusion-weighted imaging sequence and ADC mapping displayed no abnormality. These findings were suggestive of thrombotic microangiopathy, probably due to a relapse of HUS, rather than RPLS-related abnormalities.

He was immediately treated with daily plasma exchanges (PE) that led to a complete neurological recovery within 2 days although hypertension had remained uncontrolled. He received daily PE for 1 week, progressively tapered to twice a week. After a total of 10 sessions within 4 weeks, plasma exchanges were replaced by weekly plasma infusions during hemodialysis sessions. The fourth brain MRI after 10 weeks of weekly plasma infusion was normal and clinical examination remained normal, except for high blood pressure.

Discussion

Central nervous system involvement (irritability, drowsiness, convulsions, cortical blindness, hemiparesia or coma) is the most frequent extrarenal complication in HUS, and MRI findings are diverse. Two situations may be radiologically delineated: RPLS-related lesions and microangiopathic lesions. The clinical symptoms in both situations are similar.

Brain MRI RPLS-related lesions are associated with a posterior white matter hyperintensity and sometimes posterior cortex hyperintensity [2], probably secondary to high blood pressure during the acute phase of HUS. White-matter hyperintensity is predominant in parieto-occipital regions.

Another type of brain MRI lesions is also described during the acute phase of HUS, with bilateral and symmetrical thalami, brainstem, and deep white matter involvement [3, 4], but with diffusion weighted imaging [5]. Bilateral basal ganglia involvement is characterized by hypersignal on T2-weighted and hypo-signal on T1-weighted images, sometimes extending to the surrounding white matter [6–16]. Thalami and brainstem involvement have also been described [13, 14]. Although these lesions appear to be fairly characteristic of HUS, the pathogenic mechanism remains incompletely understood [13].

In our patient presenting with atypical HUS, the MRI features were not consistent with the diagnosis of posterior

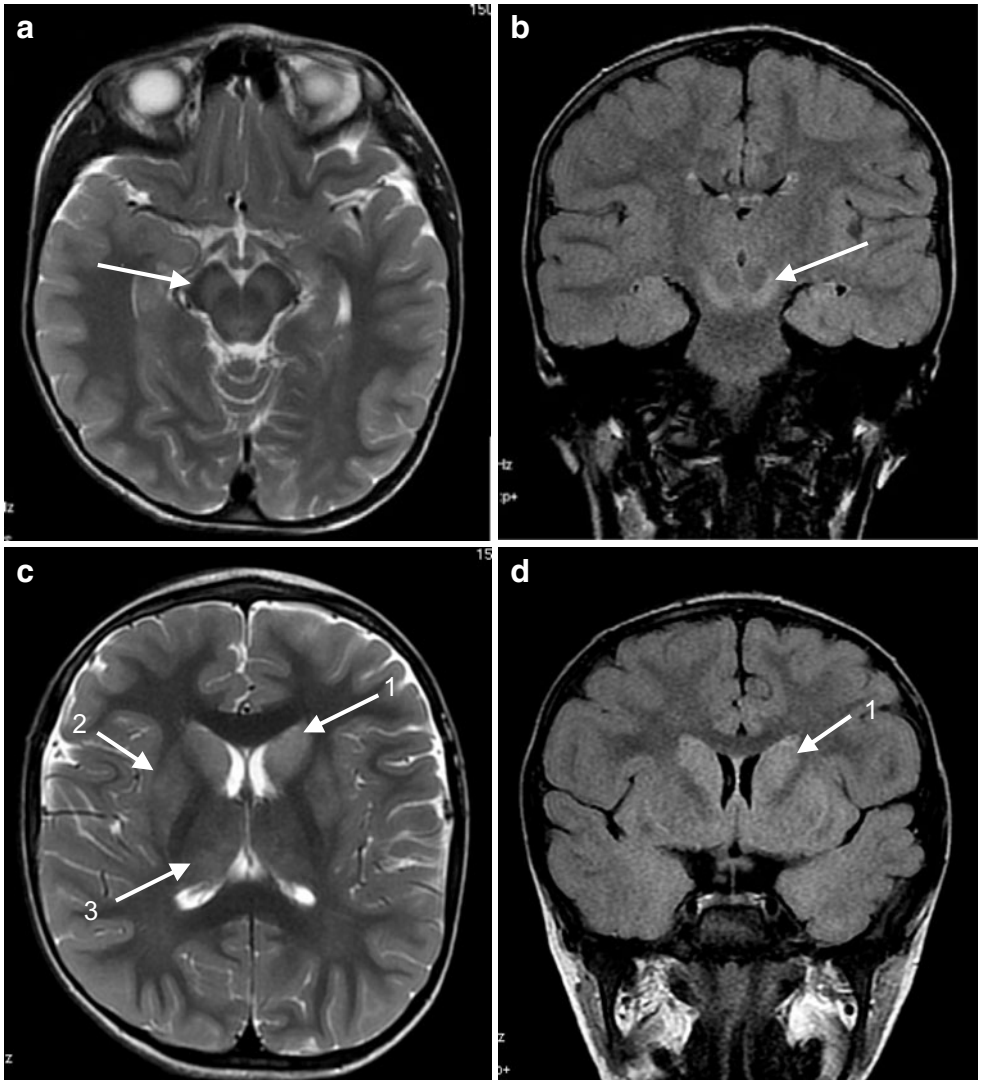

Fig. 1 Brain MRI 2 days after the third seizures episode. **a–c** Axial T2-weighted sequences, **b–d** coronal FLAIR sequences, **a**, **b** bilateral cerebral peduncula hypersignal (arrows), **c, d** bilateral hypersignal of caudate nuclei (1), putamens (2) and thalami (3)

reversible encephalopathy syndrome, although clinical and biological data were suggestive of hypertensive complications. The MRI lesions were similar to those observed in typical HUS, suggesting a HUS relapse because the patient displayed the characteristic bilateral and symmetrical basal ganglia involvement described in the literature, with brainstem and thalami lesions also reported in a few publications. The similarity of radiological lesions between typical and atypical HUS favors a common pathogenesis, i.e. cerebral thrombotic microangiopathy. In typical HUS (post-diarrhea HUS), it has been suggested that vascular endothelial injury caused by Stx plays a crucial role in the development of neurological involvement [17, 18]. Since the MRIs following the first and the second seizures were normal, we cannot exclude other etiologies for the two first episodes, such as drug side effects (anesthetics, antibiotics) or a hypertensive peak. However, drug doses were adapted to renal function, blood pressure was normal at the time of the seizures, and it seems very unlikely that the three similar neurological events were secondary to three independent causes. We may hypothesize a delay between clinical signs and radiological images or a lack of MRI sensitivity. Thus, the normality of the fourth MRI does not rule out the persistence of brain TMA lesions, but the disappearance of the MRI hyperintensities observed after the third burst of seizures is reassuring.

We report the first case of atypical HUS with cerebral MRI images suggestive of TMA. In our patient, the genetic analyses found a hybrid *CFH/CFHL1* gene. Similar to *CFH* point mutations, this hybrid gene is a susceptibility factor for atypical HUS [19]. Venables et al. [19] described a pedigree of eight individuals from four generations of atypical HUS segregating with this hybrid *CFH/CFHL1* gene. Two displayed neurological symptoms: grand mal convulsion in a 19-year-old woman who died 8 weeks after presentation and a short history of headaches and lethargy in a 28-year-old man. However, no imaging details are provided. The prevalence of neurological involvement in

this family with a hybrid *CFH* is not higher than that of other *CFH* mutation-related HUS, suggesting that the neurological involvement is secondary to the thrombotic microangiopathy and not a consequence of the genetic defect. A larger number of patients with a hybrid *CFH/CFHL1* gene is needed to confirm this hypothesis. Brain MRI findings were very useful to guide diagnosis and therapeutic strategy in our patient, as it led to the diagnosis of an HUS relapse rather than hypertensive encephalopathy. This was confirmed by the successful intensive plasmatherapy with complete clinical and radiological remission, although blood pressure had remained uncontrolled.

In conclusion, brain MRI allows the differentiation of thrombotic microangiopathy lesions from a hypertensive complication such as RPLS in patients with atypical HUS and neurological manifestations. Therapeutic implications are important, since treatment would consist of blood pressure control in one case and intensive plasmatherapy in the other case. An accurate diagnosis of neurological involvement is particularly important as lesions may be reversible after appropriate treatment.

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