Non-atheromatous arterial stenoses in atypical haemolytic uraemic syndrome associated with complement dysregulation

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Abstract

Background. A child, who presented atypical haemolytic uraemic syndrome (aHUS) at the age of 1 month, developed cerebral ischaemic events at the age of 10 years. Results. Stenoses of both carotid arteries, left subclavian and vertebral arteries, several intracranial, right humeral, several coronary, and all pulmonary arteries were demonstrated. At the age of 13 years, left subclavian and right cervical carotid arteries were occluded. Right carotid recanalization induced intracranial dissection and death. The child had a Lys350Asp factor B mutation. Conclusion. Arterial steno-occlusive lesions appear as potential complications of dysregulated complement activation in aHUS. Endovascular treatment should be considered cautiously in this setting.

Keywords: angioplasty; arterial stenosis; atypical haemolytic uraemic syndrome; complement factor B; complement factor H

Background

Approximately 60% of atypical haemolytic uraemic syndromes (aHUS) are related to complement dysregulation, secondary to mutations in the genes encoding factor H (CFH), membrane co-factor protein, factor I (CFI), factor B (CFB), C3 or thrombomodulin, or to anti-factor H antibodies [1–5]. The underlying lesion is a thrombotic microangiopathy (TMA) which predominantly affects the renal microvasculature.

We report one child with aHUS and a CFB mutation, who developed stenoses of cerebral and extra-cerebral arteries. Cerebral artery stenoses have also been reported in a child with aHUS and a CFH mutation [6]. These observations suggest that inappropriate complement activation can induce arterial steno-occlusive lesions.

Case report

This girl, the second of three children from healthy unrelated parents, had aHUS at the age of 1 month and began haemodialysis at the age of 4 months. Bilateral nephrectomy was performed at the age of 1 year because of hypertension, persistent haemolysis and thrombocytopaenia. Plasma C3 and CFB levels were low [C3 170–230 mg/L (normal 660–1250 mg/L); CFB 55–80 mg/L (normal 90–320 mg/L)], and C4 levels were normal. A de novo heterozygous gain of function CFB mutation (Lys350Asp) was demonstrated [7]. The child received a cadaveric kidney at the age of 19 months. HUS recurred 15 days after transplantation, unresponsive to plasma exchanges, but improved by intravenous immunoglobulin. She returned to dialysis at the age of 6 years, and nephrectomy of the graft was performed. At the age of 10 years, she started having episodes of hemiparesis affecting on both sides of the body and loss of consciousness lasting minutes. These episodes occurred spontaneously and when blood pressure decreased to <90/50 mmHg during haemodialysis. Vascular imaging showed bilateral stenoses of intracranial carotid and middle cerebral arteries, left anterior and posterior cerebral arteries (Figure 1A), extracranial internal carotid arteries (ICA) (Figure 2A), and left subclavian and vertebral arteries (Figure 3A). Cerebral parenchyma was normal. Vascular imaging at the age of 12 demonstrated no changes. Perfusion magnetic resonance (MR) showed

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preserved cerebral circulation. Computed tomography angiography (CTA) of the thorax, cardiac catheterization and angiography demonstrated stenoses of all branches of pulmonary arteries (Figure 4A), distal pulmonary oligaemia (Figure 4B), moderate pulmonary arterial hypertension, and stenoses of distal anterior interventricular, right and marginal coronary arteries, right humeral artery, celiac trunk and splenic artery. At the age of 13 years, the child was of normal intelligence but suffered from visuo-spatial apraxia. CTA was chosen to document cerebral vascularization before listing the patient for kidney transplantation under eculizumab. MR angiography was not performed due to recent awareness of nephrogenic systemic fibrosis hazard from gadolinium [8]. All stenoses had worsened, and occlusions of the left subclavian and right cervical carotid arteries were demonstrated (Figures 1B, 2B and 3B). No calcifications were seen in arterial walls. Single-photon emission computed tomography showed right hemispheric cerebral hypoperfusion. Recanalization of the occluded right ICA was considered as the less risky endovascular therapy to restore cerebral blood flow. This endovascular procedure allowed right cervical ICA recanalization. The attempt to perform carotid siphon angioplasty was complicated by dissection leading to
massive hemispheric infarction and brain oedema resistant to craniotomy. The patient died 4 days later.

**Discussion**

HUS and the underlying TMA are diseases of microvascularization. The endothelial injury is secondary to the effects of Shiga toxin in Shiga toxin-producing *Escherichia coli* (STEC)–HUS or complement mediated in aHUS [1–5]. We report one child with aHUS and genetic complement dysregulation, who developed large artery stenoses.

The patient presented with aHUS at the age of 1 month, started dialysis at the age of 4 months and had a functioning kidney transplant from the age of 19 months to 6 years despite HUS recurrence. She presented transient ischaemic attacks since the age of 10, related to intra- and extracranial artery stenoses. Stenoses of several large thoracic and abdominal aorta branches, and pulmonary and coronary arteries were detected.

We could demonstrate that the Lys350Asp gain of function *CFB* mutation of our patient (Patient 3 in [7]) induces a hyperactive C3 convertase, with C3b deposition on quiescent and adherent glomerular cells and human umbilical vein endothelial cells, together with enhanced formation of sC5b-9 complexes and deposition of C3 fragments at endothelial cell surfaces [7]. This demonstrated that the hyperfunctional C3 convertase in patients with *CFB* gain of function mutations is capable of inducing endothelial damage. It is likely that these cells then exhibit a pro-

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Fig. 3. Imaging of left subclavian and proximal left vertebral arteries. (A) Digital angiography at the age of 10 demonstrated stenoses of the left subclavian and the left vertebral arteries. (B) CT angiography, 3 years later: thin-slab coronal MIP showed a short occluded segment of the left subclavian artery (large arrowhead) and distal subclavian artery stenoses (small arrowheads). Worsening of left vertebral artery stenosis at the ostium was also depicted.

Fig. 4. Pulmonary vessel imaging. (A) Pulmonary angiography at the age of 12 demonstrates stenoses of all branches of pulmonary arteries (here, left pulmonary arteries). (B) Computed tomography angiography of the thorax at the age of 12: MIP axial view with parenchymal windowing demonstrates rarefaction of distal pulmonary vascularization.
thrombotic, pro-inflammatory phenotype. Interestingly, stenosis of proximal cerebral arteries has also been reported in a 15-year-old girl with aHUS (Figure 5) [6] and a Ser1191Leu CFH mutation [9], shown to disrupt the CFH self-surface recognition process which underlies complement regulation locally [10]. Although local complement dysregulation most probably contributed to the pathogenesis of arterial stenoses in the two patients, it is difficult to know whether the stenotic process evolved independently of manifestations of HUS or progressed concomitantly with flares of the disease, including post-transplant recurrence. Complement dysregulation might also participate in accelerated atherosclerosis. Complement activation occurs both in human and experimental atherosclerosis, and the deposition of C5b-9 correlates with the disease state [11–14]. In mouse models, deficiency of complement regulators CD59 [15,16] or decay-accelerating factor [17] accelerates atherosclerotic lesions, while anti-C5 antibody attenuates them [15]. Arterial stenoses could also be a non-specific consequence of vascular injury during episodes of HUS, whatever the cause of HUS. However, only one child has been reported with stenosis of the right middle cerebral and both carotid arteries associated with moyamoya disease, 3 months after STEC–HUS [18].

Stenoses of large arteries have never been reported as a complication of renal replacement therapy (RRT) in children [19–22]. However, children with renal failure have risk factors for atherosclerosis, and cardiovascular disease accounts for most deaths in young adults with childhood-onset chronic renal failure [19,21,22]. Noteworthy, risk factors for atherosclerosis (blood pressure, calcium, phosphorus, parathormone, haemoglobin, homocysteine levels, albuminaemia and lipid profile) were maintained within the recommended range [19,21–23] during the whole course of RRT in our patient. Echocardiography did not show left ventricular hypertrophy or dysfunction as observed in systemic atherosclerosis in patients on RRT. Additionally, arterial abnormalities included no calcifications. Therefore, it seems very unlikely that the arterial stenoses were of atheromatous origin as a complication of RRT. Moreover, the unusual and very severe complication of angioplasty suggests a particular arterial fragility. We hypothesize that a local complement attack, rather than atherosclerosis, could be the main factor of large artery endothelial damage. Regrettfully, no arterial wall pathological specimen was available in our patient.

Our report suggests that aHUS with complement dysregulation, a disease of microvascularization, may also involve large arteries. Imaging of large vessels, especially supra-aortic vessels, should be considered. Nonetheless, endovascular treatment should be cautiously discussed. Inhibition of the complement system by anti-C5 antibody is under investigation in aHUS [24–28]. Our report emphasizes the logic of this approach.

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Conflict of interest statement. None declared.

References

Home dialysis in nonrenal solid organ transplant recipients

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Abstract

Background. Chronic kidney disease (CKD) is a common complication of solid organ transplantation with a substantial risk of progression to end-stage renal disease (ESRD). The impact of dialysis modality on morbidity and mortality is unknown in these patients. The aim of the present analysis was to describe our experience with home dialysis [peritoneal dialysis (PD) and home haemodialysis (HHD)] to assess the feasibility of this modality in patients who developed ESRD after nonrenal solid organ transplant (NRSOT).

Methods. A retrospective observational cohort study with consecutive patients initiated on home dialysis after NRSOT from 2000 to 2009 was conducted. We collected data on patient demographics, laboratory parameters and blood pressure as well as clinical adverse events using our electronic clinical database.

Results. Between 2000 and 2009, 25 patients [median age, 56 years; interquartile range (IQR), 43–65 years] initiated home dialysis. Ten patients started HHD and 15 patients initiated PD. The types of NRSOT were liver (n=11), heart (n=8), lung (n=5) and heart–lung (n=1). The median vintage of NRSOT at the time of dialysis initiation was 8.7 years (IQR, 6.3–11.4 years). The median home dialysis follow-up was 24 months (IQR, 15–53 months). The median values of blood pressure, phosphate, calcium, parathyroid hormone and haemoglobin were within the K/DOQI targets. The hospitalization and infection rates were 1 episode every 22 and 29 patient-months, respectively. Three patients switched to in-centre conventional HD during follow-up and eight patients died.

Conclusions. Home dialysis (PD and HHD) is a feasible and sustainable modality for patients with ESRD after