

Moyamoya Vasculopathy in a Child after Hemolytic Uremic Syndrome: A Possible Etiopathogenesis

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Key words

- hypertension
- renal failure
- seizures
- moyamoya disease

Abstract



Moyamoya disease is a cerebral vasculopathy of unknown etiology frequently seen in the Asian population. We report a case of moyamoya vasculopathy in an African-American child who had renal failure followed by cerebral ischemia. Our patient presented with hemolytic uremic syn-

drome (HUS) and renal failure, and later developed seizures. We believe that in this patient HUS led to the pathogenesis of moyamoya disease. We suggest that patients with HUS who develop any neurological symptoms should be investigated for moyamoya vasculopathy for early diagnosis and treatment.

Introduction



Moyamoya disease is a progressive occlusive vasculopathy of unknown etiology affecting the cerebral vessels – particularly the circle of Willis, and is more often seen in the Asian population. This steno-occlusive cerebrovascular involvement is usually bilateral with development of abnormal collateral vascular networks adjacent to the stenotic vessels. Moyamoya disease shows a bimodal distribution, with the first peak seen in children less than 10 years of age and a second smaller peak seen around the age of 40 years [9]. The cerebrovascular events in children are usually ischemic, while in adults they are predominantly hemorrhagic [3].

Various diseases like Grave's disease, hypomelanosis of Ito, Apert syndrome, Down syndrome, neurofibromatosis type I, Marfan syndrome, tuberous sclerosis, Turner syndrome, Behcet's disease, von Recklinghausen disease and Hirschsprung disease have been associated with moyamoya disease in the past, but no scientific basis of their co-existence has ever been proposed [7,9]. This has led to term the moyamoya syndrome for the above conditions with cerebro-ischemic vasculopathy [8]. Our effort to hypothesize the underlying etiology would make this pathology a phenomenon of angiographic moyamoya disease or moyamoya vasculopathy, hence the use of these terms in this case report. We describe a new association of moyamoya vas-

culopathy in a 6-year-old African-American female child who initially presented with hemolytic uremic syndrome (HUS) and propose a hypothesis for this pathogenesis.

Case Report



An African-American female presented at the age of 4 years with acute onset vomiting to the emergency department. She had no significant past medical history and was developmentally normal for her age. She was sent home with home rehydration instructions assuming acute viral gastritis. Three days later, she was brought back with bloody diarrhea, drowsiness and irritability and poor oral intake. In the ER her rectal temperature was 99.3 degree F (37.4 °C), heart rate 135/min and blood pressure was 142/95 mmHg. Initial laboratory investigations revealed total white blood cell count 8600/ μ L, hemoglobin 10.3 g/dL, platelet count 110 000/ μ L, sodium 134 mEq/L, potassium 5.1 mEq/L, calcium 9.4 mg/dL, bicarbonate 18 mEq/L, creatinine 3.7 mg/dL and urea 38 mg/dL. Blood smear showed some fragmented red blood cells. Urine analysis showed specific gravity 1.030, with mild proteinuria and hematuria. *E. coli* 0157:H7 was detected in the stool. D-dimer, C3 and CH50 were reported normal.

Three days after the admission, she developed hypertension and renal failure; peritoneal dialy-

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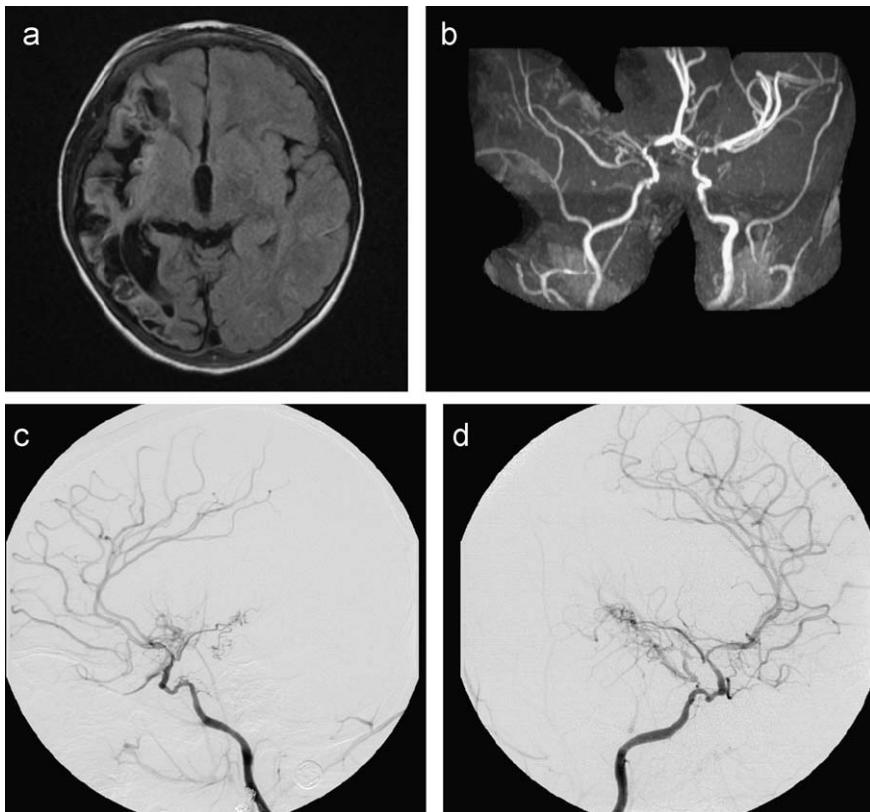


Fig. 1 **a** MRI of the brain: Axial T₂ FLAIR sequence showing right middle cerebral artery territory (MCA) infarction with areas of encephalomalacia, ventricular dilatation and gliosis. **b** MRA of the head showing occlusion of the distal internal carotid arteries bilaterally. **c, d** Digital subtraction angiogram (DSA) images: internal carotid artery injections showing occlusion of the distal internal carotid artery with multiple small collaterals at the base of brain characteristic of moyamoya disease.

sis was started. Three months after the HUS, she started having tonic movements of the left leg and left arm, transient loss of vision, and intermittent dysarthria. Her parents reported that she had a preference for using the right hand and kept the use of left hand to the minimum. Later, her focal seizures progressed to generalized seizures. On examination, her vitals were within normal limits for her age. The neurological exam correlated with the history and showed decreased visual acuity and left hemiparesis. EEG showed generalized sharp waves. CT scan of the head showed acute infarction in the right middle cerebral artery (MCA) territory, and MRI confirmed the same (● Fig. 1a). MRA showed a long segment of stenosis and irregularity involving the M1 segment of the right MCA, and "puff of smoke" appearance, characteristic of moyamoya disease (● Fig. 1b). The digital subtraction angiogram (DSA) demonstrated moderate irregularity with stenosis along bilateral intracranial internal carotid artery segments, worse on the right (● Fig. 1c, d). A renal angiogram was normal. Serum analysis of factor H, von Willebrand factor protease, homocystinemia, proteins C and S, and antithrombin III were all normal. Mutation analysis of factor V Leiden, factor II, and methyltetrahydrofolate reductase were also normal. In addition there was no significant family history of HUS, sickle cell disease, moyamoya disease or any other coagulation anomaly in the family. The patient underwent revascularization surgery and will have a renal transplant soon. Currently, she has mild weakness of the left side of her body and is on peritoneal dialysis.

Discussion

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We present a case of moyamoya vasculopathy in a child in whom we think that the *E. coli* O157: H7 D(+)HUS led to angiographic moyamoya in addition to the renal failure. Moyamoya disease

typically presents with recurrent transient ischemic attacks or a complete stroke. In addition, focal epileptic seizures, headache, and developmental delay are clinical hallmarks of moyamoya disease in children [4]. The early diagnosis is advantageous for planning surgery, treatment and favorable prognosis. Poor prognostic factors for pediatric moyamoya disease after operation are preoperative multiple cerebral infarctions, early onset at a young age, high blood pressure, perioperative complications such as ischemic events, high Suzuki stages on cerebral angiography, and the surgical procedure itself [11].

The etiology of moyamoya disease is unknown, but HLA-B51 and genetic associations do exist [1]. Our patient presented with HUS and later developed angiographic moyamoya, an association that has never been reported. We think that this is not by chance and propose an explanation for this concurrence. The *E. coli* O157:H7 toxin and Shiga toxin associated HUS have been shown to increase the secretion of transforming growth factor- β 1 (TGF- β 1) and basic fibroblast growth factor (bFGF) [10, 13]. TGF- β 1 is known to promote cell growth, proliferation and differentiation in addition to its role as chemoattractant for proinflammatory cells, while the bFGF is a major player in the angiogenesis and neovascularization. In addition, the HUS associated toxins cause endothelial damage leading to activation of coagulation cascade and hence thrombotic microangiopathy.

In patients with moyamoya disease, transforming growth factor- β 1 (TGF- β 1), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) are also elevated [5, 6, 16, 17]. These cytokines lead to low levels of inflammatory response and angiogenesis. These microangiopathic changes are then followed by macroangiopathic changes [2] that may lead to ischemic manifestations of moyamoya disease and encephalopathy. We hypothesize that this angiopathy-induced ischemia leads to development of neurological symptoms and produces

an angiogenic stimulus due to the release of cytokines, hence the "puff of smoke" appearance. This hypothesis can explain the development of moyamoya disease in this patient and can also account for the involvement of systemic vessels in moyamoya disease. The reason why moyamoya disease is sometimes localized versus widespread is not clear. We think that there may be a (genetic) variation in the expression of the cytokine receptors in various tissues leading to different responses to the same cytokine or the cytokine milieu may be different in each individual leading to a variable degree of stenosis and angiogenesis. In the past, Yamada et al., suggested the correlation between *P. acnes* and certain immunological phenomenon in moyamoya disease [15], and Tanigawara et al., have isolated the EBV DNA more frequently in moyamoya disease patients suggesting some possibility of a viral causative agent [12]. But to date no infectious agent has been strongly associated with moyamoya disease. So considering these studies it is not unreasonable to hypothesize the role of verotoxigenic *E. coli* or Shiga toxin in the pathogenesis of moyamoya disease.

Many cases of moyamoya disease patients have been reported that have undergone successful renal transplants. Most patients undergo the revascularization surgery, followed by renal transplant, as has been planned for our patient [14]. With early diagnosis of moyamoya disease it may be possible to anticipate renovascular hypertension and renal failure. We suggest that moyamoya disease should always be ruled out in HUS patients with unexplainable cerebrovascular accidents or neurological symptoms like seizures, so that an early intervention can effectively prevent ischemic events and thus improve the neurological deficit, cognitive developments and intelligence.

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