

Ischemic stroke in pediatric moyamoya disease associated with immune thrombocytopenia—a case report

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Received: 15 August 2014 / Accepted: 25 January 2015
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Abstract

Case report A 10-year-old boy developed refractory bleeding and was diagnosed with immune thrombocytopenia (ITP). He was treated with steroids and intravenous immunoglobulin (IVIG). Five months later, however, he developed right homonymous hemianopsia, sensory aphasia, agraphia, and agnosia. MR imaging demonstrated multiple cerebral infarction in the bilateral cerebral hemispheres, and MR angiography revealed severe stenosis of the bilateral internal carotid arteries. He was diagnosed with moyamoya disease and successfully underwent surgical revascularization on both sides under IVIG therapy. However, multiple cerebral infarcts developed in the bilateral cerebral hemispheres 10 days after the second surgical revascularization when platelet counts were within normal limits. Furthermore, chronic subdural hematoma gradually increased in size after each surgery, which required burr hole surgery to resolve increased intracranial pressure, when platelet counts decreased to less than $10 \times 10^9/L$.

Conclusion This is the first report presenting a case with moyamoya disease coincident with ITP. Critical managements would be essential to reduce perioperative complications, because ITP is known to provoke both hemorrhagic and ischemic events through multiple mechanisms.

Keywords Moyamoya disease · Immune thrombocytopenia · Chronic subdural hematoma · Cerebral infarction · Surgical revascularization

Introduction

Moyamoya disease is an uncommon cerebrovascular disease that is characterized by progressive occlusion of terminal portion of the internal carotid artery and its main branches within the circle of Willis. This occlusion results in the formation of a fine vascular network (moyamoya vessels) at the base of the brain [1, 2]. Clinical features of moyamoya disease substantially differ between children and adults. Most pediatric patients with moyamoya disease develop transient ischemic attack (TIA) or cerebral infarction, whereas about half of adult patients develop intracranial bleeding and half develop TIA or cerebral infarction [1, 2]. Nowadays, it is well known that surgical revascularization improve cerebral hemodynamics and prevent further ischemic and hemorrhagic stroke [3].

Immune thrombocytopenia (ITP) is a bleeding disorder characterized by autoantibody-mediated destruction of circulating platelets resulting in thrombocytopenia [4]. Pediatric ITP frequently develops after proceeding viral infections, vaccination, and *Helicobacter pylori* infection [5, 6]. Steroids and intravenous immunoglobulin (IVIG) are used as first-line therapy for ITP. When response to initial treatment was insufficient or risk of bleeding remains significant, splenectomy and rituximab (anti-CD20 antibody) are considered as second-line therapy [7].

In this report, the authors describe a quite rare pediatric case that developed ischemic stroke due to moyamoya disease in the persistent period of ITP. This case also repeated ischemic stroke and chronic subdural hematoma in perioperative periods after bypass surgery for moyamoya disease. The authors precisely discuss on the mechanisms of these episodes in moyamoya disease associated with ITP.

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Case report

A 10-year-old male was admitted to our affiliate hospital because of refractory epistaxis and subcutaneous bleeding. Initial laboratory investigation demonstrated low platelet count of $7 \times 10^9/L$ with elevated platelet-associated immunoglobulin (PA-IgG) of $312.8 \text{ ng}/10^7$ cells (normal $<46 \text{ ng}/10^7$ cells). Antinuclear antibody titre was $\leq 1:40$. Consequently, he was diagnosed as ITP and was treated with methylprednisolone (mPSL) of $1.67 \text{ mg}/\text{kg}/\text{day}$ and intravenous immunoglobulin (IVIG) of $1.0 \text{ g}/\text{kg}/\text{day}$. Platelet counts increased immediately after IVIG but decreased to less than $10 \times 10^9/L$ within several weeks once again, so he was repeatedly treated with mPSL ($1.67 \text{ mg}/\text{kg}$ every other day) and IVIG ($1.0 \text{ g}/\text{kg}/\text{day}/\text{once}$ a month). Five months after the onset of ITP, however, he suddenly developed right homonymous hemianopsia, sensory aphasia, agraphia, and agnosia and was admitted to our hospital. On admission, platelet count was within normal limit ($411 \times 10^9/L$), but magnetic resonance (MR) imaging demonstrated fresh, multiple cerebral infarcts in the bilateral frontal, the left occipital, and right temporo-parietal lobes. The dilated perforating arteries could be observed in the bilateral basal ganglia (Fig. 1a). MR angiography showed severe stenosis of the terminal portion of bilateral internal carotid arteries and the bilateral posterior cerebral arteries (Fig. 1). These findings met the criteria of guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis) set by the Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis [8]. Therefore, he was diagnosed with moyamoya disease. Single-photon emission computed tomography (SPECT) revealed a decreased cerebral blood flow (CBF) in the bilateral occipital lobes and the reduction of cerebrovascular reactivity (CVR) to acetazolamide in the bilateral frontal

lobes and right temporo-parietal lobes (Fig. 2). Prior to surgical revascularization, he was treated with IVIG ($1.0 \text{ g}/\text{kg}$) and his platelets increased from $73 \times 10^9/L$ to $200 \times 10^9/L$. Four days later, he successfully underwent superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis with indirect bypass, encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) on the left side [9]. Postoperative course was uneventful, and his neurological symptoms did not deteriorate. However, follow-up radiological examinations demonstrated subdural hematoma in the left parieto-occipital region, which gradually increased in size (Fig. 3). He complained of headache and nausea, and his platelets decrease up to $90 \times 10^9/L$ at 23 days after surgery. So, subdural hematoma was irrigated through a burr hole. Subsequently, he was treated with platelet transfusion (10 units) and IVIG ($1.0 \text{ g}/\text{kg}$). Four days later, he underwent STA-MCA anastomosis and EDMAPS on the right side. Postoperative course was uneventful, but he developed the weakness of the left arm 10 days after surgery. Platelet count was $304 \times 10^9/L$. MR imaging revealed fresh cerebral infarcts in the right frontal, temporal, insular, and the left parietal cortex (Fig. 4). Subsequently, platelet count rapidly decreased to $90 \times 10^9/L$ and plain CT scan at 18 days after the second bypass surgery identified subdural hematoma. Although he showed no sign of elevated intracranial pressure, he was treated with $1.0 \text{ g}/\text{kg}$ of IVIG, and subdural hematoma was completely irrigated through a burr hole. His neurological symptoms gradually improved, and he was discharged 40 days after the second bypass surgery. Figure 5 summarizes platelet counts during admission. He has experienced no further episode of ischemic and hemorrhagic stroke for these 18 months after surgery. Platelet counts have been kept more than $100 \times 10^9/L$ during follow-up period. However, he needs to go to the support class because of cognitive impairment.

Fig. 1 Radiological findings on admission. **a** FLAIR imaging shows multiple cerebral infarction in the bilateral frontal, left occipital, and right temporo-parietal lobes. Note that the dilated moyamoya vessels in the bilateral basal ganglia (*arrowheads*). **b** MR angiography demonstrates the severe stenosis of the terminal portion of the bilateral internal carotid arteries. Note almost no flow signal in the bilateral middle and anterior cerebral arteries. The bilateral posterior cerebral arteries are also involved and severely stenotic (*arrowheads*)

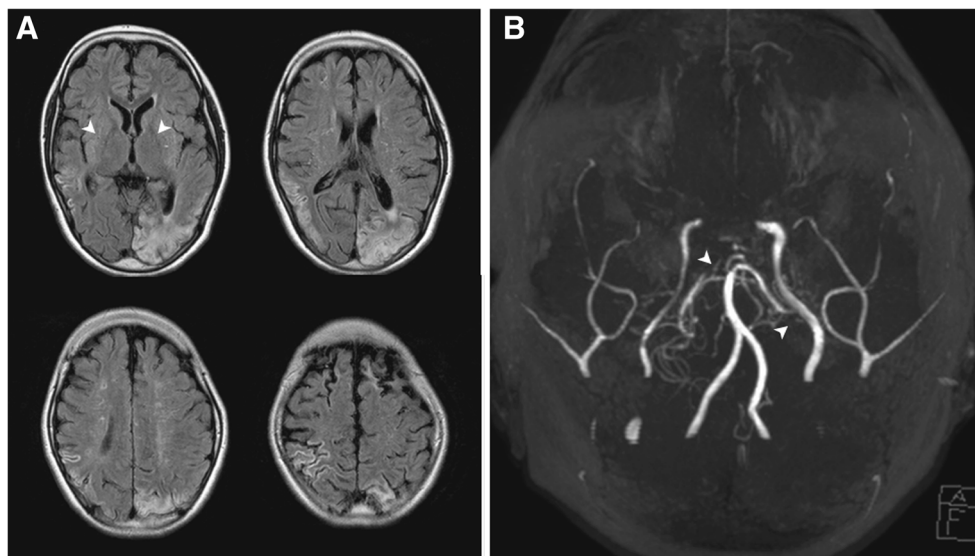
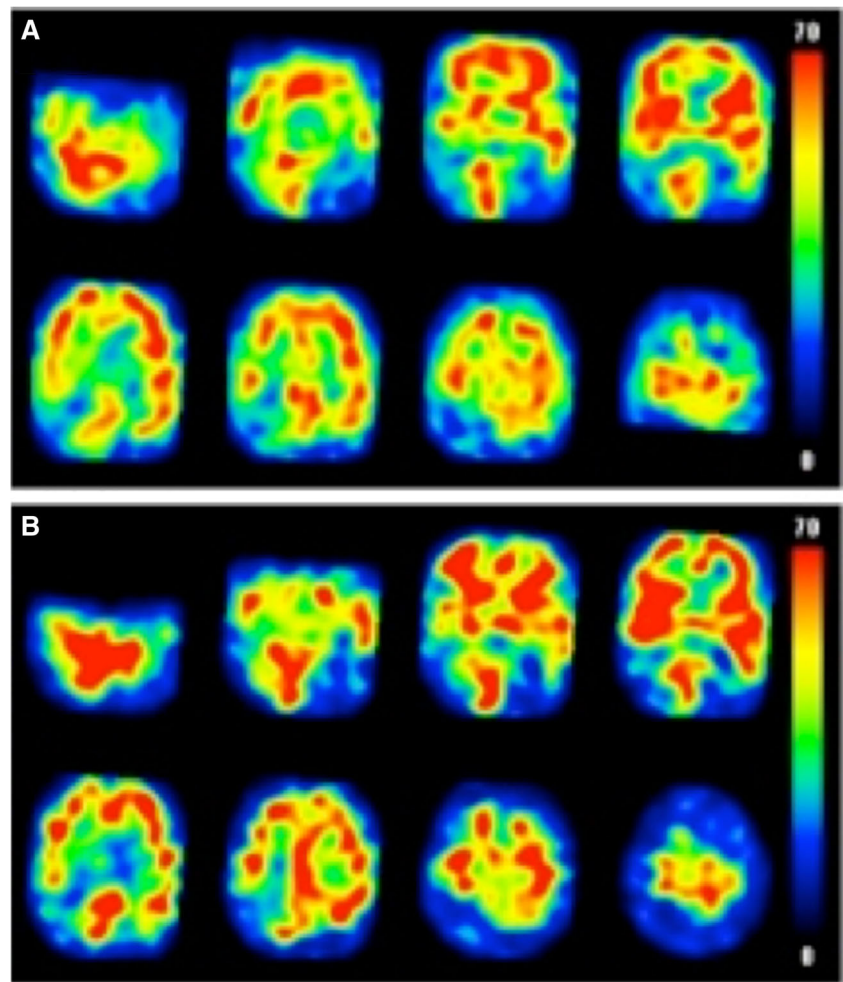


Fig. 2 Single-photon emission tomography before (a) and after intravenous injection of acetazolamide (b). Note a decreased cerebral blood flow in cerebral infarct and reduced reactivity to acetazolamide in the bilateral frontal lobes and right temporo-parietal lobes

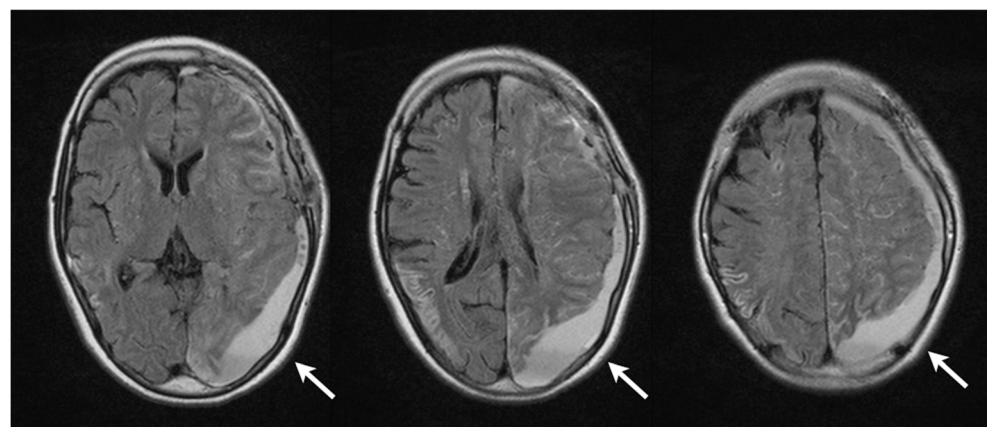


Discussion

To date, this is the first report presenting a case with moyamoya disease associated with ITP. As aforementioned, ITP is an autoimmune bleeding disorder in which antiplatelet autoantibodies bind to antigens on the surface of platelets and

accelerate their destruction. Impaired platelet production may also contribute to the lowering of platelet counts [6, 10]. There are no articles that describe the association between ITP and moyamoya disease. However, ITP is one of the autoimmune diseases. Considering the fact that hyperthyroidism is widely known as one of the underlying disorders for moyamoya

Fig. 3 FLAIR imaging demonstrates chronic subdural hematoma over the left cerebral hemisphere 23 days after surgical revascularization on the left side



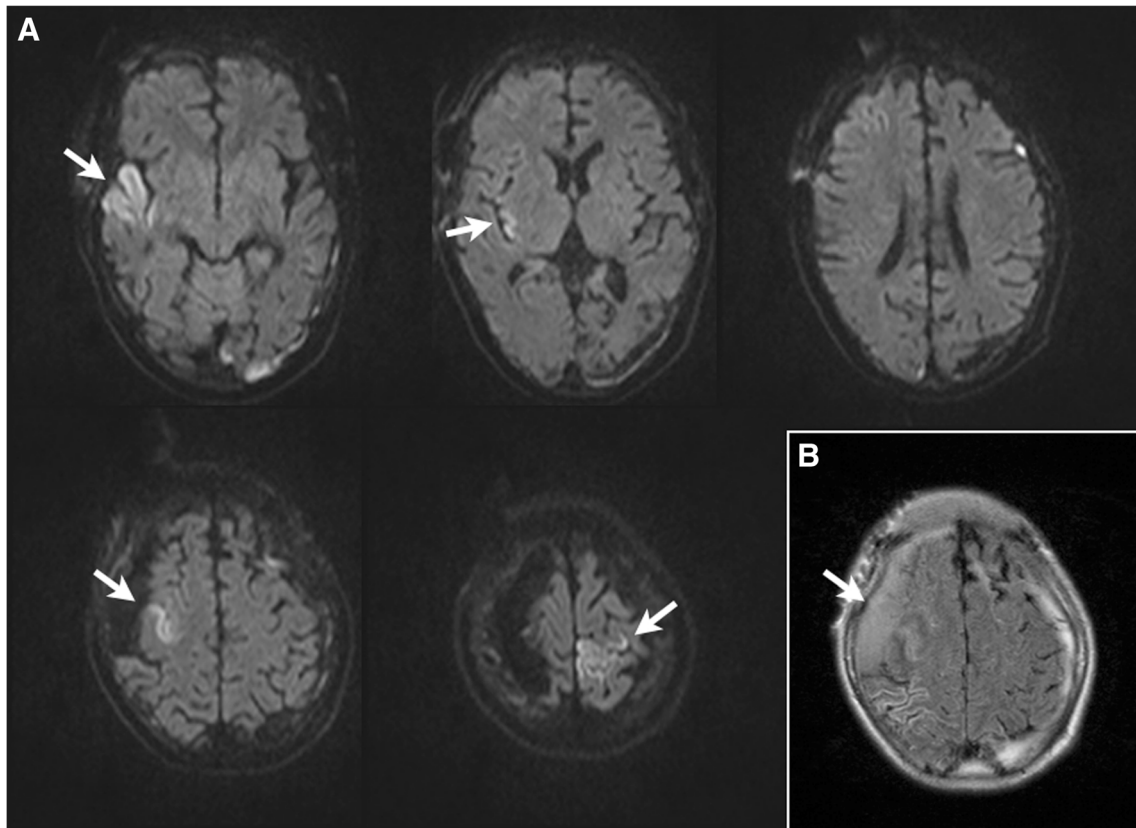


Fig. 4 Radiological findings at 10 days after the second surgical revascularization on the right side. (A) Diffusion-weighted imaging reveals multiple, fresh cerebral infarction in the right frontal and temporal

lobes, right insular cortex, and left parietal lobe (arrows). (B) Simultaneously, FLAIR imaging demonstrates chronic subdural hematoma over the right frontal convexity (arrow)

syndrome, ITP may also provoke moyamoya phenomenon in this case. According to disease duration, ITP is usually

classified into three types: newly diagnosed (within 3 months), persistent (between 3 and 12 months), and chronic (longer

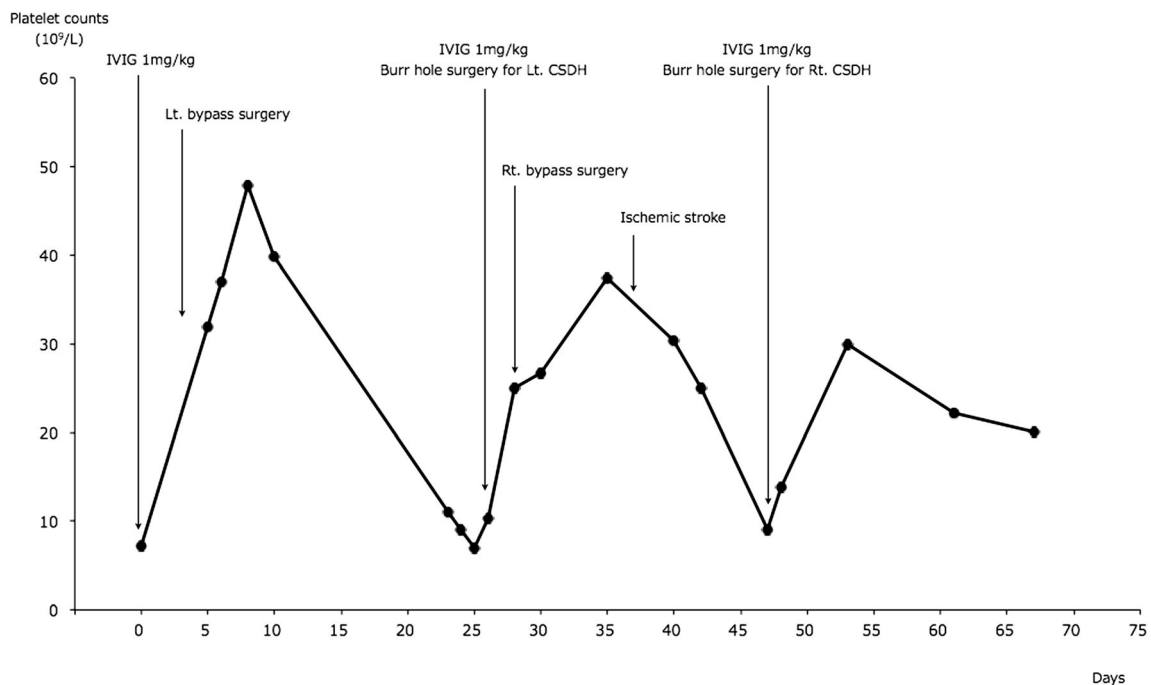


Fig. 5 Line graph shows temporal profile of platelet counts during admission. *IVIG* intravenous immunoglobulin, *CSDH* chronic subdural hematoma

than 12 months) [4]. In a majority of pediatric patients, ITP occurs in acute fashion, lasting within 6 months and often resolve spontaneously or after short-term treatment with prednisolone. However, other reports have suggested that ITP frequently progresses and lasts for 6 months or longer in the teenagers, compared with infants [11]. Although its epidemiological features in Japan still remain unclear, very recent largest study has shown that the annual incidence is 2.16 per 100,000 populations in Japan. Female predominance is observed in patients over 4 years, while male predominance is observed in those below 4 years. Mean platelet count is $12.8 \times 10^9/L$ in patients younger than 15 years [12]. Therefore, ITP was very severe at the onset in the present case. Most children with ITP present purpura (92.6 %) and epistaxis (29.7 %), but intracranial bleeding is very rare. Most of them are treated with IVIG (66.0 %) and/or prednisolone (44.0 %) [12].

Clinical course in the present case is quite peculiar. That is, he developed multiple cerebral infarcts at the onset. He repeated multiple cerebral infarcts on both sides 10 days after the second bypass surgery on the right side, which is a very rare complication after surgery for moyamoya disease in usual situation [9, 13]. Platelet counts were within normal limits when he experienced both episodes of cerebral infarction. Furthermore, he developed chronic subdural hematoma that required burr surgery after each surgery. Platelet counts were quite low when chronic subdural hematoma maximally increased in size.

It is known that ITP also induces thrombotic complications, including acute myocardial infarction, cerebral infarction, and venous thrombosis in spite of thrombocytopenia. Thus, Theeler and Ney recently reported a 63-year-old male who developed ischemic stroke coincident with ITP [14]. Yagmur et al. also reported a 49-year-old female who experienced acute myocardial infarction associated with ITP [15]. Nørgaard reported that the patients with ITP have a more than twofold higher risk of venous thrombosis, compared with general populations [16]. In fact, Aledort et al. reviewed their 205 patients with ITP and found thrombotic events in 4–5 % of them [17]. However, it should be reminded that these thrombotic complications occurred in adult patients with ITP. Therefore, it is extremely rare for pediatric patients with ITP to repeat ischemic stroke.

There are several hypotheses about the mechanisms through which thrombotic events occur in patients with ITP. First, antigenic similarity between the platelets and endothelial cells induces endothelial damage through immune reactions by autoantibodies against the platelets, resulting in thrombotic events such as ischemic stroke [18] and acute myocardial infarction [19]. Second, platelet destruction releases humoral factors and platelet microparticles (PMPs). Circulating PMPs are known to activate thrombin and other coagulation factors and promote intravascular thrombosis [20]. Third, IVIG or steroid therapy itself may provoke the potential risk for

thrombosis [21]. IVIG is known to increase plasma viscosity for several days after general administration [22]. A rapid surge of platelet count after IVIG therapy may also increase plasma viscosity and cause vasospasm of cerebral vasculatures [23, 24]. In fact, the present case always developed ischemic stroke when platelet count improved after IVIG therapy (Fig. 5). Therefore, careful managements would be essential to prevent perioperative ischemic stroke when surgical revascularization is planned for patients with moyamoya disease coincident with ITP. For example, we should consider the dose of IVIG to avoid excessive increase in platelet count so that the incidence of ischemic complication would decrease, because IVIG treatment may improve ITP in a dose-dependent manner [25].

In conclusion, the authors reported a very rare pediatric case of moyamoya disease coincident with ITP. It should be reminded that ITP has the potential risk to provoke not only hemorrhagic but also ischemic stroke in moyamoya disease through multiple mechanisms.

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