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Case Report

Early manifestation of Moyamoya syndrome in a 2-year-old child with Down syndrome ☆,☆☆

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ABSTRACT

Moyamoya is a rare occlusive cerebrovascular disease characterized by progressive stenosis of the terminal portion of the internal carotid artery and the circle of Willis. Over time, collateral arteries are usually formed at the basal ganglia, the so-called Moyamoya vessels. The exact cause of Moyamoya disease is unknown, while Moyamoya syndrome refers to Moyamoya-like vasculopathy due to autoimmune diseases, neurofibromatosis type I, sickle cell disease, radiation, or rarely Down syndrome. Down syndrome is one of the most common genetic conditions, characterized by typical physical traits, associated with intellectual disability and a heterogeneous group of structural defects that may vulnerable the patient for the development of Moyamoya syndrome. The reported case is an unusual case of a 2-year-old boy with Down syndrome who presented to the hospital with seizures and right-side weakness. Brain MRI shows acute as well as old lacunar infarctions in both cerebral hemispheres. Catheter angiography of the patient demonstrates severe stenosis and occlusion of the large vessels of the circle of Willis, predominantly on the right side. The collateral vessels with the typical pattern of "puff of smoke" were also depicted in the right basal ganglia, which is a characteristic imaging finding for Moyamoya. The patient was managed conservatively and eventually discharged with a minimal improvement of the right-sided weakness. This case report is noteworthy because of the rarity of Moyamoya syndrome as a cause of a stroke as well as its possible association with Down syndrome.

Abbreviations: ACA, anterior cerebral artery; CT, computed tomography; CTA, computed tomography angiography; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; ECA, external carotid artery; FLAIR, fluid-attenuated inversion recovery; ICA, internal carotid artery; MCA, middle cerebral artery; MMD, Moyamoya disease; MMS, Moyamoya syndrome; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; SWI, susceptibility-weighted imaging; TIAs, transient ischemic attacks; 3D-TOF, 3D time-of-flight.

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Background

Moyamoya is a rare occlusive cerebrovascular disease characterized by progressive stenosis of the terminal intracranial portion of the internal carotid artery (ICA) and circle of Willis, resulting in cerebral ischemia and infarction. Collateral vessels as basal (parenchymal) collaterals from perforator arteries, leptomeningeal collaterals from the posterior cerebral arteries (PCAs), and transdural collaterals from the external carotid arteries (ECAs) are usually formed around the stenotic arteries to compensate for this blockage. These collateral vessels are too small, weak, and prone to bleeding and thrombosis. In general, stenosis and/or obstruction of the bilateral internal carotid arteries (ICAs) occurs in this disease, although in 18% of cases, unilateral involvement has been observed in angiographic studies [1,3]. Moyamoya is a Japanese term, which means something delicate like smoke or steam, so-called "puff of smoke." The name was chosen because of the tangled appearance of small vessels that form to compensate for clogged arteries. The disease was first described in Japan by Takeuchi and Shimizu in 1957 and then termed by Suzuki and Takaku in more detail in 1969 [3]. The Moyamoya disease (MMD) is more commonly seen in children, however, the symptomatic disease is seeming to have a bimodal distribution, the first peak is usually seen in the first decade (5-9 years) and the second peak in the fourth decade of life (45-49 years) [4]. The exact cause of MMD is unknown. Experts believe that a variety of factors, from genetic defects to head injuries and radiation, may trigger the process of narrowing of the intracranial carotid arteries and its branches. The incidence of the disease is slightly higher in girls than boys and is commonly seen in Asian children than children of other ethnicities. Moyamoya syndrome (MMS) is referring to the Moyamoya-like vasculopathy with associated risk factors, such as autoimmune diseases, neurofibromatosis type I, sickle cell disease, thyroid disease, head and/or neck irradiation, skull base tumor, fibromuscular dysplasia, or rarely Down syndrome [1,3,10,11].

Down syndrome is one of the most common genetic abnormalities, characterized by typical physical traits and clinical manifestations which is associated with intellectual disability and a heterogeneous group of structural defects that may make the patient vulnerable to develop vascular abnormalities including MMS [15,16].

Clinical manifestations of MMD/MMS vary depending on the patient's age. Adults with this condition usually present with signs and symptoms of stroke (hemorrhage or ischemic), or transient ischemic attack (TIA). During these events, blood flow and oxygen delivery to the brain is disrupted causing weakness or numbness of one arm/leg, paralysis of one side of the body, fainting, difficulty of speaking, blurred vision, headache (commonly seen in hemorrhagic stroke), and cognitive problems. If left untreated, the disease will progress and may lead to severe brain damage and death. Moyamoya usually causes a TIA or seizures in children. Other symptoms of Moyamoya in children include involuntary and uncontrollable movements, developmental disabilities, headaches, speech disorders, and cognitive decline. In Asian populations, ischemic stroke is commonly seen in children, whereas hemorrhagic stroke is common in the adult [12,14].

Case presentation

A 2-year-old boy with Down syndrome was presented to our hospital for the investigation of seizure and left side weakness, which had recently worsened. There was also a history of previous sudden falls. The patient has no fever or history of head injury. His clinical evaluation at the age of 17 months showed an irritable, retarded childhood with stigmata of Down syndrome and the patient's further examination confirmed the diagnosis of trisomy 21. On physical examination of the patient, a significant reduction in spontaneous movements of the left arm and left leg was observed and the muscle strength decreased significantly on this side as well. The grip on the left side was weaker and the deep tendon reflexes were exaggerated. Blood and CSF examination was normal and the electroencephalography showed poor background activity. To rule out any significant heart problems, cardiac counseling was requested by his physician, and the results of echocardiography and electrocardiography showed no significant abnormal findings.

Brain MRI was performed that shows 2 foci of acute lacunar infarction in the subcortical areas of the right parietal lobe (Fig. 1a-b). Multiple old lacunar infarctions were also depicted in both cerebral hemispheres in the watershed zones (Fig. 1c-e). Atrophy of the cerebral cortex and encephalomalacia and gliosis due to old ischemic insult was also observed in the right frontal lobe (Fig. 2a-c). Considering the patient's acute and chronic multiple lacunar infarctions and defining the possible causes of these recurrent ischemic events, the patient underwent cerebral angiography. Angiographic findings demonstrate occlusion of the right MCA and ACA in the proximal parts with a delayed filing of its distal portions via the choroidal and splenial collaterals known as Moyamoya vessels, which form the typical appearance of a "puff of smoke" in the right basal ganglia (Fig. 3a-b). The M1 segment of the left MCA, as well as the A1 segment of the left ACA, was also quite narrowed (Fig. 3c). Severe stenosis of the P1 segment of right PCA was also noted (Fig. 4a-b). These characteristic imaging findings were typical for the diagnosis of unilateral MMS causing acute and chronic lacunar infarctions. The patient was managed conservatively for his seizure and recent infarction and eventually discharged with a minimal improvement of the right-sided weakness. Some medications such as sodium valproate for seizure and aspirin as a blood thinner to reduce the risk of recurrent stroke were prescribed to him.

Discussion

Moyamoya is a rare occlusive cerebrovascular disease characterized by progressive stenosis of the terminal portion of the internal carotid arteries and the circle of Willis, resulting in impaired blood flow to the brain and ischemic events. Over time, collaterals known as Moyamoya vessels are usually

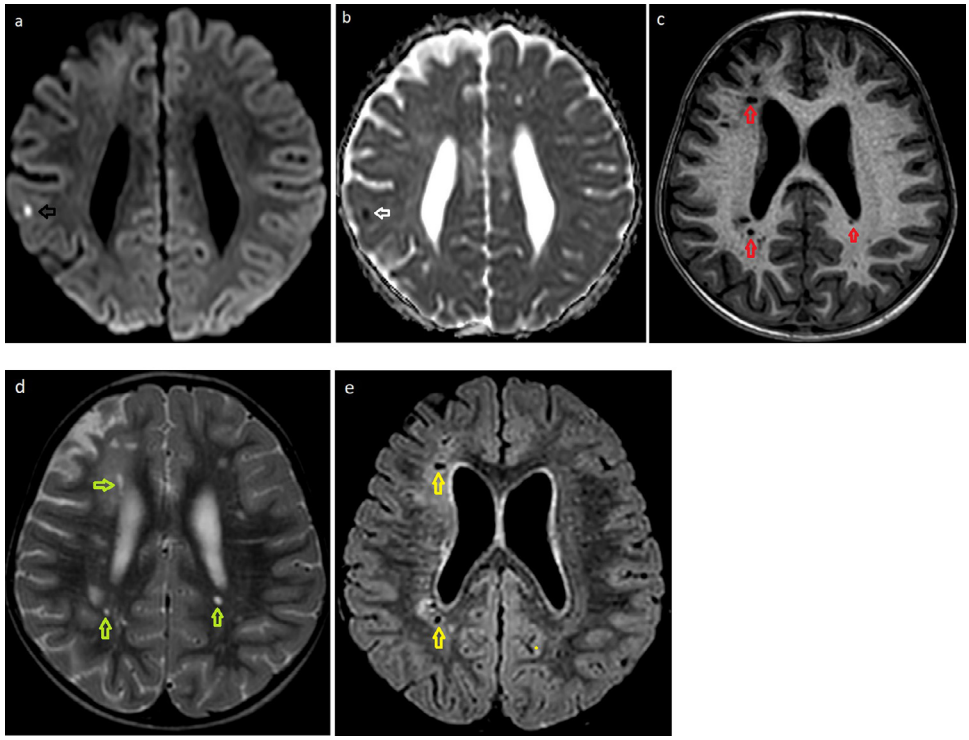

Fig. 1 – DWI (a) and ADC (b) images of the patient, showing a small acute lacunar infarction in the subcortical area of the right parietal lobe (arrows). Axial T1W (c), T2W (d), and FLAIR (e) images showing multiple old lacunar infarctions in the white matter of both cerebral hemispheres in the watershed zones (indicated with red, green, and yellow arrows, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

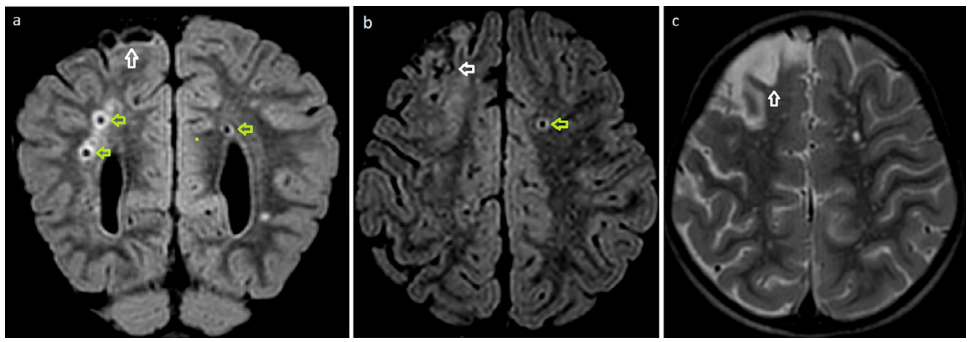

Fig. 2 – Coronal (a) and axial (b) FLAIR images as well as T2WI (c) of the patient demonstrating atrophic changes of the right frontal cerebral cortex with the area of encephalomalacia and gliosis (white arrows) due to old ischemic insult. Foci of old lacunar infarctions are also seen in axial and coronal images (green arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

formed at the basal ganglia. The exact cause of MMD is unknown, while MMS refers to Moyamoya-like vasculopathy due to autoimmune diseases, neurofibromatosis type I, sickle cell disease, radiation to the head/neck, or rarely Down syndrome [2,10,15]. The key imaging findings characteristic for the diagnosis of MMD is based upon angiographic abnormalities of cerebral vasculature such as stenosis of the distal ICAs and/or proximal circle of Willis's vessels, along with the presence of prominent basal or parenchymal collaterals (Moyamoya vessels) in conventional angiography, magnetic resonance angiography (MRA) or computed tomography angiography (CTA) [2,7-9].

Cerebral angiography is the standard method for the diagnosis of MMD/MMS [2,6]. Cerebral angiography is an invasive procedure providing direct information of the carotid and cerebral arteries including the degree of collateral circulation. Characteristic findings of cerebral angiography include occlusion or stenosis of the ICA (the supraclinoid segment) and extensive parenchymal, transdural, and leptomeningeal collateral vessels supplying the ischemic brain. On conventional

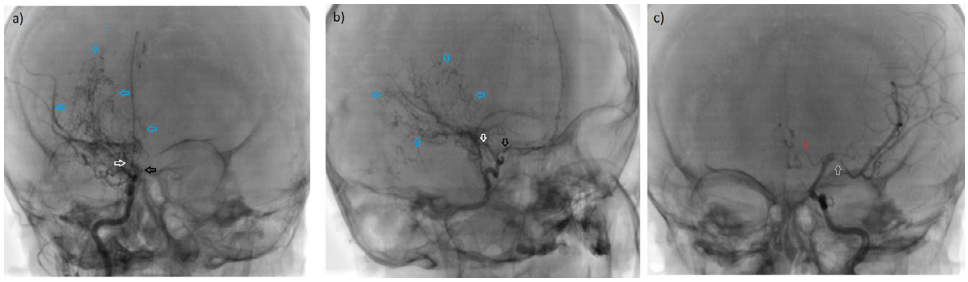

Fig. 3 – Coronal (a) and sagittal (b) catheter cerebral angiograms demonstrating occlusion of the right MCA (white arrows) and right ACA (black arrows) in the proximal portions with a delayed filing of its distal portions via the collateral vessels (Moyamoya vessels), forming the typical appearance of "puff of smoke" (blue arrows). Coronal (c) catheter angiograms demonstrating severe narrowing of the M1 segment of the left MCA (white arrow), as well as the A1 segment of the left ACA (red arrow) without any obvious collateral vessel formation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

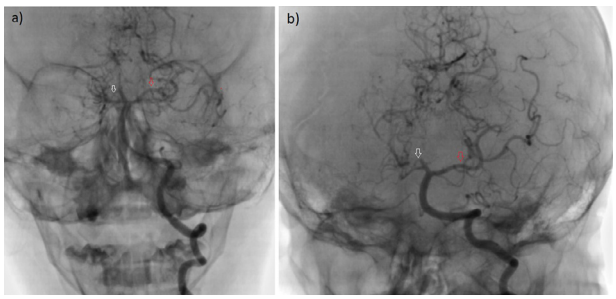

Fig. 4 – Coronal (a) and sagittal (b) catheter cerebral angiograms demonstrating severe stenosis of the P1 segment of the right PCA (white arrows) in comparison to the normal P1 segment of the left PCA (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

direct angiography, these thin abnormal vessels will look like "puff of smoke" [4,7]. The progression of MMD can be classified into the following stages based on angiographic findings: (i) Narrowing of the ICA fork (only terminal portion of ICA), (ii) Initiation of basal Moyamoya vessels (stenosis of all terminal branches of ICA), (iii) Further increases of basal Moyamoya vessels ("puff of smoke" appearance on angiography), (iv) Reduction of Moyamoya arteries and increases of collateral vessels, (v) Reduction of Moyamoya vessels, a significant narrowing of ICAs, and eventually destruction of Moyamoya vessels, (vi) Disappearance of Moyamoya and complete occlusion of ICAs with significant increases of collaterals arteries from ECA [4].

Recent advances in MRI, which improve tissue characterization, speed, and spatial resolution of images, are very useful in diagnosing various neurovascular pathologies, including MMD. MR imaging can reveal stenosis and/or occlusion of the ICA, Moyamoya vessels, brain ischemia and infarction, cerebral atrophy, and ventriculomegaly. Different MR sequences including FLAIR imaging, diffusion-weighted imaging (DWI), perfusion, and contrast-enhanced imaging are used for the diagnosis of Moyamoya [7,8]. T2W images seem to be better for direct visualization of the stenotic arteries, but FLAIR images are better for showing subtle parenchymal changes. FLAIR and postcontrast T1W images may demonstrate leptomeningeal involvement as a linear pattern of increased signal in the leptomeninges, perivascular spaces, and medullary veins that show "ivy sign", which is correlated with decreased cerebrovascular reserve. Vascular enhancement corresponding to collateral arteries as well as enhancing subacute infarcts can be better seen on contrast-enhanced T1WI [5,7,8]. DWI can depict diffusion restriction which is highly sensitive for small and acute infarctions. Gradient echo (T2*) MRI sequences and susceptibility-weighted imaging (SWI) are very sensitive methods for evaluating blood products including chronic microbleeds and prominent deep medullary veins within areas of impaired perfusion highlighting the "brush sign" [6-8]. The accuracy of MRA is reported to be comparable with that of conventional angiography in diagnosing MMD [9]. The 3-dimensional time-of-flight (3D-TOF) MRA technique can better map the lumen of the main ICA and ECA and their major branches without the need for a gadolinium-based intravenous contrast agent. Because MRA is a noninvasive imaging technique, it is valuable for assessing postoperative changes [7,8].

Computed tomography (CT) may reveal ischemic changes as low-attenuation parenchymal spots, ex-vacuo dilatation of ventricle (s) indicating volume loss, and hemorrhage which is nonspecific findings. CTA can also demonstrate abnormal vessels of MMD, including its collaterals. The characteristic appearance of "puff of smoke" is not always visible in the CTA and MRA due to the low flow and lower spatial resolution of these methods [7]. Perfusion imaging of the brain in MMD demonstrates impaired perfusion of the ischemic areas including those perfused by the collateral vessels [7].

Surgical treatment of MMD should be highly considered for symptomatic patients. Early diagnosis and intervention for pediatric patients, before any irreversible brain damage occurs are mandatory. Surgical treatment for preventing both ischemic and hemorrhagic stroke is usually done by bypassing the arteries or creating a new blood source for the affected areas of the brain [13]. The overall prognosis of MMD is variable and most patients may have a progression overtimes. Some factors that may predict poor prognosis are hemorrhagic strokes at presentation, female gender, familial history, age of onset, concomitant thyroid disorder, and

smoking. Early diagnosis and surgical revascularization have a preferable prognosis [4].

Conclusion

Moyamoya is a rare occlusive cerebrovascular disease that may occur as a primary disease or as a MMS associated with a variety of conditions. The reported case of MMS has appeared in a 2-years-old child with Down syndrome, suggesting that ischemic cerebrovascular disease can occur earlier in life in children with Down syndrome. Despite the rarity of MMS as a cause of stroke, clinicians should be aware of the nonembolic etiology of stroke in children with Down syndrome. Structural abnormalities associated with Down syndrome may make the patient vulnerable to develop vascular abnormalities and MMS, which may lead to ischemic cerebrovascular disease.

Patient consent

Written informed guardian consent for publication has been obtained.

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