

CASE REPORT

Moyamoya Syndrome in a Child with Down Syndrome

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Moyamoya syndrome has rarely been reported in association with Down syndrome. We report a case of an 11-year-old female child with Down syndrome who presented with hemiparesis and facial palsy. Imaging investigations (magnetic resonance angiography and digital subtraction angiography) revealed the classical Moyamoya pattern. Work-up for prothrombotic and autoimmune disorders was negative. The neurological deficits recovered well. The association of Moyamoya syndrome in patients with Down syndrome has been highlighted. The possible causes for the association and management have been reviewed briefly. © 2005 IMSS. Published by Elsevier Inc.

Key Words: Angiography, Artery, Coagulation, Immunity, Hemiparesis, Surgery, Trisomy.

Introduction

Stroke in childhood is a rare event with an incidence of approximately 2.5–2.7 cases per 1,000,000 per year (1). The etiologies include vascular occlusion (infarction without hemorrhage due to arterial ischemia or sinovenous thrombosis), vascular rupture (hemorrhagic stroke) and thromboembolism (resulting from cardiac disease, prothrombotic disorders, infection, dissection, dehydration and vasculitis) (1). Moyamoya disease (MMD) or Moyamoya syndrome (MMS) is an uncommon cause of stroke in childhood (1). The incidence of MMS in patients with Down syndrome (DS) is about three times higher than the incidence of MMS in the general population (1–5). The occurrence of MMS in DS is rare, and only about 43 cases have been reported so far (17 cases in English literature) (1,2,6,7). We report such a case of Moyamoya syndrome in a child with Down syndrome. This is the first report of its kind from India.

Case Report

An 11-year-old-female child, a documented case of Down syndrome, was admitted with sudden onset of weakness

in the right upper and lower limb with deviation of angle of mouth towards the left side during the past 4 days. Symptoms of fever, headache, seizures, and altered sensorium were absent. There was no history of trauma or cardiac disorder. The child had moderate mental retardation and was a special-school student.

The vital parameters and peripheral pulses were normal. Physical examination revealed features of Down syndrome in the form of low set ears, hypertelorism, depressed nasal bridge, protruding tongue, flat facies, clinodactyly, brachydactyly, bilateral simian crease, and hypotonia. On neurological examination, she was alert, conscious and oriented. Right upper motor neuron type of facial palsy was present with right-sided hemiparesis. The muscle power in the right upper limb was 0/5 and lower limb was 2/5. The deep tendon reflexes were exaggerated on the right side and the right plantar reflex was extensor. Cardiac examination was normal and cardiac murmur was absent. Examination of other systems was normal.

Brain magnetic resonance imaging (MRI) showed hyperintense signal in left frontoparietal region, centrum semi-ovale and in the head of left caudate nucleus on T2-weighted images (Figure 1). MR angiography revealed concentric narrowing in the supraclinoid segments of internal carotid arteries and middle cerebral arteries bilaterally. Digital subtraction angiography (DSA) confirmed occlusive arteriopathy involving bilateral internal carotid arteries, anterior cerebral arteries and middle cerebral arteries (Figures 2A and 2B). There was a “puff of smoke” appearance due to presence of collaterals (Figures 2A and 2B). Radiographs of

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Note: This case was presented as a Poster at the International Pediatric Update 2004 held in Mumbai, India (from 15th to 17th October 2004) and a similar abstract has been published in the Proceedings and Abstract Book of the International Pediatric Update 2004.

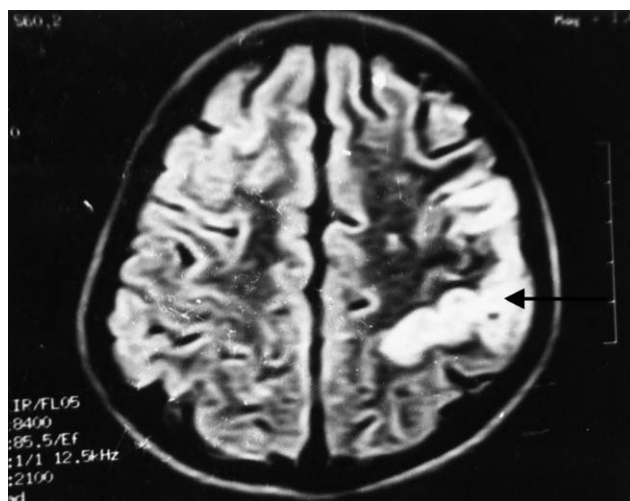


Figure 1. Brain MRI (axial view): note the hyperintense signal in left frontoparietal region (arrow).

the chest and cervical spine were normal. Electrocardiogram was normal, as was the color Doppler examination of the heart. Investigations for autoimmune (ANA, dsDNA, anti-cardiolipin antibodies, antiplatelet antibodies), prothrombotic (protein C, S and antithrombin III deficiency) and metabolic disorders (homocysteinuria) were normal. Her karyotype was 47 XX, +21. The patient improved during the next 12 days. On discharge from the hospital, the muscle power in her right lower limb was 4/5 and that in the right upper limb was 3/5. The right-sided facial palsy had recovered.

Discussion

Children with Down syndrome are at an increased risk for cerebral infarction (due to thromboembolism secondary to an underlying cardiac malformation) (1). Increased susceptibility to bacterial infection, including meningitis and infective endocarditis leading to cerebrovascular occlusion and stroke, is also known in patients with Down syndrome (1). MMD is a chronic progressive non-inflammatory vasculopathy (occlusive cerebrovascular disorder) with progressive stenosis of arteries of the circle of Willis (1–3,7,8). MMD is more frequently seen in Japanese and Asian populations and is of unknown etiology (1,2). The vessels mainly involved are the intracranial internal carotid arteries, and progression occurs to involve middle, anterior and posterior cerebral arteries (1–3,7). Small collateral vessels arise distal to the stenosed vessels creating a typical “puff of smoke” appearance on imaging studies (1,2,7). MMD occurs with bimodal onset: a peak in the first decade associated with ischemic strokes and another peak in the fourth decade associated with hemorrhagic strokes (2,3). However, Aylett et al. have described a case of DS-MMS with subarachnoid hemorrhage at presentation (an unusual presentation in children

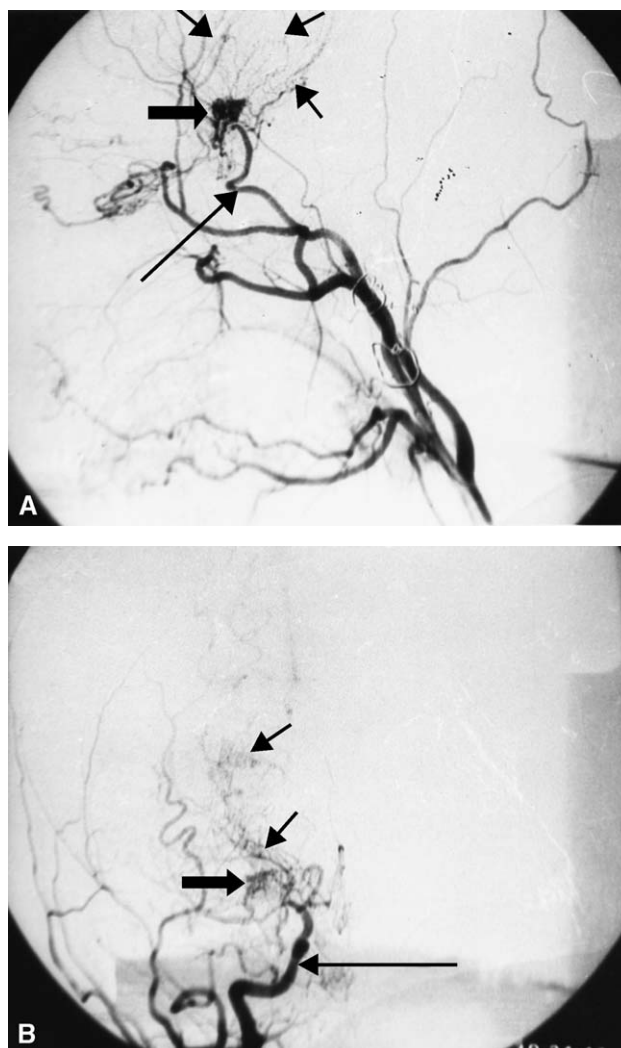


Figure 2. (A) Digital subtraction angiography (left lateral view): occlusion of terminal left internal carotid artery (long arrow) with hypertrophied striate collaterals (short thick arrow) giving “puff of smoke” appearance (short thin arrows); (B) digital subtraction angiography (right frontal Towne’s view): occlusion of terminal right internal carotid artery (long arrow) with hypertrophied striate collaterals (short thick arrow) giving “puff of smoke” appearance (short thin arrows).

<15 years) (3). Hemorrhage in thalamus, hypothalamus and basal ganglia may result from rupture of pseudoaneurysms and microaneurysms of fragile collateral vessels and may be accompanied by intraventricular or subarachnoid extension (3). Secondary forms of MMD are termed as MMS (2,7,8). MMS also shows a similar angiographic pattern to that of Moyamoya disease (2). The underlying vasculopathy is usually secondary to autoimmune disease, brain pathologies such as tumors, neurofibromatosis, post-radiation therapy for brain tumor, Down syndrome or other risk factors (homocysteinuria, tuberous sclerosis, fibromuscular dysplasia, Fanconi anemia and sickle cell disease) (1,3,7,9). In children, MMD or MMS can present with either transient or permanent neurological deficits (1). A case of MMD and

sagittal sinus thrombosis in a child with DS has been reported (10). An interesting report of a patient with DS with MMS who presented with extensive multiple cerebral infarction during measles infection has also been described (11). Fever, dehydration, activation of coagulation associated with the infection, relatively decreased cerebral blood flow during status epilepticus and central nervous invasion by the measles virus were thought of as possible contributory factors in development of the infarction (11).

The exact mechanism of vascular occlusion in DS with MMS is not known and several hypotheses have been proposed (4,7). Patients with DS are generally predisposed to vascular disease (seen in abnormal nailbed capillary morphology, congenital heart disease and abnormalities of retinal vessels and primary intimal fibroplasia) (1,3,5). Frequency of abnormalities of the circle of Willis in patients with DS has been reported to be higher than that of patients with isolated congenital heart disease (1). Regarding the molecular basis, several proteins encoded on chromosome 21 are associated with an increased risk for vascular diseases (including the alpha chains of collagen type VI, superoxide dismutase I, interferon gamma receptor and cystathionine beta synthase) (1,2,4,7). Autoimmunity has also been postulated as another possible mechanism linking the two disorders (1). Patients with DS have an increased prevalence of autoimmune disorders such as autoimmune thyroid disease (1,4). Also, MMD is associated with the presence of antiphospholipid antibodies, which may predispose to arterial thrombosis (1,4). In a 21-year-old man with trisomy 21 and MMD with Graves' disease, anti-thyroid microsome antibodies and antiphospholipid antibodies has been reported (4). Upper cervical subluxation (atlanto-axial instability) can produce cerebral circulation insufficiency predisposing the patient to develop MMD (1,12). The possibility of protein C deficiency causing thromboembolism has been proposed by Gururaj et al. in their report of a child with DS-MMS who presented with recurrent strokes with full recovery (7). The autoimmune work-up and work-up for hypercoagulation was negative in our case. Radiographs of the cervical spine were normal. A familial association has also been reported in MMD (3). The HLA types need to be studied in cases of DS with MMS (3).

The average age of presentation of patients with MMS with DS has been reported to be 5–7 years (2,3). Usually it takes 1–2 years to develop a classic Moyamoya pattern (8). Dai et al. have reported a 20-month-old girl with Down syndrome and Moyamoya syndrome who presented with seizure and hemiparesis (the youngest patient reported with MMS and DS) (8). The age of patients affected with MMS-DS ranged from 2 to 18 years in a study by Cramer et al. (2). Hemiplegia and aphasia were the common presentations of MMS-DS (2). All patients had multiple infarcts and bilateral infarcts were seen in six of the seven cases reported (2). In addition to motor deficits, these patients may present with sensory impairment, involuntary movements

(chorea), headache, seizures, or cognitive impairment (1,3,6,13). Of the 26 patients reported with Down syndrome and Moyamoya disease, 80% presented with cerebral infarction, 15% with a transient ischemic attack and 5% with intracranial hemorrhage (1). As in our case, motor recovery was excellent in five of the seven cases of MMS-DS reported by Cramer et al. (2). Recovery mechanisms in MMS-DS involve synaptogenesis, axonal growth, dendritic growth and changes in neurotransmitters (2). Transient and often recurrent weakness is common, and posterior circulation is involved less frequently (2,6,7).

Definitive diagnosis of MMD or MMS requires the use of appropriate imaging techniques, and conventional cerebral angiography provides a definitive means of visualizing the blood vessels (1). MRA is a non-invasive alternative to conventional angiography, but small- and medium-sized arteries may not be reliably visualized, and conventional angiography is recommended if the MRA appears normal or equivocal or prior to surgery (1,7,10,13). The infarcts in Moyamoya disease are usually distributed unevenly in the cortex and subcortical areas of the anterior-middle and middle-posterior cerebral arterial border zones and less frequently in the basal ganglia, thalamus or the anterior cerebral artery distribution (7). The secondary changes in advanced cases include white matter disease, brain atrophy, hemorrhage and cortical laminar necrosis (7,14).

Management of MMD or MMS includes medical management and surgical intervention. Medical management includes supportive care and antithrombotic therapy (1). Low-dose aspirin is recommended in patients with normal perfusion reserve as shown by PET or SPECT scanning (1). Surgical intervention is indicated for patients with reduced perfusion reserve (1). Direct revascularization involves anastomosis of the superficial temporal artery to the middle cerebral artery but is surgically challenging and recommended for older children (1). Indirect revascularization surgeries include encephalo-duro-arterio-synangiosis, encephalo-myo-synangiosis, bilateral pial synangiosis and multiple burr holes (1,2). These methods allow growth of new vessels to revascularize the ischemic cerebral arteries (1). Pial synangiosis results in luxuriant collateralization and patients have been stroke-free during a follow-up of 1.3–4 years (2). If cerebral infarction occurs and surgery is indicated, this should be done 3 to 4 weeks after onset of the infarction in order to avoid reperfusion injury (1).

This case is being reported to discuss the unusual association of MMS and DS. A high index of suspicion is required to make the diagnosis, and it is recommended that MMS should be considered as a differential diagnosis (and accordingly investigated for) in patients with DS manifesting with neurological abnormalities (1,3,6).

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