Case Report

Down Syndrome with Moyamoya Disease: A Case Series

Pawan Kumar, Inusha Panigrahi, Naveen Sankhyan, Chirag Ahuja1, Prasoon K. Goyadi

Down syndrome (DS), resulting from trisomy 21, is a common cause of mental retardation. Around 20,000 babies with DS are born every year in India. There is an increased risk of cerebral infarction in children with DS, the common causes being thromboembolism secondary to atrioventricular canal defects, right-to-left shunting, myocardial dysmotility, or cardiac valvular abnormalities. Stroke due to other causes can also occur in patients with DS, and one of these is moyamoya disease. This can be diagnosed by magnetic resonance imaging and/or angiography in these patients. Here we report four cases of moyamoya disease in young patients with DS aged 2–3½ years, of a total of 500 cases with DS registered in the Genetic Clinic.

Keywords: Aneuploidy, chromosomal disorder, hemiparesis, MRA, stroke

INTRODUCTION

Down syndrome (DS) is the most frequently occurring chromosomal abnormality leading to mental retardation in males and females. Few cases of DS with coexisting moyamoya disease (MMD) have been reported. MMD is a nonatherosclerotic condition characterized by progressive stenosis of terminal internal carotid artery (ICA) and proximal part of anterior cerebral artery (ACA) and middle cerebral artery (MCA). It is a rare cause of stroke in young age. The term “moyamoya disease" is used when there is bilateral ICA stenosis with associated collaterals, with no other related disease. The clinical features depend on the age of presentation: ischemic symptoms are more common in the young while the risk of hemorrhage increases with age. Children with MMD can present with clinical features ranging from transient ischemic attack to permanent neurological deficits, including sensory and motor deficits, headache, seizures, and involuntary movements. The diagnosis requires a high index of clinical suspicion and confirmation by cerebral angiography and magnetic resonance angiography (MRA).[1–4] Etiopathogenesis of MMD in DS is sparse. We report four cases of DS admitted with stroke and diagnosed to have MMD.

CASE REPORTS

Of more than 500 patients of DS registered in the Genetic Clinic of the institute, median maternal age at conception in DS pregnancies was 28 years (range 18–42 years). We observed cardiac defects in more than 30% of the cases and MMD in four (~0.8%) of the cases of DS. The work-up and management of these four patients are described in Table 1. The MRA findings of Case 1 are shown in Figure 1.

Case 1

A 3-year-old boy, follow-up case of DS with history of transient ischemic attack 8 months back, presented with acute onset right hemiparesis with facial weakness. Examination revealed pallor with weakness, upper motor neuron (UMN) facial palsy, and UMN signs of right side. Possibility of acute ischemic stroke involving left MCA territory was kept. Noncontrast computed tomography (NCCT) of the head was suggestive of infarct in left parietotemporal area with a gliotic focus in the right hemisphere, possibly an old infarct. The child was started on aspirin, and neuroprotective strategy was ensured. For doubtful history of seizures, the child was started on phenytoin maintenance at 5 mg/kg/day. Magnetic resonance imaging (MRI) of the brain was also suggestive of large infarct in left parietotemporal area, and MRA showed extensive

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Address for correspondence:
Dr. Inusha Panigrahi,
Genetic Metabolic Unit, Advanced Pediatric Centre,
Postgraduate Institute of Medical Education and Research,
Sector 12, Chandigarh, India.
E-mail: inupan@yahoo.com

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collaterals in posterior circulation consistent with MMD [Figure 1]. Neurosurgery consultation was taken and conservative management was advised. The child was discharged on aspirin, and on short follow-up, the right hemiparesis was on improving trend with the child being hemodynamically stable.

**Case 2**

A 2-year-old boy presented with sudden onset left-sided hemiparesis and facial weakness since 18 days. The weakness was maximum at onset and started improving since day 2 of illness. On examination, the child had dysmorphism in the form of mongoloid slant, depressed nasal bridge, sandal gap, signs of rickets along with weakness, UMN facial palsy, and UMN signs of left side. Possibility of acute ischemic stroke involving right MCA territory was kept, and MRI and MRA of the brain were performed, which identified acute infarct in right cerebral hemisphere with subacute infarct in left temporal lobe and atrophic left cerebral hemisphere, suggestive of MMD. The child was started on aspirin, neuroprotective strategy along with seizure control. Oral aspirin was started and the child was discharged. At 6-month follow-up, right hemiparesis was on improving trend and the child was hemodynamically stable.

**Case 3**

A 3½-year-old boy was a follow-up case of DS with previous history of left-sided hemiparesis 3 months earlier, which was on improving trend. He presented again with sudden onset altered sensorium with right-sided hemiparesis. Because of low Glasgow Coma Scale score, the child remained intubated, subsequently found to have raised intracranial pressure, which was managed conservatively and became passive in next 36h. At day 6 of hospital stay, sensorium of the child improved and was extubated. CT scan of the head showed bilateral gyral hyperintensities
However, in our study, the youngest DS child with MMD was only 2 years old.

The abnormalities seen in the circle of Willis are much more frequent in patients with DS as compared to cases with isolated congenital heart disease. Several hypotheses have been proposed regarding the mechanism of DS-associated MMD. Cases with DS are predisposed to vascular disease and show retinal vessel abnormalities, abnormal capillary morphology of the nail beds, primary intimal fibroplasias, congenital heart disease, and high pulmonary vascular resistance. Vascular dysplasia seen in DS may be responsible for the pathogenesis of MMD. Chromosome 21 encodes for certain proteins such as superoxide dismutase I, α-chains of collagen type VI, interferon-γ receptor, and cystathionine β-synthase. These proteins are associated with increased risk for vascular diseases in DS. The role of autoimmunity is also proposed in the pathogenesis of MMD, in view of the fact that there is increase in autoimmune disorders such as autoimmune thyroid disease in DS. MMD has also been found to be associated with antiphospholipid antibodies, predisposing these patients to arterial thrombosis.

Children with MMD commonly present with hemiplegia. Transient or recurrent weakness and chorea are also seen. In our case series also, the most common presentation was with hemiparesis, and one child had history of seizures. There was no predilection for involvement of left or right side of the body. Three criteria are required for the diagnosis of MMD: (a) stenosis of distal intracranial segment of ICA and proximal ACA and MCA, (b) abnormal vascular network near the stenosis, arising from thalamoperforate and lenticulostriate arteries, and (c) exclusion of other associated factors such as trauma, meningitis, sickle cell disease, tumor, or radiation therapy. Management of these cases is still controversial with different opinions. Some authors recommend only medical treatment with aspirin, whereas some favor surgical treatment. The use of long-term anticoagulants for MMD is not recommended due to risk of hemorrhages in these patients. Surgical methods to revascularize areas of cerebral ischemia have been attempted; however, results are not very satisfactory. These are encephaloarteriosynangiosis, encephalomyosynangiosis, superficial temporal artery to MCA anastomosis, and omental transplantation. A recent report has suggested pial synangiosis to be a good modality of therapy in the patients with DS. Increased risk of MMD has also been seen in microcephalic osteodysplastic primordial dwarfism, neurofibromatosis, and lysinuric protein intolerance.
These may be having a common pathophysiology, and there are also genetic loci mutations that would, in addition, indicate higher susceptibility for MMD. In a 2-year-old girl presenting with early onset of moyamoya syndrome with underlying DS, the genetic variant RNF213 p.R4810K was identified.

CONCLUSION

The knowledge regarding the association of MMD in a patient with DS with stroke is important so as to reach a correct diagnosis and establish an appropriate management plan. The reason of this association is still not clear. The evaluation must include an MRA. Further advanced imaging, autoimmune work-up, or epigenetic studies are needed to find out underlying basis for increased incidence of MMD in trisomy 21 cases.

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Conflicts of interest
There are no conflicts of interest.

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