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Moyamoya syndrome in a child with Down syndrome

唐氏綜合症兒童的Moyamoya綜合症

Moyamoya syndrome has been reported in association with Down syndrome. In paediatric patients, the usual presentation is that of ischaemic stroke. We report a 9-year-old boy with Down syndrome and moyamoya syndrome who presented with acute-onset left hemiparesis. This is the first such reported case in Hong Kong. There is growing evidence that the chromosomal abnormalities in patients with Down syndrome may contribute to a vulnerability for the development of moyamoya syndrome. A high index of suspicion is necessary to make the correct diagnosis. Medical and surgical management strategies for this disease are discussed. Surgical intervention should proceed without delay, if indicated, to prevent further neurological deterioration. A multidisciplinary approach is recommended for the rehabilitation of these patients.

Moyamoya綜合症與唐氏綜合症的聯繫早已有文獻記載。在兒童患者中，常見的病徵是局部缺血性中風。我們報告一名患有唐氏綜合症和moyamoya綜合症的9歲男童，病人呈現急性左偏癱。這是在香港首次報告的同類型病例。越來越多的證據顯示，唐氏綜合症患者中的染色體變異可能是導致moyamoya綜合症發病的因素。要正確診斷這種情況，醫護人員必需要有高度的警覺性。除報告病例外，本文亦討論了這種病的內科及外科治療策略。有需要時，應儘快施行外科手術，以防止病者有進一步的神經損傷。就病者的康復方面，本文亦推薦了誇專科的方法。

Key words:
Cerebrovascular disorders;
Child;
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關鍵詞：
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Introduction

Stroke in childhood is rare, with an incidence of approximately 2.5 to 2.7 cases per 100 000 per year.[1,2] It is defined as a sudden occlusion or rupture of the cerebral arteries or veins, resulting in focal cerebral damage with clinical neurological deficits lasting for more than 24 hours. Several types of stroke are described. Bland infarction without visible haemorrhage is caused by vascular occlusion, which can be due to arterial ischaemia or sinovenous thrombosis. Haemorrhagic infarction refers to bleeding into the area of bland infarction. A stroke which results from vascular rupture is called a haemorrhagic stroke.[3] Approximately 20% to 40% of patients with arterial ischaemia do not have identifiable risk factors.[4,5] Thromboembolism resulting from cardiac causes, prothrombotic disorders, infection, dissection, dehydration, and vasculitis are the most common risk factors.

Moyamoya disease or syndrome is believed to be a rather uncommon cause of stroke in childhood. Moyamoya disease is a condition of progressive idiopathic stenosis with eventual occlusion of the large cerebral arteries of the Circle of Willis. The arteries involved include the terminal portion of the internal carotid arteries (ICA), the proximal portion of the anterior cerebral arteries, or the proximal portion of the middle cerebral arteries. An abnormal network of small collateral vessels develops distal to the stenosis or occlusion, creating a typical 'puff of smoke' appearance on imaging studies. Moyamoya disease predominantly occurs in Asians and is of unknown aetiology. Moyamoya syndrome shows a similar angiographic pattern to that of moyamoya disease. The underlying vasculopathy, however, is usually secondary to autoimmune disease, brain pathologies such as tumour, cranial irradiation, Down syndrome, or other risk factors.[3]

In children, moyamoya disease or syndrome can present with either transient or permanent neurological deficits. Cerebral ischaemia predominates in children. There can be a wide range of neurological presenting symptoms including motor deficits, sensory impairment, involuntary movements, headache, seizures, or cognitive impairment.[6] A high index of suspicion is necessary to make the diagnosis. Cerebral angiography and magnetic resonance angiography (MRA) are used to diagnose moyamoya disease or moyamoya syndrome. Patients with Down syndrome have been known to develop moyamoya syndrome, although this is uncommon. We report the case of a 9-year-old boy with Down syndrome who presented with left hemiparesis and was subsequently found to have moyamoya syndrome. This is the first reported case of a Chinese paediatric patient who had Down syndrome associated with moyamoya syndrome in Hong Kong. On reviewing the English language literature, 26 paediatric cases have been previously reported.[7-9] The clinical characteristics of these reported cases and the management strategies utilised are also discussed.

Case report

A 9-year-old boy with Down syndrome was admitted to Tuen Mun Hospital on 29 June 2000, due to sudden onset of progressive left-sided weakness with a limping gait, drooling of saliva, and facial asymmetry evident for 4 days. He did not have symptoms of headache, seizure, abnormal movements, or deterioration of consciousness or mental function on admission. A history of a fall injury to the left arm 2 days prior to the onset of the weakness was reported. There was no associated head and neck injury or infection, and no history of loss of consciousness. Concerning past health, the boy had Down syndrome (karyotype 47XY+21). He was cognitively impaired and was studying in a special school. There was no history of gastrointestinal, cardiac, or endocrine complications. Physical examination revealed typical features of Down syndrome. The boy was alert, conscious, and oriented. Neurological signs were compatible with left hemiparesis. There was an associated upper motor neuron lesion of the left facial nerve. The fundi were normal. The peripheral pulses were normal and regular. The heart sounds were normal with no murmur heard. No carotid bruits could be detected. Examination of other systems was unremarkable.

Following admission, echocardiography did not detect any cardiac lesions or evidence of endocarditis. Radiographs of the cervical spine showed no evidence of atlantoaxial instability. Non-enhanced computed tomography of the brain showed multiple hypodense lesions in the right frontoparietal region. Magnetic resonance imaging was performed for further lesion characterisation. Multiple hyperintense lesions were found in the right frontal and parietal lobes, the left genu of the corpus callosum, and bilaterally in the centrum semiovale on T2-weighted images (Fig 1). Diffusion imaging revealed restricted diffusion in the right frontal and parietal lobe lesions, consistent with multiple acute cerebral infarctions. Single voxel magnetic resonance spectroscopy (MRS) of the right fronto-parietal brain region was performed and showed a marked decrease of N-acetylaspartate, an increased choline level, and a large lactate doublet. The MRS findings were characteristic of acute cerebral infarction. Magnetic resonance angiography showed supraclinoid occlusion of the ICA bilaterally and absence of the anterior and middle cerebral arteries (Fig 2).

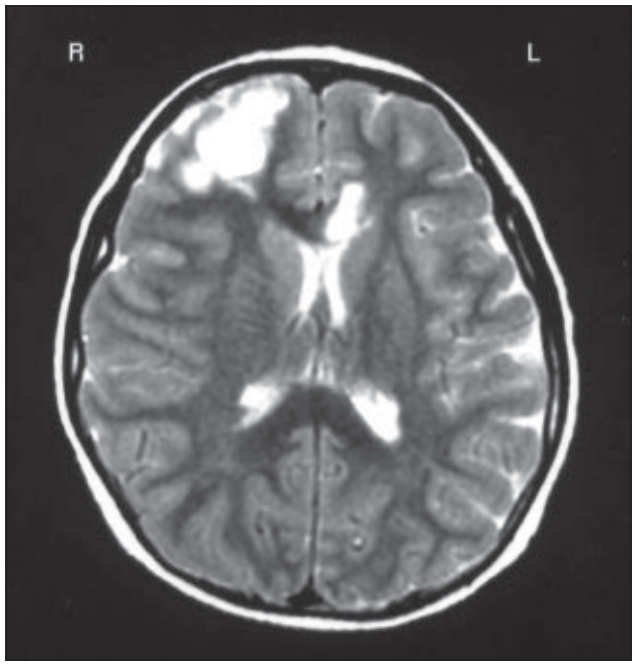

Fig 1. Axial T2-weighted image shows multiple hyperintense lesions in the right frontal lobe. A small high signal lesion is also noted at the left genu of the corpus callosum

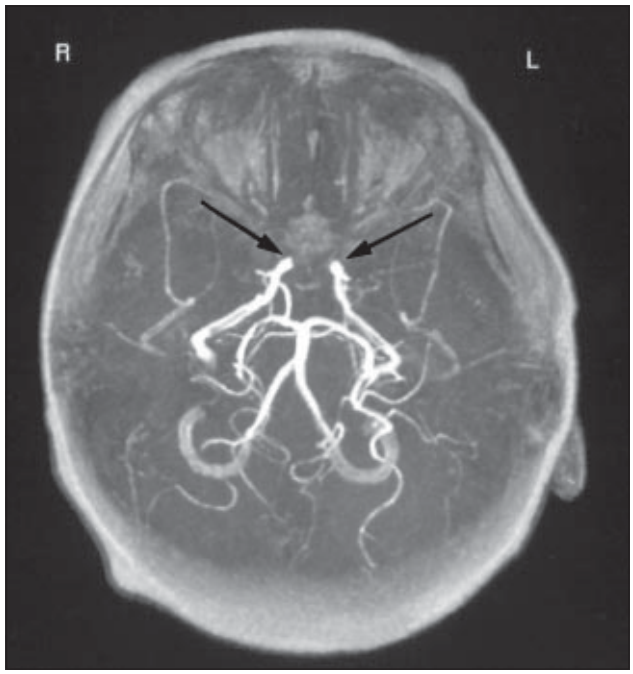

Fig 2. Magnetic resonance angiography (three-dimensional collapsed view) of the Circle of Willis reveals supraclinoid occlusion of the internal carotid arteries bilaterally and the absence of both middle and anterior cerebral arteries

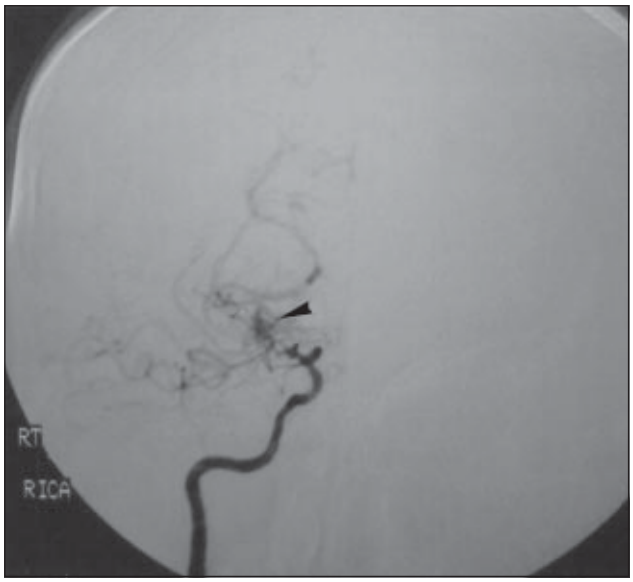

Fig 3. Right internal carotid angiogram in the arterial phase confirms the supraclinoid occlusion of the right internal carotid artery and reveals hypertrophied lenticulostriate collaterals (arrowhead). The left internal carotid angiogram (not shown) showed similar, but less pronounced findings

Digital subtraction cerebral angiography confirmed occlusion of both the ICA and the middle cerebral arteries bilaterally, and the presence of moyamoya vessels (Fig 3). Transcranial doppler ultrasonography, single photon emission computed tomography (SPECT), and electroencephalography were not performed. Screening for autoimmune, prothrombotic, and metabolic disorders were negative. Protein C, protein S, and antithrombin III assays were 94%, 103%, and 89% of controls, respectively (all within normal limits). Serum for anticardiolipin immunoglobulin G was 9 U/mL (normal level, <15 U/mL) and immunoglobulin M was less than 1 U/mL (normal level, <13 U/mL). Lupus anticoagulant activity was not detected. Serum testing for antinuclear factors and antineutrophil cytoplasmic antibody was negative. Antimicrosomal antibody testing was not completed. Urine aminoacid chromatography showed a normal pattern, with no increase in homocystine excretion evident.

Muscle power of the boy's left upper and lower limbs was graded 2-3 on admission, and showed gradual improvement to grade 4 by 8 July 2000. An indirect revascularisation procedure using two burr holes in the right frontal and parietal bones was performed on 17 July 2000. The operation and postoperative recovery were uneventful. Aspirin (2 mg/kg/day) was given postoperatively. The boy was discharged on 2 August 2000, with regular out-patient physiotherapy scheduled. Magnetic resonance imaging and MRA were repeated on 1 August 2000, 23 August 2000, and 16 January 2001 and showed no subsequent changes. At the last assessment in February 2002 (20 months after the operation), the patient had no residual weakness of the left upper and lower limbs. No recurrence of stroke or haemorrhage was observed during the follow-up period.

Discussion

Children with Down syndrome are at an increased risk for cerebral infarction. The majority of cases occur due to thromboembolism secondary to an underlying cardiac malformation. There is also an increased susceptibility to bacterial infection, including meningitis and infective endocarditis, leading to cerebrovascular occlusion and stroke. Pearson et al,[10] in an analysis of stroke in 37 children with Down syndrome, found seven patients with angiographic abnormalities consistent with moyamoya syndrome.[10] The incidence of moyamoya syndrome in patients with Down syndrome has been noted to be three times the estimated incidence of moyamoya disease in the general population.[11]

Several hypotheses for the mechanism of Down syndrome–associated moyamoya syndrome have been proposed. Patients with Down syndrome are predisposed to vascular disease generally. This is seen in abnormal nail-bed capillary morphology, high pulmonary vascular resistance, congenital heart disease, abnormalities of the retinal vessels, and primary intimal fibroplasia.[7] The frequency of abnormalities of the Circle of Willis in patients with Down syndrome has been reported to be higher than that of patients with isolated congenital heart disease.[10] Vascular dysplasia may result in a structural defect that is important in the pathogenesis of moyamoya disease. With respect to the molecular basis of Down syndrome, several proteins encoded on chromosome 21 are associated with an increased risk for vascular diseases. These include the α-chains of collagen type VI, superoxide dismutase I, the interferon gamma receptor, and cystathionine β-synthase.[7]

Autoimmunity has been postulated as another possible mechanism linking the two disorders. Patients with Down syndrome have an increased prevalence of autoimmune disorders, such as autoimmune thyroid disease. Moyamoya disease has been associated with the presence of antiphospholipid antibodies, which may predispose these patients to arterial thrombosis. This phenomenon was observed in a patient with Down syndrome who developed Graves' disease and moyamoya syndrome, and was subsequently found to have multiple thromboses of the anterior cerebral artery in the presence of antiphospholipid antibodies.[12] An autoimmune assay in our patient was negative, however. Upper cervical subluxation can also produce a cerebral circulation insufficiency that predisposes a patient to the development of moyamoya disease. In this patient, there was no evidence of such subluxation.

Of the 26 reported patients with Down syndrome and moyamoya disease, 80% presented with cerebral infarction, 19% with a transient ischaemic attack, and 5% with intracranial haemorrhage. The average age of onset of symptoms was 6 years.[7] Definitive diagnosis of moyamoya disease or syndrome requires the use of appropriate imaging techniques. Conventional cerebral angiography provides a definitive means of visualising the vasculature. There is,

however, a 1% chance of stroke after the procedure, although the risk may be lower in centres with greater experience with the procedure and in patients who do not have vascular stenosis.[13] The recent development of MRA provides a non-invasive alternative to conventional angiography. Small- and medium-sized cerebral arteries, however, may not be reliably visualised. Conventional angiography is currently recommended if MRA appears normal or equivocal, or if there is evidence of moyamoya vessels and surgery is planned.[14]

The management of moyamoya disease or syndrome is challenging. Medical treatment includes supportive care after stroke and antithrombotic therapy. General supportive care includes optimising blood pressure and fluid management, and controlling blood glucose and body temperature. Any associated seizures should be treated aggressively. The efficacy of antithrombotic therapy for these patients remains uncertain. Ikezaki[15] recommends that aspirin be given to patients with normal perfusion reserve as shown by positron emission tomography or SPECT scanning. For further management, paediatricians should look for any predisposing factors for moyamoya syndrome and treat these accordingly. Surgical intervention is indicated for patients with reduced perfusion reserve. Direct or indirect revascularisation surgery can be performed. Direct revascularisation surgery involves the anastomosis of the superficial temporal artery to the middle cerebral artery. This requires advanced surgical skill and is only recommended for older children. Indirect revascularisation surgery includes encephalo-duro-arterio-synangiosis, encephalo-myo-synangiosis, pial synangiosis, and multiple burr holes. The encephalo-duro-arterio-synangiosis procedure uses a branch of the superficial temporal artery that is sutured to the dural surface of the brain via an opening in the skull. The encephalo-myo-synangiosis procedure involves placement of the temporalis muscle on the brain surface via a skull opening. Pial synangiosis refers to direct suturing of the superficial temporal artery adventitia to the pial surface. Multiple burr holes are made, for instance, in bilateral frontal areas for vascularisation. The above-mentioned methods allow growth of new vessels to revascularise the ischaemic cerebral arteries. Any one of these indirect revascularisation methods is relatively safe and can be performed for a younger age-group. According to the treatment strategy suggested by Ikezaki,[15] surgical intervention is recommended for those patients with documented reduced perfusion reserve. This is because unnecessary bypass surgery may cause maldevelopment of collaterals, which may, in turn, lead to increased intracranial pressure. If cerebral infarction occurs and surgery is indicated, this should be done 3 to 4 weeks after the onset of the infarction in order to avoid reperfusion injury.[15]

Conclusion

This is the 27th case of moyamoya syndrome in association with Down syndrome reported in the literature. Several risk factors can underlie the development of stroke in patients with Down syndrome. A high index of suspicion is required to make the appropriate diagnosis. Conventional angiography remains an important imaging technique for diagnosis of this condition. Magnetic resonance angiography is also gaining popularity. In order to prevent further neurological deterioration, moyamoya disease or syndrome should be managed promptly. Appropriate surgical indications should be considered and, when available, bypass surgery should be performed without delay.

References

1. Broderick J, Talbot GT, Prenger E, Leach A, Brott T. Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage. J Child Neurol 1993;8:250-5.
2. Schoenberg B, Mellinger J, Schoenberg D. Cerebrovascular disease in infants and children. Radiology 1978;28:763-8.
3. Swaiman KF, Ashwal S. Paediatric neurology principle and practice. Missouri: Mosby; 1999.
4. Ball WS Jr. Cerebrovascular occlusive disease in childhood. Neuroimaging Clin N Am 1994;4:393-421.
5. Martin PJ, Enevoldson TP, Humphrey PR. Causes of ischaemic stroke in the young. Postgrad Med J 1997;73:8-16.
6. Fukui M. Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis ('moyamoya' disease). Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare, Japan. Clin Neurol Neurosurg 1997;99(Suppl 2):238S-40S.
7. Dai AI, Shaikh ZA, Cohen ME. Early-onset Moyamoya syndrome in a patient with Down syndrome: case report and review of the literature. J Child Neurol 2000;15:696-9.
8. Del-Rio Camacho G, Orozco AL, Perez-Higueras A, Camino Lopez M, Al-Assir I, Ruiz-Moreno M. Moyamoya disease and sagittal sinus thrombosis in a child with Down's syndrome. Pediatr Radiol 2001;31: 125-8.
9. Takasugi H, Maemoto T, Kitazawa K, Honda A. A case of Down syndrome with moyamoya syndrome presenting extensive multiple cerebral infarction during measles infection [in Japanese]. No To Hattatsu 2000;32:39-43.
10. Pearson E, Lenn NJ, Call WS. Moyamoya and other causes of stroke in patients with Down syndrome. Pediatr Neurol 1985;1:174-9.
11. Kawai M. A genetic study of idiopathic spontaneous multiple occlusions of the circle of Willis (moyamoya disease) [in Japanese]. Zasshi Tokyo Ika Daigaku 1985;55:427-41.
12. Leno C, Mateo I, Cid C, Berciano J, Sedano C. Autoimmunity in Down's syndrome: another possible mechanism of Moyamoya disease. Stroke 1998;29:868-9.
13. Kirkham FJ. Stroke in childhood. Arch Dis Child 1999;81:85-9.
14. Ganesan V, Savvy L, Chong WK, Kirkham FJ. Conventional cerebral angiography in children with ischaemic stroke. Pediatr Neurol 1999; 20:38-42.
15. Ikezaki K. Rational approach to treatment of moyamoya disease in childhood. J Child Neurol 2000;15:350-6.