Case report

Moyamoya syndrome associated with Down syndrome: Clinical and radiological features

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Abstract

Moyamoya syndrome has been rarely associated with Down syndrome. In pediatric patients, the usual presentation is the ischemic stroke. We report a 8 year old girl with Down syndrome and Moyamoya syndrome, who presented with focal seizure and acute left onset hemiparesis. The aim of this study is to describe the clinical and radiological features of the patient, the managment and the possible causes that could explain these two syndrome's associations have been reviewed.

Keywords: Cerebrovascular disorders. Down syndrome. Ischemic stroke. Moyamoya syndrome.

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Introduction

People with Down syndrome (DS) have a greater risk of cerebrovascular disease than the general population, mainly because of the association with congenital cardiopathies, among other factors (1). Among the cerebrovascular disorders associated with DS, particular attention should be paid to Moyamoya syndrome.

Moyamoya disease is a chronic occlusive vascular disorder, characterised by the progressive stenosis of the supraclinoid segment of the internal carotid artery and the main branches of Willis' polygon (2). As a consequence of chronic arterial stenosis, an abnormal collateral vascularisation network appears at the base of the cerebrum to compensate for the lack of irrigation to the areas distal to the obstruction. Two clinical forms are described, one of which is idiopathic or primary, called "Moyamoya disease", occurring frequently in Japan and Asia in general, and a secondary form known as "Moyamoya syndrome" (MMS), which has been linked to various conditions, such as autoimmune vascular diseases, brain tumours, neurofibromatosis, radiotherapy, homocystinuria, tuberous sclerosis, Fanconi syndrome, sickle cell disease, and DS (3, 4, 5).

MMS was first reported in association with DS in 1977 (6). Since then, various hypotheses have been put as to the link between the two. This article aims to underscore the association and update the recommended diagnostic and treatment guidelines. We present clinical and neuroradiological findings in an eight-year-old girl with DS and MMS.

Clinical observation

The patient was an eight-year-old female with congenital heart disease, interventricular communication and patent ductus arteriosus, operated on at the age of six, with no complications and favourable evolution. Pregnancy, birth and the neonatal period were normal. The girl is currently attending a mainstream school where she receives psychoeducational support and speech therapy. There is no family history of note; the parents and 16-year-

old brother are all healthy, and there is no history of epilepsy or cerebrovascular disease. At the age of seven years and four months, the patient suffered two partial convulsive seizures, characterised by orofacial and upper left limb clonic contractions. The first attack lasted for ten minutes, and the second, similar in nature, lasted for 30 minutes, with a loss of strength in the upper right limb that led to hospital referral.

Upon arrival at the hospital, the patient was haemodynamically stable, normotensive, hydrated, with DS phenotypic traits. Neurological examination revealed that the patient was fully conscious and alert, and her pupils were isocoric and normally reactive, with no change in ocular motricity. There was evidence of predominantly brachial left hemiparesis. Osteotendinous and myotatic reflexes were normal, with no change in superficial and deep sensibility, maintained cerebellar functions, and negative Romberg's test. Auscultation of the heart and both carotid arteries showed no evidence of murmurs.

Additional tests, blood chemistry and coagulation within normal limits, ECG showing no changes. Magnetic resonance imaging (MRI) showed T2, FLAIR, EPI, and diffusion-weighted enhancement in the right parieto-occipital area compatible with acute ischaemic stroke (Fig. 1). There were multifocal white matter lesions in the semioval centres, hyperintense in T2 and FLAIR, suggesting chronic ischaemic phenomena. Also, non-enhancing serpiginous structures compatible with vascular collaterals were observed in the region of the basal ganglia and thalamus. This finding, associated with a reduction in the calibre of the intracavernous internal carotid arteries, gave reason to suspect MMS; therefore, cerebral MR angiography was performed, confirming the MMS diagnosis with the revelation of stenosis of the internal carotid arteries, particularly in the supraclinoid segment, with significant collateral circulation through lenticulostriate, thalamic and posterior circulation vessels (Fig. 2). Cerebral angiography, performed as part of the study and assessment protocol for possible revascularisation surgery, reconfirmed the aforementioned findings (Fig. 3).

Subsequent to the convulsive seizure, treatment commenced with oxcarbamazepine, which the patient tolerated sufficiently. Since then, there have been no more convulsive episodes or any other neurological symptoms in connection with new ischaemic episodes. The neurological examination two weeks later revealed a complete recovery from hemiparesis, and treatment commenced with 100mg of aspirin daily. The patient has been asymptomatic for the past six months and is awaiting pial synangiosis revascularisation surgery.

Figure 1. Brain MRI (three days after the convulsive seizure). T2 right parieto-occipital signal hyperintensity in relation with acute ischaemic stroke.

Discussion

It is well known that children with DS have a greater risk of cerebral infarction, particularly because of the association with congenital heart disease, as well as being more susceptible to bacterial infections such as meningitis and endocarditis, which lead to thromboembolisms, vascular occlusion and ischaemia. MMS is among the causes of cerebral infarction associated with DS although, until 2005, there were only 47 published cases associating the two (7).

In a study of 37 children with ischaemic stroke and DS, cerebral angiography revealed that seven of them had features compatible with MMS (3). The incidence of MMS among the population with DS is three times higher than the incidence observed among the general population (7).

Moyamoya disease was first described in Japan in 1975 by Takeuchi and Shimizu (8). The small basal collateral vessels observed in patient angiograms bring to mind "puffs of smoke", called "moyamoya" in Japanese (9). The disease tends to be bilateral, although unilateral occurrences have been described (9).

The onset of symptoms in patients with MMS and DS shows bimodal distribution, with a peak in the first decade of life, between five and seven years of age, and a peak in the fourth decade of life (3, 9). The youngest known patient with MMS and DS was 20 months old (10). There is a slight female predominance in the association of both syndromes, with a ratio of 1.7:1 (9).

Paediatric patients with MMS typically present with ischaemic stroke, as opposed to adults, among which haemorrhagic strokes are predominant. Of 26 patients

reported with MMS and DS, 80% suffered cerebral infarction, 15% transient ischaemic stroke, and only 5% intracranial haemorrhage (3), the latter being the result of the rupture of microaneurysms or pseudoaneurysms originating from the fragile collateral vessels (4).

From a clinical point of view, unilateral neurological motor deficit is the most frequent form of occurrence; in a recent study, 13 out of 16 patients with MMS and DS were observed with hemiparesis or alternate hemiplegia. As well as the motor symptoms, patients can suffer sensory symptoms, involuntary movements, headaches, convulsions and cognitive deterioration (9). In the majority of cases, a good recovery can be made from the motor deficit. A DS and MMS case presenting with sagittal sinus thrombosis has been described (11).

In our case, the patient's age (seven years), sex (female), the association with congenital heart disease (interventricular communication and patent ductus arteriosus) and the form of occurrence – ischaemic stroke with convulsions and hemiparesis with complete recovery a few weeks afterwards – match the most frequent descriptions of occurrence and correspond to the information described in literature.

The pathogenesis of vascular occlusion in patients with DS and MMS is unknown, although various hypotheses have been put forward. Currently, it would appear that an imbalance between a metalloprotease inhibitor protein and metalloprotease itself triggers the deterioration of the intima (5, 7). A greater frequency of malformations of the vessels forming Willis' polygon in patients with DS and congenital cardiopathy has been observed in comparison to patients with congenital cardiopathy without DS (7). It should be noted that approximately 50% of those patients with DS and MMS reported also suffered congenital cardiopathies (9).

There are various proteins encoded in chromosome 21 that are said to be associated with a higher risk of vascular disease (type IV collagen alpha chain, superoxide dismutase I, the gamma interferon receptor and cysthationine beta synthase) (3, 4, 5, 7). Autoimmunity has also been put forward as another possible mechanism associated with these two syndromes: a greater prevalence of autoimmune thyroiditis in patients with DS and the presence of antiphospholipid antibodies in patients with MMS support this hypothesis (3, 7). Cervical subluxation (atlantoaxial instability) can cause circulatory insufficiency and a predisposition to develop MMS (3, 7). The association with protein C deficiency as a factor triggering thromboembolisms has also been observed in a patient with MMS and DS (5).

A number of factors can contribute to the development of infarctions in these patients, such as dehydration, fever, the activation of coagulation in relation with infectious processes, and the relative reduction in cerebral flow during epileptic states, among other things. It is important to be aware of these

Figure 2. MR angiogram: stenosis can be observed in the internal carotid arteries, particularly the supraclinoid segment, with significant collateral circulation through lenticulostriate, thalamic and posterior circulation vessels.

Figure 3. Cerebral angiogram: capillary ectasia at the level of the basal nuclei, together with the formation of collateral vessels characteristic of Moyamoya disease..

and take the necessary measures to control them. In the case at hand, none of these triggering factors was identified. Coagulation tests, family history and immunological and metabolic studies were normal, as was the x-ray of the cervical spine.

A definitive MMS diagnosis requires neuroimaging techniques. MRI may suggest this diagnosis, but only cerebral angiography or MR angiography (MRA) can confirm it, as was the case with our patient. MRA is increasingly employed, with the advantage of being non-invasive and an alternative to angiography, although the drawback is that it has less resolution to view medium- and small-calibre vessels. For this reason, it should be considered a complementary technique; standard angiography should be performed whenever MRA is normal or suspect, and prior to any surgery (3, 5, 7).

Infarctions in MMS primarily affect the area of the middle and posterior cerebral arteries. Advanced cases may display changes in white matter, cerebral atrophy, haemorrhage and cortical laminar necrosis (3, 7).

MMS is managed medically and surgically in a similar way to that described for Moyamoya disease. The medical approach is based on antithrombotic treatment with low doses of aspirin (80-100mg/day), as well as investigation and prevention of possible triggering factors. Surgical treatment is advised for those patients with a reduction in perfusion reserve. Many techniques, direct and indirect, have been described, but the technique most used among the paediatric population is pial synangiosis (indirect technique), which entails suturing the superficial temporal artery directly to the pia mater, in order to promote the development of new vessels to enable revascularisation (3, 9). It is important to note that, if the patient has had a cerebral infarction, as was the case with our patient, it is necessary to wait three to four weeks before performing surgery to avoid injury through reperfusion (3, 9). For adult patients, some neurosurgeons prefer a direct arterial bypass in which the superficial temporal artery is anastomosed to the middle cerebral artery, as the capacity for neoangiogenesis is not the same as it is in children. This is obviously a more complex technique.

In a recent review of 16 patients with MMS and DS, all were treated with pial synangiosis and low doses of aspirin. With six months to twelve years' follow-up, there were complications in 4% of cases and 0% mortality. None of the patients suffered new ischaemic episodes beyond 30 days subsequent to surgery, and MRA carried out at 1-year followup bore out clinical improvement subsequent to surgery in over 50% of patients and adequate development of revascularisation in 95% of the patients (9). It is important to highlight that the primary immediate surgical and post-surgical risk is cerebral ischaemia. Anaesthetic control and monitoring at the Intensive Care Unit are essential in order to keep the patient haemodynamically stable (normovolemia, normotension and hydration) and avoid hypocapnia.

In all patients with DS suffering ischaemic stroke, it is necessary to consider MMS as part of the differential diagnosis, as early diagnosis will enable suitable treatment with a view to preventing new ischaemic episodes and controlling the progression of the disease.

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