Acta neurol. belg., 2002, **102**, 63-66

Moyamoya disease and Down syndrome : Case report and review of the literature

Valérie DE BORCHGRAVE[1], Françoise SAUSSU[1], Anne DEPRE[2] and Thierry DE BARSY[1]

[1]Centre Neurologique William Lennox, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, 1200 Brussels ;
[2]Clinique du Parc Léopold, Brussels

Abstract

We present the case of a 29-year-old woman with Down syndrome who developed bilateral frontal ischemic stroke. Cerebral angiography demonstrated an occlusion of the both supraclinoid internal carotid arteries associated with dilated collateral vessels, consistent with moyamoya disease.

We review the clinical and radiological features of moyamoya disease associated with Down syndrome and discuss a few major physiopathologic hypotheses to explain this association.

Key-words : Moyamoya disease ; Down syndrome ; Chromosome 21.

Introduction

Moyamoya disease (MMD) is a chronic occlusive cerebrovascular disorder characterised by progressive stenoses of the arteries of the circle of Willis. The disorder initially involves the intracranial portion of the internal carotid arteries and progresses to involve the middle, anterior and posterior cerebral arteries. It is associated with the formation of an abnormal collateral vascular network, due to compensatory dilatation of lenticulo striate and thalamostriate arteries. It results in characteristic angiographic appearances to which the Japanese expression for "something hazy, such as a puff of cigarette smoke drifting in the air" (moyamoya) has been applied. The disease affects all ethnic groups, although examples are more frequently reported in Japan (Suzuki and Kodama, 1983). Primary and secondary forms of the disease are recognized. In 1988, the Japanese Ministry of Health and Welfare defined primary MMD as an idiopathic bilateral stenoses of arteries of the circle of Willis with collateral vascular networks, demonstrated on angiography. Secondary forms are termed moyamoya syndrome (MMS) and have been identified in a large number of conditions such as atherosclerosis, neurofibromatosis, postradiation therapy, sickle cell disease and more recently in association with Down syndrome (DS) (Fukushima *et al*., 1986).

Case report

A 29-year-old woman with trisomy 21 was admitted to the emergency room because she suddenly became unable to walk or speak. She had been operated in early childhood for an interatrial communication but subsequent cardiac evaluations revealed no evidence of functional impairment. The rest of the patient's history was blank. She had a moderate mental retardation in accordance with her DS but was autonomous for her daily activities. At admission, general physical examination showed no abnormalities. The patient was awake but mute and slightly aggressive. She was unable to walk alone but segmental motor examination revealed no paresis. The deep-tendon reflexes were brisk and symmetric ; the plantar responses were extensor. A grasp reflex was also observed bilaterally. A first computed tomographic (CT) scan of the brain, without intravenous administration of contrast material, showed hypodensities in the territory of both anterior cerebral arteries (Fig. 1). Magnetic resonance imaging (MRI) of the brain showed increased signals on T2-weighted images in the territory of both anterior cerebral arteries, consistent with an acute infarction. Multiple ischemic lesions were also seen in the white matter. Laboratory test, including coagulation, were performed and revealed no abnormalities. Transoesophagal echocardiography showed no right-to-left shunt, thrombus or valvular abnormalities. Cerebral angiography (Fig. 2) revealed bilateral occlusions of the supraclinoid portion of the internal carotid arteries, decreased flow in the right middle cerebral artery and nonvisualization of the left anterior and middle cerebral arteries. Lenticulostriate arteries were dilated and made a new vascular network. The verterbrobasilar territory was normal. The left vertebral artery enabled reopacification of the territories of both middle cerebral arteries through leptomeningeal anastomoses.

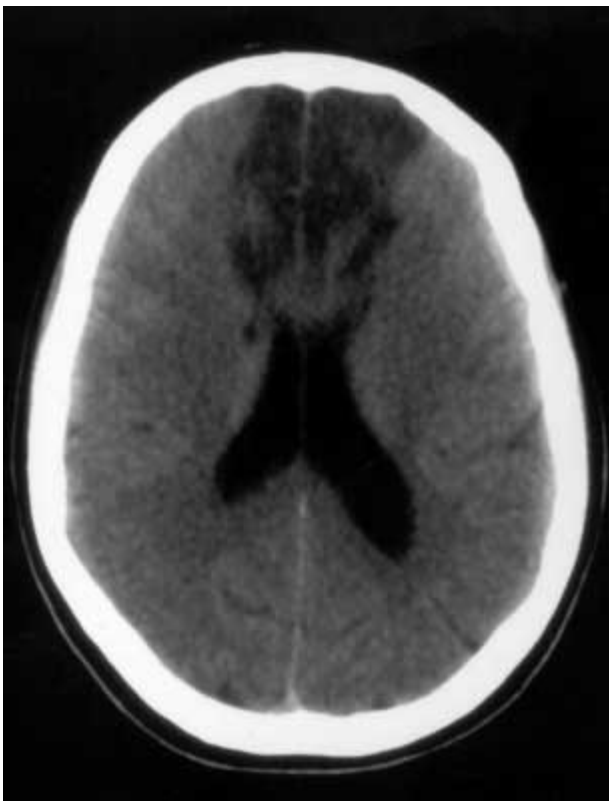

FIG. 1. — CT scan of the brain without contrast, at admission, showing bilateral hypodensities in the territory of both anterior cerebral arteries.

The patient was treated with an oral dose of 160 mg acetylsalicylic acid daily. After 8 weeks of revalidation, she recovered progressively a normal speech output. She was again able to walk alone. However she didn't retrieve her previous level of autonomy since, she became dependent for all daily activities. Urinary and faecal incontinence were present. Neuropsychologic tests were consistent with a persistent frontal syndrome.

Discussion

Patients with DS show an increased risk for stroke. In the majority of the cases, the strokes are secondary to cerebral embolism stemming from atrioventricular defects, right-to-left shunting, myocardial dysmobility or valvular abnormalities. An increased proneness to meningitis and bacterial endocarditis predisposes also these patients to make strokes (Pearson *et al*., 1985). More recently, it was determined that strokes can also result from moyamoya vasculopathy. MMS has been estimated to be more frequent in children with DS than in a general paediatric population. Fukushima *et al*. (1986) report this association in one case out of 532 DS. The incidence of MMS in DS is about three time greater than in the general population (0,07%). Since 1977, when this association was

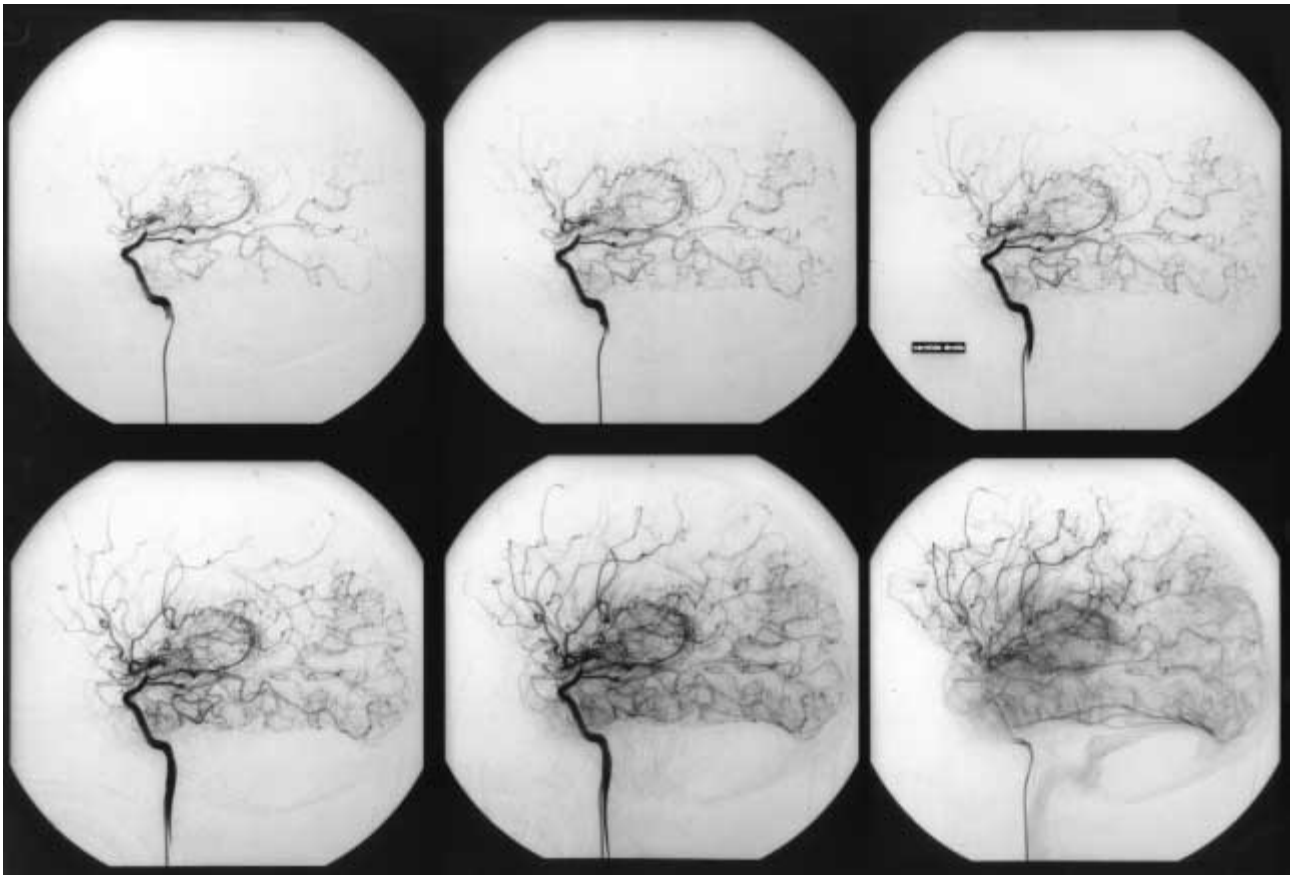

FIG. 2. — Right internal carotid angiogram. Occlusion of the internal carotid in the supraclinoid portion associated with extensive parenchyrnal (moyamoya) collaterals.

described for the first time, more than twenty case reports have been published, especially in young children (Cramer *et al.,* 1996 ; Soto-Ares *et al*., 1996 ; Nagasaka T. *et al*., 1996 ; Takeda *et al*., 1997 ; Dai *et al.,* 2000 ; Del-Rio Camacho *et al*., 2001). The average age of onset is 7 years in a series of seven cases (Cramer *et al*., 1996), similar to the average age (6 years) of other patients reported in the literature. Case reports concerning adults with DS are rarer (Leno *et al*., 1998 ; Park *et al*., 1996). The clinical features are similar to those of primary MMD. Hemiplegia is the most common mode of presentation in children. Transient, and often recurrent, weakness is common. One patient had a chorea (Takanashi *et al.,* 1993). In our patient, the presentation mode was unusual because of the age of onset, the absence of motor deficit or of any previous symptom. Bilateral anterior cerebral artery stroke was not previously described as far as we know. Intra-axial and extra-axial haemorrhages are most often described in adults, but are rare in trisomy 21. Ischemic stroke in MMD affects the cerebral cortex, often in watershed areas (Bruno *et al*., 1988) and deeper structures as well. Brain imaging demonstrates multiple bilateral infarcts, less often in the posterior circulation.

This pattern was seen in our patient. Angiographic features were similar to those observed in primary MMD.

The diagnosis of MMD is based on three main criteria (1) stenosis or obstruction of the distal intracranial segment of the internal carotid arteries and the proximal anterior and middle cerebral arteries, (2) abnormal vascular network (moyamoya) on the arterial side near the obstruction or stenosis, arising from lenticulostriate and thalamoperforate arteries and (3) exclusion of meningitis, sickle cell disease, tumor, traumatism or radiation therapy. Although unilateral presentations of MMD have been reported (Olds *et al*., 1987 ; Gaggero *et al*., 1996), bilateral involvement is considered as another criterion of diagnostic.

Therapeutic attitude is debated. Some authors recommend only a medical treatment with acetylsalicylic acid, others favour surgical treatment. Anticoagulants are ruled out considering the potential risk for haemorrhages. Surgical treatment for MMD is basically an attempt to revascularize areas of cerebral ischemia (Matsushima *et al*., 1992). Techniques used are encephalo-arterio-synangiosis, encephalo-myosynangiosis, superficial temporal to middle cerebral artery anastomosis and omental transplantation. Actual results are not completely satisfactory and the attitude to adopt remains a matter of controversy.

Pathological changes in moyamoya patients include intimal thickening with fibrous tissue, abnormalities of internal lamina elastica, variable lipid deposition and virtual absence of inflammatory reaction in the blood vessels (Takebayashi *et al*., 1984). One neuropathological examination of the brain of a 4-year-old child with DS and stroke showed intimal thickening with collagen deposition, all histological features characteristic of MMD (Mito and Becker, 1991). It was demonstrated that the frequency of abnormalities of the circle of Willis in patients with DS is higher than in patients with isolated congenital heart disease. Other vascular abnormalities are also frequently observed in DS including abnormal nail-bed capillary loops and renovascular hypertension (Jansen *et al*., 1990). These findings suggest that in DS there exists an abnormality of vascular development, which also plays a role in the pathogenesis of MMD. It has been submitted that a protein encoded on chromosome 21 might be linked to the pathogenesis of MMD (Cramer *et al.,* 1996). A role for collagen in the genesis of MMD is suggested by the report of a familial form associated with abnormal connective tissue (Richman *et al.* 1977). Collagen type VI, found in the intima of large arteries and increased in cerebral arteries as a result of some vascular insults, has its α-chains encoded on chromosome 21. Excessive vascular thickening may be related to overexpression of collagen type VI in some forms of MMS especially in case associate with DS. More recently, the higher frequency of autoimmune processes and autoantibodies in trisomy 21 patients was thought to play a role in the pathogenesis of MMS. Moreover, MMD itself has been associated with antiphospholipid antibodies (Fujiwara *et al.,* 1993). According to these authors, MMS could result from an immune disturbance that will cause a non-specific vascular reaction (Leno *et al.,* 1998). In our patient, no autoantibodies were detected and the patient did not have any other autoimmune disease.

In conclusion, the association between DS and MMS is now well documented. If a patient with DS has a stroke, it is important to know about this association in order to make a correct diagnosis and establish the appropriate treatment. The evaluation must include a cerebral angiography. The reason of this association is still unknown. It may provide a good opportunity for better understanding how idiopathic MMS and MMS associated with trisomy 21. The hypothesis of a protein (collagen type VI) encoded on chromosome 21 which could be implicated in the pathogenesis needs further studies. The autoimmune hypothesis should be reevaluated as well.

REFERENCES

Bruno A., Adams H. P., Biller J., Rezai K., Cornell S., Aschenbrener C. A. Cerebral infarction due to moyamoya disease in young adults. *Stroke*, 1988, **19** : 826-833.

Cramer S. C., Robertson R. L., Dooling E. C., Scott R. M. Moyamoya and Down syndrome

Clinical and radiological features. *Stroke*, 1996, vol. 27, **11** : 2131-2135.

DAI A. I., SHAIKH Z. A., COHEN M. E. Early onset Moyamoya syndrome in a patient with Down syndrome : case report and review of the literature. *J. Child Neurol*., 2000, **15** : 696-699.

DEL-RIO CAMACHO G., OROZCO A. L., PEREZ-HIGUERAS A., CAMINO LOPEZ M., AL-ASSIR I., RUIZ-MORENO M. Moyamoya disease and sagittal sinus thrombosis in a patient with Down's syndrome. *Pediatr. Radiol*., 2001, **31** : 125-128.

FUJIWARA S., MIYAZONO M., TSUDA H., FUKUI M. Intraventricular hemorrhage and cerebral ischernic attacks in the presence of lupus anticoagulant mimicking moyamoya disease. *J. Neurosurg. Sci*., 1993, **37** : 161-164.

FUKUSHIMA Y., KONDO Y., KUROKI Y., MIYAKE S., IWAMOTO H. *et al*. Are Down syndrome patients predisposed to moyamoya disease ? *Eur. J. Pediatr*., 1986, **144** : 516-517.

GAGGERO R. TORTORI DONATI P., CURIA R., DE NEGRI M. Occlusion of unilateral carotid artery in Down syndrome. *Brain Dev.*, 1996, **18** : 81-83.

JANSEN J. N., DONKER A. J., LUTH W. J., SMIT L. M. Moyamoya disease associated with renovascular hypertension. *Neuropediatrics*, 1990, **21** : 44-47.

LENO C., MATEO I., CID C., BERNACIO J., SEDANO C. Autoimmunity in Down's syndrome : another possible mechanism of moyamoya disease. *Stroke*, 1998, vol. 29, **4** : 868-869.

MATSUSHIMA T., INOUE T,. SUZUKI S.O., FUJII K., FUKUI M., HASUO K. Surgical treatment of moyamoya disease in paediatric patients – comparison between the results of indirect and direct revascularization procedures. *Neurosurgery*, 1992, **31** : 401-405.

MITO T., BECKER L. E. Vascular dysplasia in Down syndrome : a possible relationship to moyamoya disease. *Brain Dev.,* 1992, vol. 14, **4** : 248-251.

NAGASAKA T., SHIOZAWA Z., KOBAYASHI M., SHINDO K., TSUNODA S., AMINO A. Autopsy findings in Down's syndrome with cerebrovascular disorder. *Clin. Neuropathol*., 1996, **15** : 145-149.

OLDS M. V., GRIEBEL R. W., HOFFMAN H. J., CRAVEN M., CHUANG S., SCHULTZ H. The surgical treatment of childhood moyamoya disease. *J. Neurosurg*., 1987, **66** : 675-680.

PARK M. J., RAILA F. A., RUSSEL W. F. Moyamoya disease in an adult with Down syndrome : comparison of magnetic resonance angiography and conventional angiography. *South Med. J*., 1996, vol. 89, **1** : 89-92.

PEARSON E., LENN N. J., CAIL W. S. Moyamoya and other causes of stroke in patients with Down syndrome. *Pediatr. Neurol*., 1985, **1** : 174-179.

RICHMAN D. P., WATTS H. G., PARSON D., SCHMID K., GLIMCHER M. J. Familial moyamoya associated with biochemical abnormalities of connective tissue. *Neurology*, 1977, **27** : 382.

SUZUKI J., KODAMA N. Moyamoya disease : a review. *Stroke*, 1983, **14** : 104-109.

SOTO-ARES G., HAMON-KERAUTRET, M. LECLERC X., VALLEE L., PRUVO J. P. Moyamoya associé d'un syndrome de Down. *J. Radiol*., 1996, **77** : 441-444.

TAKANASHI J., SUGITA K., HONDA A., NUMI H. Moyamoya syndrome in a patient with Down syndrome presenting with chorea. *Pediat. Neurol*., 1993, **9** : 396-398.

TAKEBAYASHI S., MATSUO K., KANEKO M. Ultrastructural studies of cerebral arteries and collateral vessels in moyamoya disease. *Stroke*, 1984, **15** : 728-732.

TAKEDA K., TAKAHASHI S., HIGANO S., KURIHARA N., HAGINOYA K. *et al*. Cortical laminar necrosis in a patient with moyamoya associated with Down syndrome : MR imaging findings. *Radiat. Med*., 1997, **15** : 59-63.

V. DE BORCHGRAVE,
Centre Neurologique William Lennox,
Allée de Clerlande, 6,
B-1340 Ottignies (Belgium).
E-mail : debarsy@nops.ucl.ac.be