

year.¹ This is similar to the pediatric population's baseline risk of stroke. The exact etiology of migraine stroke is uncertain. Stroke is more common in migraine with aura and has a predilection for the posterior circulation. The etiologies of these events have been based on abnormal vascular tone and increased platelet aggregability associated with migraine headaches. In a report by Bogousslavsky et al,¹⁹ it was determined that migraine itself was the most important phenomenon causing cerebral infarction. It is also important to note that this study did not find arterial wall dissection to be the cause of stroke during a migraine attack.

The incidence of transient neurologic deficits with migraine is much more common. Neurologic dysfunction in classic migraine has a predilection for the posterior circulation. Caplan, in a review on migraine and vertebrobasilar ischemia,¹⁶ describes severe vasoconstriction to the point of occlusion in the vertebral and the basilar artery, but he does not discuss arterial wall dissection of the cervicocephalic arteries as related to migraine. Angiography during migraine has demonstrated marked vascular spasm, which can then lead to significant trauma to the intima and media of the vessel.¹⁵ Although arterial wall dissection has not been found to be the cause of stroke acutely, perhaps recurrent arterial injury due to vasospasm makes arterial wall dissection and subsequent stroke more likely.

Arterial wall dissection is the cause of stroke in 5% to 20% of young patients.²⁰ In addition to eliciting a history for possible trauma, the patient also should be screened for risk factors of spontaneous arterial wall dissection, including migraine headaches. Conversely, if a patient presents with an atypical migraine, especially in conjunction with persistent neurologic findings, the possibility of arterial wall dissection should be considered and additional neuroradiologic imaging explored.

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Early-Onset Moyamoya Syndrome in a Patient With Down Syndrome: Case Report and Review of the Literature

ABSTRACT

Moyamoya disease is a chronic occlusive cerebrovascular disorder. It can occur as a primary disease or as a syndrome associated with a variety of conditions. Usually it takes 1 to 2 years to develop a classic moyamoya pattern. We report a 20-month-old girl with Down syndrome and moyamoya syndrome who presented with seizure and hemiparesis. To our knowledge, this is the youngest case reported with moyamoya syndrome and Down syndrome. The prognosis and current treatment of moyamoya syndrome and its relation to Down syndrome are reviewed. There is some reason to speculate that the abnormalities associated with Down syndrome might create a vulnerability for the development of moyamoya syndrome. (*J Child Neurol* 2000;15:696-699).

Moyamoya disease (or syndrome) is a slowly progressive cerebrovascular insufficiency, which becomes symptomatic when developing arterial collaterals fail to compensate for ischemia produced from bilateral stenosis or occlusion of the intracranial carotid arteries at their bifurcation into the middle and anterior cerebral arteries. This results in an inefficient arterial network feeding the basal ganglia. This process initially involves the basal portion of the internal carotid arteries with subsequent progression to involve other arterial channels making up the circle of Willis.

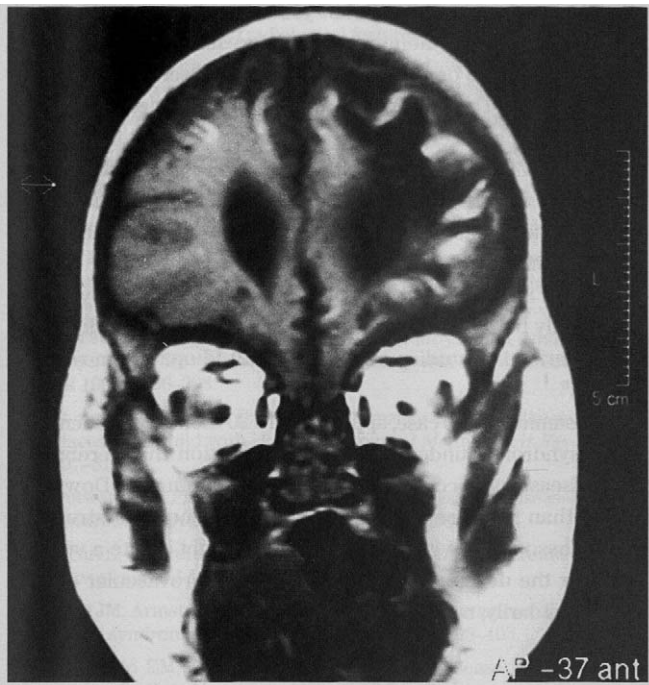


Figure 1. T₁-weighted magnetic resonance images in the coronal projection showing left hemispheric cortical atrophy and areas of encephalomalacia with porencephaly (TE:20; TR:450).

Secondarily, small-vessel collateralization develops distal to the stenosis or occluded vessels. Neuroimaging with either magnetic resonance angiography (MRA) or conventional angiography confirms the diagnosis by visualizing the stenosis or the occlusion of the terminal portion of the internal carotid arteries. The entire development of a moyamoya disease pattern usually occurs over 1 to 2 years.¹

Moyamoya disease occurs with a bimodal onset. A peak in children in the latter half of the first decade of life is associated with ischemic strokes, and a peak in adults in the fourth decade is associated with hemorrhagic strokes. Hemiparesis is the most common symptom of presentation in both groups.^{2,3} Hemorrhagic stroke occurs less and ischemia more frequently in American than in Japanese patients.^{4,5}

In children, the disease can present either with frequent transient ischemic attacks manifesting as seizures (in 70% to 80%) or motor disturbance secondary to ischemia (in 20% to 30%).⁶ Moyamoya disease can occur in patients with sickle cell anemia, neurofibromatosis, Sjögren's syndrome, radiation therapy, tuberculous meningitis, and Down syndrome, among others.⁷ This should be termed moyamoya syndrome, rather than moyamoya disease, which is considered a separate, idiopathic entity.

Patients with Down syndrome are known to develop moyamoya syndrome; however, this is rare. In the English-language literature 23 pediatric cases have been reported.⁷⁻²¹ The average age at onset of affected patients with Down syndrome is approximately 7 years.⁷⁻²¹ We report Down syndrome with moyamoya syndrome in a 20-month-old girl. To our knowledge, this is the youngest patient reported with moyamoya syndrome and Down syndrome.

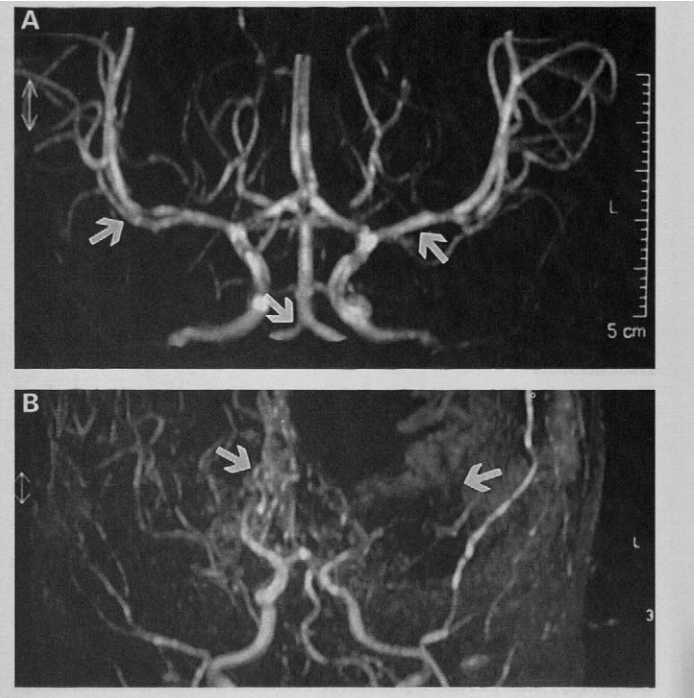


Figure 2. A, Magnetic resonance angiography of a healthy 16-month-old girl showing normal distribution of the circle of Willis. Arrows point to the normal middle cerebral and basilovertbral arteries. B, MRA of our patient. The arrow points to abnormally proliferated thalamostriate vessels. The arrow on the left indicates limited blood flow in left middle cerebral artery distribution.

Case Report

A 20-month-old girl with Down syndrome was referred for investigation of episodes of stiffening of her arms and legs. Two days prior to admission, she developed respiratory symptoms secondary to active respiratory syncytial virus bronchiolitis and hypoxia. She was admitted to the intensive care unit and placed on albuterol and prednisone.

Her medical history included surgical repair of an atrioventricular canal defect, ventriculoperitoneal shunt placement for hydrocephalus, a gastrostomy tube placement for vocal-cord paralysis, and a right diaphragmatic plication. Chromosome studies confirmed trisomy 21. At 14 months of age, following a 24-hour prodrome of malaise, vomiting, and dehydration secondary to viral gastroenteritis, she was found to have right-extremity weakness. She was febrile (38.7°C) and had decreased movements of the right arm and leg. Serum electrolytes, glucose, and noncontrast computed tomographic scan of the head were normal. The weakness fluctuated without clearing over the next 6 months.

Evaluation at 20 months showed an irritable, retarded child with stigmata of Down syndrome. Significant decreased spontaneous movements of the right arm and leg were noted. She was afebrile, had a grade 4 systolic ejection murmur, and moderate respiratory distress. Cranial nerves were normal except for a right visual field defect. Strength was markedly decreased in all the muscle groups of the right arm and leg. Grip was weaker on the right side. Deep tendon reflexes were pathologically increased, including sustained ankle clonus. A Babinski reflex was present.

Hospital course was complicated by multiple staring spells and episodes of generalized tonic stiffness. An electroencephalogram showed poorly developed background activity with slow-wave and high-voltage beta activity in the left centrotemporal area. She was treated with phenobarbital.

Magnetic resonance imaging of the brain was consistent with an infarct in the distribution of left middle and anterior cerebral arteries. Cortical atrophy and areas of encephalomalacia were also observed in the same areas (Figure 1). MRA of the brain revealed abnormal flow in the left

middle cerebral artery distribution and to a lesser extent in the distribution of the right middle cerebral artery. The distal anterior cerebral arteries were also involved. The thalamostriate vessels were thinner and increased in number, suggesting early moyamoya syndrome (Figure 2).

The patient was discharged home 2 weeks later with minimal improvement of the right-sided weakness. A right homonymous hemianopia persisted. She remained on gastric tube feedings.

Six months later, at the age of 26 months, because of a progressive left spastic hemiparesis, and in an effort to reverse the vascular defect, she underwent an encephaloduroarteriosynangiosis. She remains stable without further episodes. We cannot be sure if the stabilization is a result of the surgery.

Discussion

Children with Down syndrome are at increased risk for cerebral infarction. In the majority of cases, the strokes are secondary to cerebral embolism, originating from atrioventricular canal defects, right-to-left shunting, myocardial dysmotility, or cardiac valvular abnormalities. An increased susceptibility to bacterial infection, including meningitis, septicemia, and subacute bacterial endocarditis, also can lead to cerebrovascular occlusion and stroke. Leukemia is a less common mechanism for stroke in Down syndrome. Upper cervical subluxation, associated with atlantoaxial instability, can produce posterior cerebral circulation ischemia. There remain cases of stroke in Down syndrome for which the etiology and pathogenesis have not been ascertained. As reported in this case, stroke, and subsequently moyamoya syndrome, can occur in children with Down syndrome. Moyamoya syndrome can result from hemodynamic ischemic effects secondary to mechanical compression in the cervical spine and from intrinsic vessel wall abnormality.¹¹

The association between congenital heart disease and moyamoya syndrome remains conjectural.¹⁸ Structural abnormalities in vessels of the circle of Willis in patients with Down syndrome suggest a possible underlying mechanism for the development of ischemic cerebrovascular disease and subsequently moyamoya syndrome.²⁶ The histopathology of affected arteries in moyamoya syndrome shows an irregular internal elastic membrane surrounding regions of marked endothelial hyperplasia.¹¹

Patients with Down syndrome are known to have a predisposition for vascular disease. These consist of abnormal nail-bed capillary morphology,²² high pulmonary vascular resistance and congenital heart disease,²³ abnormalities of retinal vessels,²⁴ and primary intimal fibroplasia.²⁵

Chromosome 21 is a logical candidate to house the moyamoya gene. This chromosome has been identified with genes that code for the α -chains of collagen type VI. This type of collagen has been associated with an increased risk for cerebrovascular disease. Several proteins affecting arterial physiology, such as superoxide dismutase I, the interferon gamma receptor, and cystathionine β -synthase, all of which are associated with an increased risk for vascular disease, are also encoded on chromosomal 21.^{8,27-33}

A genetic component for the etiology of such cases is suggested by the occasional familial occurrence and a significant association with the histocompatibility locus antigen (HLA) types Aw24, Bw46, and Bw54.³⁴

Fukuyama et al³⁶ have collected the reports of 19 patients with Down syndrome and moyamoya syndrome from the world litera-

ture. Except for an adult, aged 27 years, and a 13-year-old patient with an intracranial hemorrhage, 17 presented with transient ischemic episodes or cerebral infarction between 23 months and 15 years of age. The average age at onset in this series was 5 years.

Aspirin has been used prophylactically with little demonstrated benefit, as in this case. Empirical corticosteroid therapy has been given when there are frequent ischemic attacks or involuntary movements. Surgical revascularization, as with our patient, has been recommended in progressive cases.⁷

Motor recovery in Down syndrome with moyamoya syndrome is generally better, even after multiple and bilateral strokes, than that described in studies of patients with idiopathic moyamoya disease.⁸

In summary, this case, appearing in a 20-month-old patient with Down syndrome, underscores the observation that cerebrovascular disease can occur earlier in life in children with Down syndrome than in those without Down syndrome. The structural defects associated with Down syndrome might create a vulnerability for the development of ischemic cerebrovascular disease and, secondarily, moyamoya syndrome.

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Asperger's Syndrome, X-Linked Mental Retardation (MRX23), and Chronic Vocal Tic Disorder

ABSTRACT

Pervasive developmental disorders are severe disorders of development with no consistent neurobiologic etiology and most often an idiopathic etiology. We report a 12-year-old male who met criteria for a pervasive developmental disorder (Asperger's syndrome) and a chronic tic disorder. The child also has an X-linked cognitive impairment (MRX23). The presence of tic symptomatology, pervasive developmental disorder, and fragile X syndrome has previously been reported. Since no singular etiology for Asperger's syndrome has been found, the possibility of other cases of Asperger's syndrome occurring with concurrent abnormalities on the X chromosome should be considered by clinicians, especially if tic symptomatology is present. (*J Child Neurol* 2000;15:699–702).

Pervasive developmental disorders are a group of severe developmental disorders that include autism, Rett's syndrome, Asperger's syndrome, and childhood disintegrative disorder. Pervasive developmental disorders are distinguished and classified by their symptomatologic presentation with autism as the most prevalent and therefore the most studied. Singular etiologies for autism, Asperger's syndrome, and other pervasive developmental disorders remain obscure, although there is evidence of a substantial genetic vulnerability for these disorders. For instance, the recurrence risk of autism in siblings of children with autistic probands is 2% to 5%.^{1–4} This represents about a 50-fold increase in risk over the general population where the population prevalence is 1 in 2500 or 0.04%.^{3,4} In families with multiple cases of autism, the recurrence risk is about 8%, which is over 200 times the general population risk.⁵ The average concordance risk from several twin studies is 3% to 9% for dizygotic twins and 64% to 81% for monozygotic twins.^{1,2,4,6} The monozygotic/dizygotic twin concordance ratio is 25.⁴ Although genetic disorders are commonly reported with autism, no genetic disorder is uniformly associated with autism or any other pervasive developmental disorder, and similar cases of autism occur in children with and without known genetic disorders.

Asperger's syndrome is a pervasive developmental disorder characterized by marked problems in social interactions, all-absorbing narrow interests, adherence to inflexible routines, and abnormalities of motor behavior.⁷ The current diagnostic criteria for Asperger's syndrome according to the *Diagnostic and Statistical Manual of Mental Disorders-IV* are presented in Table 1. The prevalence rate of Asperger's syndrome has been reported by Ehlers and Gillberg to be 28.5 per 10,000.⁸

Two previous cases of Asperger's syndrome have been reported in patients with chromosomal abnormalities. Asperger's syndrome was reported in a boy with a balanced de novo translocation t(17;19)(p13.3;11).⁹ A second case was reported in a girl with an autosomal fragile site fra(2)(q13) and tic symptomatology.¹⁰

Given the variability seen in all types of pervasive developmental disorders, even in groups of children who have the same genetic disorder, it seems likely that the etiology is multifactorial