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Hypomelanosis of Ito and Moyamoya Disease

ABSTRACT

Moyamoya disease is a cerebrovascular disease characterized by stenosis and occlusion of the arteries of the circle of Willis, with abnormal telangiectatic collateral circulation at the base of the brain. An association between moyamoya disease and neurofibromatosis 1, a neurocutaneous disorder, is well established in the literature. However, its association with other neurocutaneous syndromes is infrequently reported. Hypomelanosis of Ito, another neurocutaneous syndrome, is characterized by macular hypopigmented skin whorls and variable neurologic involvement. Only one case study of an association between hypomelanosis of Ito and moyamoya disease has been reported in the English literature. We report a 17-year-old girl with both hypomelanosis of Ito and angiographic moyamoya disease. She presented with intractable seizures, progressive left hemiparesis, and skin manifestations of hypomelanosis of Ito. Although one might consider a coincidental association, this second case points to an association between the two disorders. Detailed neuroimaging, in particular angiography, should be considered in children with hypomelanosis of Ito and abnormal neurologic findings. (*J Child Neurol* 2005;20:924–926).

Moyamoya disease has been reported to occur in association with specific neurocutaneous syndromes, including neurofibromatosis 1, tuberous sclerosis complex, incontinentia pigmenti, and encephalotrigeminal angiomatosis.^{1–4} According to the published literature, only one case was described to have both hypomelanosis of Ito and moyamoya disease.⁵ Hypomelanosis of Ito is a neurocutaneous syndrome, first described by Ito in 1952.⁶ It is characterized by a distinct pattern of skin involvement consisting of hypopigmented streaks and whorls, predominantly on the extremities and the trunk. A wide range of neurologic manifestations have been described with hypomelanosis of Ito.^{7,8} However, the most prevalent neurologic features include mental retardation and seizures. We report a second case of hypomelanosis of Ito with neurologic manifestations and angiographic moyamoya disease.

Case Report

A 17-year-old girl was evaluated in our tertiary care neurology clinic. She was born as a second dizygotic twin to a 30-year-old mother. The pregnancy and delivery were uneventful. Her twin sister and two male siblings, aged

21 and 22 years, were well. Although the patient's gross and fine motor milestones were achieved within the normal range, her cognitive and language development was noted to be slightly slower compared with that of her twin. Areas of abnormal skin pigmentation were first noted when she was 2 years old. At age 3 years, she had febrile and later afebrile seizures consisting of left-sided focal tonic-clonic seizures with secondary generalization. Her neurologic examination at that time was normal. Her electroencephalogram (EEG) showed right hemisphere slowing. The computed tomographic (CT) scan of the brain with and without contrast was normal. The patient was treated with carbamazepine. Three weeks later, she presented with another episode of left partial seizures associated with persistent left hemiparesis. On general examination, she was noticed to have dysmorphic features, including a high forehead, frontal bossing, hypoplasia of the supraorbital ridges, depressed nasal bridge, and hypertelorism. She had whorl-like hypopigmented areas spread over the trunk and limbs. Some of the hypopigmented lesions on the back resembled Blaschko lines. Her neurologic examination revealed poor short-term memory and cognitive delay, especially in terms of general knowledge, the ability to read, and mathematical concepts. The fundi, extraocular movements, visual fields, and cranial nerve examination were normal. She had moderate left-sided hemiparesis with increased tone and reflexes. Her plantar responses were downgoing bilaterally. Repeat CT scan of the brain with and without contrast was normal again. A radionuclide brain perfusion scan revealed a focal perfusion defect in the right posterior frontal region. Her chromosomal analysis at that time demonstrated a mosaic female karyotype with two cell lines involving the short arm of chromosome 6 [46,XX, inv(6) (p21p25)/46,XX,6p+]. The chromosomal analysis of her parents revealed a normal karyotype, suggesting de novo occurrence of an abnormal chromosome. Based on the skin findings, the diagnosis of hypomelanosis of Ito was made (Figure 1). An increase in the carbamazepine dose resulted in seizure remission. Her left hemiparesis also improved over several months, with residual subtle left hemiparesis. A trial of discontinuation of carbamazepine after 2 years of seizure remission resulted in seizure recurrence with worsening of the left hemiparesis. Magnetic resonance imaging (MRI) and magnetic resonance angiography at that time revealed cortical and subcortical signal abnormalities in the right frontal and parietal areas suggestive of ischemic infarction and the presence of moyamoya disease (Figure 2A). An EEG showed generalized slowing of the background activity with focal intermittent slowing over the right frontal and occipital regions.

The patient continued to be followed closely in our epilepsy clinic, but the family refused further imaging to delineate the vascular abnormality. At the age of 11 years, the family agreed to further evaluation and a conventional digital subtraction angiogram was performed. The cerebral angiogram showed marked narrowing of the proximal branches of the internal carotid arteries. In addition, there was extensive collateralization from the internal carotid arteries to the branches of the middle and anterior cerebral arteries and extensive collateralization between the middle cerebral artery branches and the external carotid arteries (Figure 2B). A repeat MRI showed additional ischemic changes involving the right frontal and parietal lobes, as well as the medial temporal region on the left side. Shortly thereafter, the patient underwent a bilateral revascularization procedure on the left side first and then the right side 3 weeks later.

Postoperatively, she remained seizure free on carbamazepine. The left hemiparesis had somewhat improved following the surgery. However, significant impairment in both cognition and speech persisted. A follow-up MRI showed no new abnormality after the surgery. A follow-up EEG showed intermittent frontotemporal slowing with no epileptiform discharges. She did not have any recurrent ischemic events after the surgery.

Discussion

Our patient is the second patient reported in the English literature to have both moyamoya disease and hypomelanosis of Ito. It is of note that the two reported patients are both females. Although in hypomelanosis of Ito, there is no sex difference in frequency, in moyamoya disease, a slight female predominance has been reported.^{9,10}

Moyamoya disease is a cerebrovascular disease that is characterized by progressive stenosis or occlusion of the distal internal carotid and proximal portions of the anterior and middle cerebral arteries with the forma-

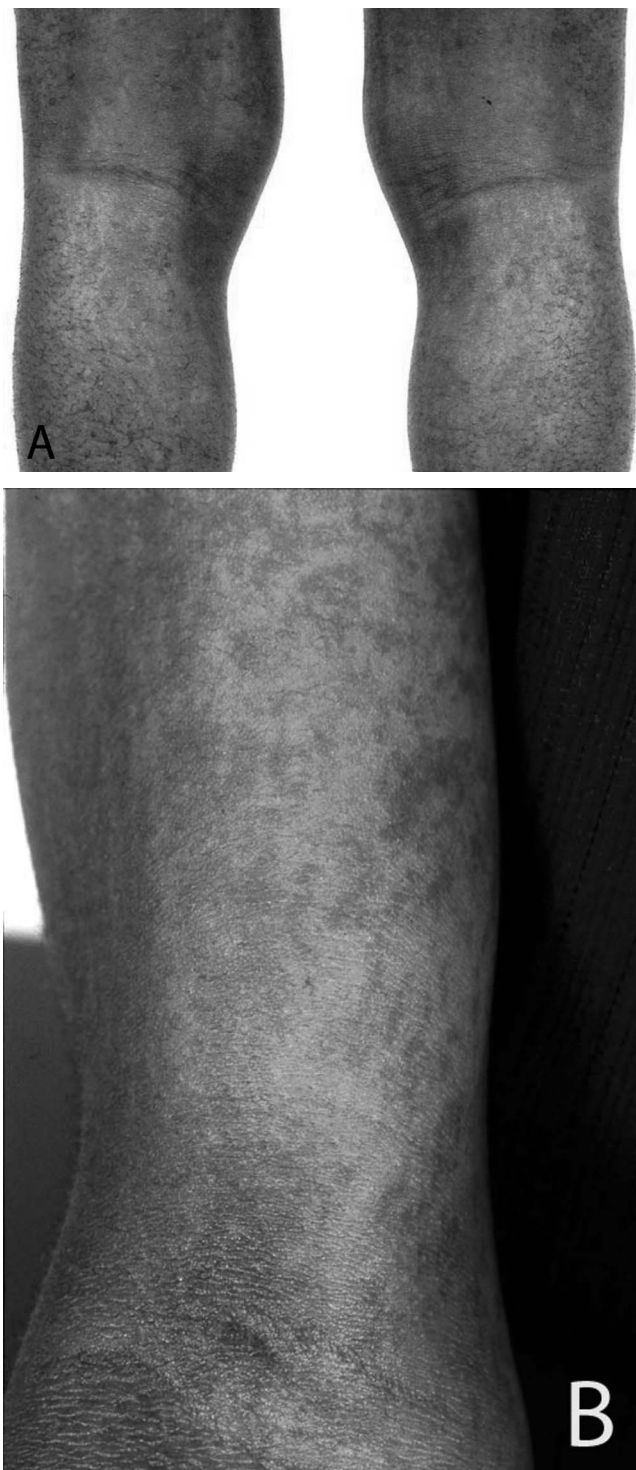


Figure 1. *A and B*, A 17-year-old girl with whorled macular hyperpigmented of hypomelanosis of Ito on the flexor aspects of the arms and hypopigmented streaks on the flexor aspects of the legs.

tion of extensive collateral vessels. It can be idiopathic or can be found in association with other systemic diseases or syndromes, in particular neurocutaneous and chromosomal disorders.^{9,10} The published literature mainly supports a strong relationship between neurofibromatosis 1 and moyamoya disease.³ Of note is the postradiation vascular sensitivity of patients with neurofibromatosis 1 who then subsequently develop angiographic moyamoya disease.¹¹ Its association with other neurocutaneous syndromes, such as

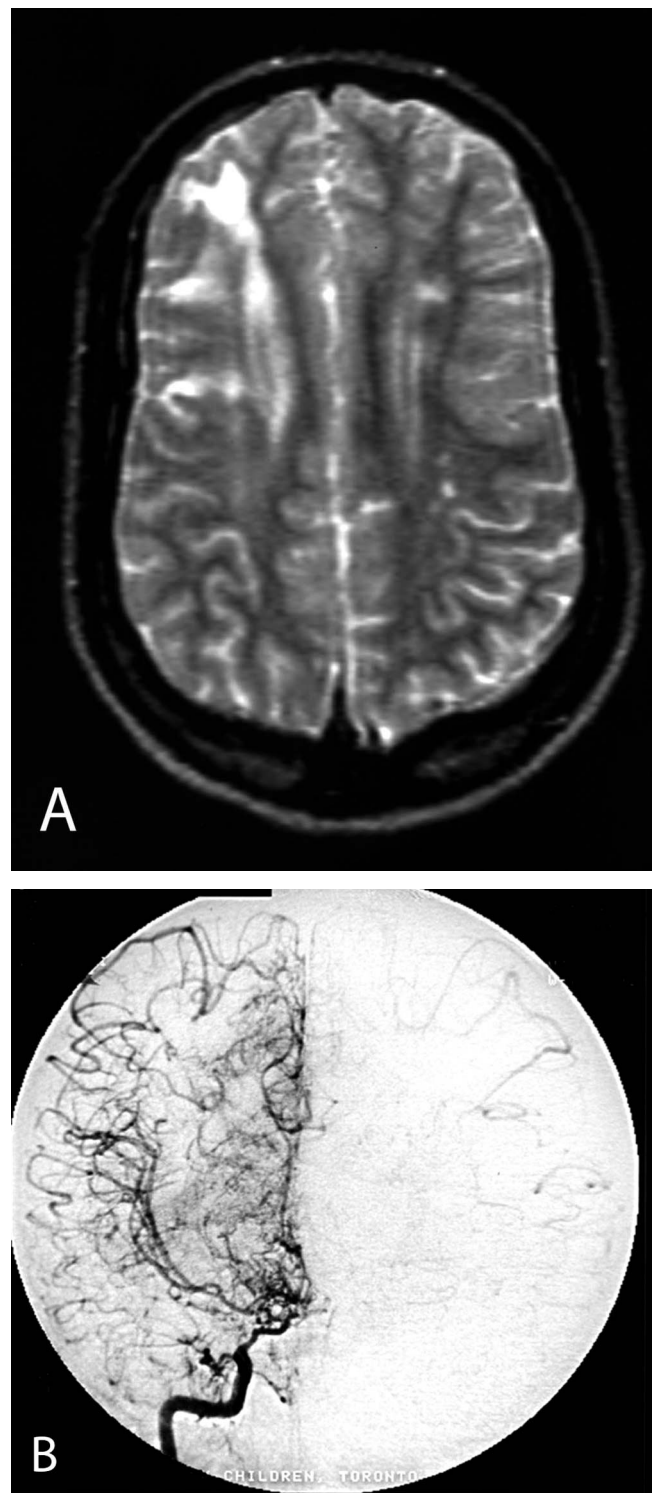


Figure 2. Fluid-attenuated inversion recovery axial unenhanced brain magnetic resonance image of the patient showing cortical and subcortical signal abnormalities in the right frontal and parietal areas. Subcortical signal abnormalities are also visible in the left hemisphere (*A*). Digital subtraction catheter angiography on right internal carotid artery injection reveals the presence of internal carotid artery stenosis and occlusion with abnormal collateral vessels (*B*).

tuberous sclerosis complex, incontinentia pigmenti, and encephalotrigeminal angiomatosis, is infrequent.¹⁻⁴ Some authors use the term "moyamoya syndrome" when it is associated with a systemic disease.¹² However, the term

"a systemic disease with angiographic moyamoya" has been suggested to replace moyamoya syndrome. This confusion in terminology is likely to persist until the etiology of idiopathic moyamoya disease is fully established.¹³

The pathogenesis of moyamoya disease remains poorly understood, and the etiology is largely unknown. Genetic factors have been implicated given the higher occurrence of the disease in Japan and Korea and the familial occurrence in both Japanese and Caucasian populations. A linkage was found between the disease and markers located on chromosomes 3, 6, and, more recently, 17.¹⁴⁻¹⁶ Hypomelanosis of Ito is often associated with chromosomal mosaicism. The most common mosaicism is trisomy 18, sex-chromosome aneuploidy, triploidy, and tetrasomy 12p.¹⁷⁻¹⁹ Our patient had mosaicism of chromosome 6, which might suggest possible associations with moyamoya disease because some cases of moyamoya disease are also linked to the same chromosome.¹⁵

A single case of hypomelanosis of Ito and moyamoya disease has been reported in the literature.⁵ Although that article suggested an association between the two disorders, it was hypothesized that this coexistence might be coincidental. Furthermore, it was postulated that the venous and arterial occlusion might be secondary to some unrecognized biologic deficit affecting coagulation. Our patient had a normal coagulation work-up and no other evidence of a coagulopathy, therefore excluding this possibility. The previously published case and our patient might favor an association between the two diseases, but the mechanism of development of moyamoya vessels remains unknown.

Our patient continued to demonstrate significant cognitive and language deficits despite the success of surgical intervention in halting further neurologic damage caused by the vascular anomaly. A decline in the IQ of children with symptomatic moyamoya disease has been reported.²⁰ Moreover, hypomelanosis of Ito has been associated with significant cognitive impairment and mental retardation. In one study, more than 60% of the patients were found to be mentally retarded, with an IQ below 70, and about 15% were described as borderline retarded.²¹ In our patient, the dual pathology could have contributed to the significant cognitive delay.

It is likely that an association might exist between the two disorders, with two cases now reported in the literature. This conclusion is supported by the lack of other predisposing factors to moyamoya disease. Furthermore, an early and detailed neuroimaging work-up, including angiography, might be valuable in hypomelanosis of Ito, particularly in patients presenting with unexplained focal neurologic deficits and intractable seizures.

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Hippocampal Dysgenesis Associated With Temporal Lobe Hypoplasia and Arachnoid Cyst of the Middle Cranial Fossa

ABSTRACT

We describe two children with left hippocampal dysgenesis in association with temporal lobe hypoplasia and arachnoid cyst of the middle cranial fossa. The hippocampus showed an abnormal globular shape and blurred internal structure in both patients. One of the patients had juvenile myoclonic epilepsy without evidence of seizure onset in the abnormal temporal region. The other patient did not have epilepsy; however, he showed developmental language disorder with a probable relationship to the left temporal abnormalities. (*J Child Neurol* 2005;20:926-930).