

Case report

Cardio-facio-cutaneous syndrome and moyamoya syndrome

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Abstract

We reported a patient with cardio-facio-cutaneous (CFC) syndrome associated with moyamoya syndrome. The patient was referred at 6 years 5 months with left hemiplegia and right-sided eye deviation. He had an apparently short stature, macrocephaly, left ptosis and atopic skin, and was odd looking. He exhibited an incomplete right bundle branch block on electrocardiogram and an atrial septal defect on ultrasound cardiography. He was diagnosed as having CFC syndrome. Head magnetic resonance imaging showed a flow void in the bilateral basal ganglia, but did not show any ischemic changes. Magnetic resonance angiography showed bilateral stenosis with an internal carotid artery at the Willis artery ring level and bilateral moyamoya. Contrast angiography demonstrated occlusion of both middle cerebral arteries. Cerebrovascular anomalies have not previously been reported in CFC syndrome. This is the first case of CFC syndrome associated with moyamoya syndrome. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cardio-facio-cutaneous syndrome; Moyamoya syndrome; Noonan syndrome; Contrast angiography

1. Introduction

Reynolds et al. first described eight patients with cardio-facio-cutaneous (CFC) syndrome in 1986 [1]. The manifestations of CFC syndrome include a congenital heart defect, a characteristic facial appearance, ectodermal abnormalities, and growth failure. Although CFC syndrome is distinguished from Noonan syndrome by the presence of abnormal hair and hyperkeratotic lesions, these two syndromes resemble each other in many ways [2,3]. Many reports have suggested the possibility that CFC syndrome and Noonan syndrome are contiguous gene syndromes [4,5].

Moyamoya disease is characterized by progressive stenosis and eventual occlusion of the large cerebral arteries at the circle of Willis. In response to arterial stenosis, an abnormal network of small collateral vessels develops, called a ‘puff of smoke’. The clinical course consists of recurrent transient cerebral ischemic attacks (TIAs) and strokes. Progressive occlusive cerebral vasculopathies, similar to moyamoya disease, occur secondary to a variety of congenital disease, such as neurofibromatosis type 1 and sickle cell disease. This condition is called moyamoya syndrome in contrast to moyamoya disease, which is thought to be of idiopathic origin.

There have been three case reports of Noonan syndrome associated with moyamoya syndrome. However, CFC syndrome associated with moyamoya syndrome has not previously been reported. We report the first patient of CFC syndrome associated with moyamoya syndrome.

2. Case report

A boy aged 6 years 5 months was referred to our hospital because of left hemiplegia and right-sided eye deviation after crying. He had no family history of inherited or cerebrovascular diseases. He was the first child of non-consanguineous parents. He was born at 39 weeks gestation to a 26-year-old mother and 29-year-old father by cesarean section due to toxemia. Left eyelid ptosis was observed immediately after birth. He exhibited hypotonia, failure to thrive, and developmental delay since early infancy. He could sit without support at 8.5 months, stand alone at 1 year 3 months, and walk at 3 years. Horizontal nystagmus was also noted from early infancy.

He experienced two febrile seizures. He had already had two TIA episodes at 5 years 5 months and 5 years 6 months. The symptoms spontaneously resolved within 1 or 2 h.

On admission, hypoplasia of the supraorbital ridges, thin eyebrows, left ptosis, posteriorly angulated ears with prominent helices, hyperkeratotic lesions, sparse and thin hair,

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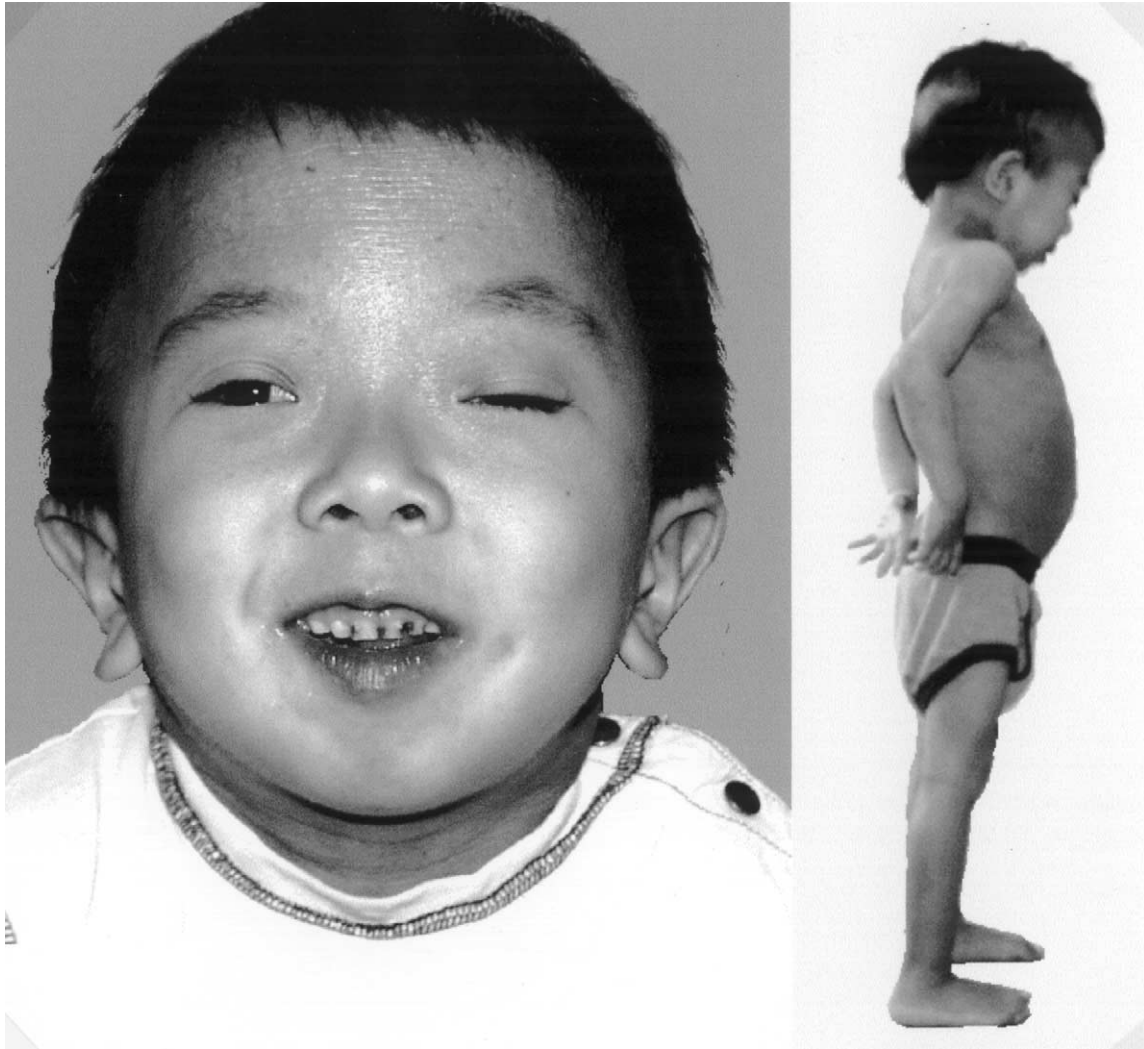


Fig. 1. Facial appearance and physical features. The boy had an apparently short stature and was odd looking. Left ptosis, depressed nasal bridge, thin hair, hypoplasia of supraorbital ridges, thin eyebrows, posteriorly angulated ears with prominent helices and pigmented hyperkeratotic lesions were observed.

and a depressed nasal bridge were observed (Fig. 1). His height was 96.8 cm (-3.7 SD) and his head circumference was 55.5 cm ($+2.0$ SD). A Levin II/VI systolic murmur and hepato-splenomegaly were detected. Hyperreflexia was present in the left lower extremity.

The serum levels of liver enzymes, lactate, pyruvate and amino acids were within normal limits. There was no abnormal coagulation system results, including the prothrombin time, activated partial thromboplastin time, anti-thrombin III, fibrinogen, protein C and protein S. Electrocardiography showed an incomplete right bundle branch block. An atrial septal defect and mild ventricular septal hypertrophy were detected on ultrasound cardiography, but the cardiac function was normal.

His facial features well-matched those of Noonan syndrome. At first, we diagnosed him as having this syndrome. However, the diagnosis was later changed to CFC syndrome considering the presence of a large prominent forehead, bitemporal narrowing, a shallow orbital

ridge, down slanting palpebral fissures, a short upturned nose and valvular pulmonary stenosis.

The hemiparesis and eye deviation disappeared gradually within 10 min after admission. We suspected that he had had a TIA. Magnetic resonance imaging (MRI) demonstrated flow voids in the bilateral basal ganglia on T1-weighted imaging, but an infarction was not detected (Fig. 2). Magnetic resonance angiography (MRA) showed stenosis of the bilateral internal carotid arteries at the circle of Willis and multiple enlarged perforating vessels. These findings were confirmed by cerebral angiography (Fig. 3). EEG revealed semi-continuous theta or delta waves in the right centro-parietal areas, which sometimes spread to the right fronto-temporal areas during non-REM sleep. During hyperventilation, high voltage theta and delta waves were observed, although re-buildup was not recognized. We diagnosed him as having moyamoya syndrome on the basis of these findings.

He had been treated with low-dose aspirin. About 10 days

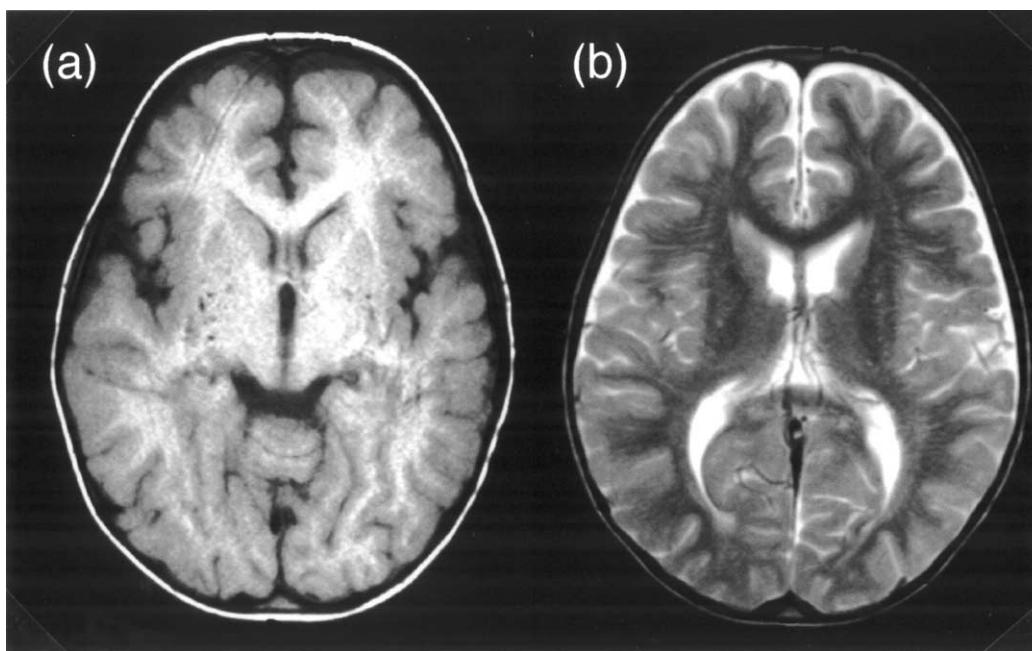


Fig. 2. (a) Axial SE T1-weighted (TR450, TE15) sequences show flow voids on bilateral basal ganglia; (b) axial SE T2-weighted (TR4000, TE120) sequences show no visible infarction.

after starting the aspirin, he had a high fever, erythema, and wheals on both legs. An infection, allergic purpura or drug allergy was suspected, so the aspirin and antibiotics were stopped. The drug-induced lymphoblast stimulation test was normal for aspirin. We gave him no drugs, however a TIA was seen after 4 months. Since aspirin was re-started, a TIA has not been seen. Surgical therapy is under consideration.

3. Discussion

Many authors have described the phenotypic overlapping between CFC syndrome and Noonan syndrome [2–5]. Neri et al. compared 16 characteristic features of these two syndromes [6]. They reported that sparse, thin curly hair and hyperkeratotic skin lesions were specific to CFC syndrome. Mental retardation is always present in CFC patients. Neck abnormalities and a familial occurrence are distinctive in Noonan syndrome and are seldom observed in CFC syndrome. Our patient had sparse, thin hair and hyperkeratotic skin, but did not have a webbed neck. The clinical features of our patient were more in accordance with CFC syndrome than Noonan syndrome. The difficulty in distinguishing these two syndromes may lie in the lack of a molecular basis. Legius et al. performed linkage analysis in a Belgian family with Noonan syndrome in some individuals and CFC syndrome in others [7]. The gene for Noonan syndrome has previously been linked to a 14 cM region in 12q24 [8]. They reported a maximum lod score of 4.43 on zero recombination for marker D12S84 in 12q24. A crossover in this pedigree narrowed the candidate gene region for Noonan syndrome to a 5 cM region between markers

D12S84 and D12S1341. The clinical data and linkage data in this family indicate that these two syndromes result from variable expression of the same genetic defect. They concluded that CFC syndrome may be a variant of Noonan syndrome. Future advances in gene analysis will allow us to differentiate these two syndromes more definitely.

Moyamoya disease should be distinguished from moyamoya syndrome, although there are some common angiographic findings and clinical symptoms in these diseases. Moyamoya disease is of idiopathic origin, but moyamoya syndrome occurs secondary to a variety of slowly progressive occlusive cerebral vasculopathies, such as sickle cell disease, neurofibromatosis type 1, Down syndrome, etc. [9–11]. We consider that our patient had moyamoya syndrome because he had CFC syndrome.

Several authors reported cerebrovascular anomalies associated with Noonan syndrome, including arteriovenous malformations and aneurysms [12,13]. There have been three patient reports on an association of moyamoya syndrome with Noonan syndrome. Ganesan and Kirkham reported a patient who exhibited activated protein C resistance and was heterozygous for the factor V Leiden mutation [14]. Schuster and Roberts described a 7-year-old girl with previously diagnosed Noonan syndrome and known aortic coarctation [15]. The patient had recurrent headaches, several episodes of transient right-sided weakness and sensory loss associated with slurred speech. Head MRI and MRA revealed bilateral distal carotid stenosis with collaterals consistent with moyamoya syndrome. She underwent bilateral encephaloduroarteriosynangiosis and balloon dilatation of the coarctation. Two years later, she had had no significant TIA episodes. Tang et al. reported a patient with

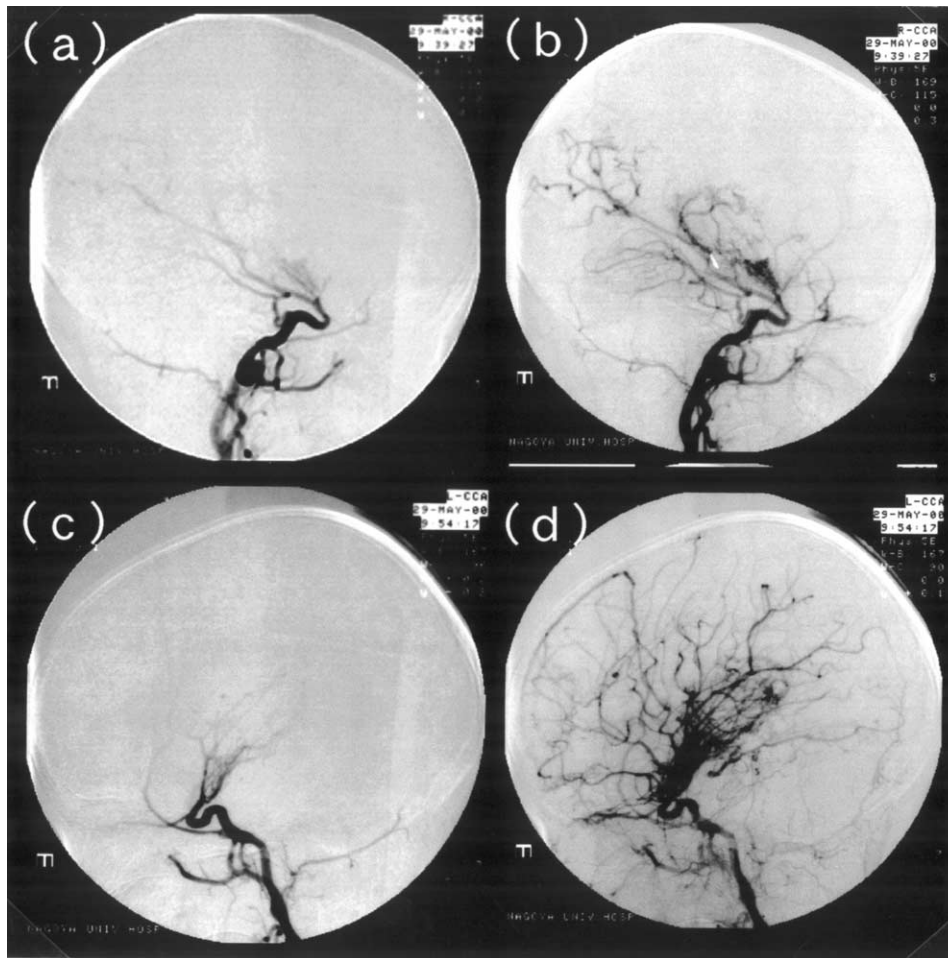


Fig. 3. (a,b) Right carotid angiography; (c,d) left carotid angiography, showing the carotid artery stenosis with moyamoya.

Noonan syndrome who had repeated TIAs due to moyamoya syndrome [16]. On the other hand, an association of CFC and moyamoya syndrome has not been described previously to the best of our knowledge. There are two explanations for this combination. One explanation is that this combination is incidental. At present, the rate of cerebrovascular diseases among patients with CFC syndrome is unclear. Another explanation is that moyamoya syndrome is one of the complications of CFC syndrome. Previous reports suggested that there may be some relation between the Noonan and moyamoya syndromes. Supposing that the Noonan and moyamoya syndromes are contiguous gene syndromes, there is a possibility that CFC syndrome is causative of moyamoya syndrome. Further studies are needed to clarify the relation between the CFC and moyamoya syndromes.

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