CASE REPORT

Moyamoya Syndrome or Fibromuscular Dysplasia? A Complex Case of Pediatric Stroke

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Port J Pediatr 2022;53:674-9
DOI: https://doi.org/10.25754/pjp.2022.22427

Abstract

Moyamoya disease and fibromuscular dysplasia are two arteriopathies that can cause stroke in pediatric age. These have been proposed to have the same pathological basis and cases of moyamoya disease with extracranial involvement have overlapping clinical features to those seen in fibromuscular dysplasia. A heterogenous genetic component is thought to play a part in both and some genes have shown simultaneous association with the two diseases. Some aspects of clinical management are also similar. We report a case of a 6-month-old infant with a rare and extensive multivessel disease that first presented as ischemic stroke and severe and refractory hypertension. A chromosomal translocation and distinctive facial characteristics were also present. Genetic investigation is underway, and it might help to better tailor therapy and define prognosis.

Keywords: Brain Ischemia/etiology; Diagnosis, Differential; Fibromuscular Dysplasia; Infant; Ischemic Stroke/etiology; Moyamoya Disease/complications; Moyamoya Disease/diagnosis; Moyamoya Disease/genetics

Keypoints

What is known:

- Moyamoya disease and fibromuscular dysplasia are two arteriopathies associated with stroke in the pediatric age. They may share a pathological and genetic basis.
- Moyamoya disease cases with affection of renal arteries and renovascular hypertension may be cases of clinical fibromuscular dysplasia without histopathological confirmation.
- Management of these diseases involves medical therapy with antiplatelet agents but may also involve interventions like revascularization procedures or percutaneous angioplasty of affected vessels. Timing these interventions appropriately poses an additional challenge.

What is added:

- To our knowledge, this is the first case in the literature where a chromosomal translocation translates with features both of blepharophymosis, ptosis and epicanthus inversus syndrome and a systemic extensive vasculopathy.

Introduction

The most frequent etiologies of pediatric stroke are arteriopathies, cardiac disorders and infection.[1,2] Cerebral arteriopathies in children can be inherited or acquired and are divided into non-inflammatory (*eg* moyamoya disease, arterial dissection, fibromuscular dysplasia) and inflammatory (*eg* auto-immune and post-infectious vasculitis) categories.

Moyamoya disease is defined by progressive bilateral stenosis of the intracranial internal carotid arteries and their proximal branches, leading to reduced blood flow in the major vessels of the anterior cerebral circulation.[3,4] This leads to the development of collaterals originating from the superficial vessels of the cortex and leptomeninges, branches of the external carotid artery and rarely from the posterior circulation.[3] These characteristics account for the typical angiographic findings of the disease.[3,4] The exact etiology remains to be fully clarified and both genetic and environmental factors have been implicated.[3] Patients that appear to have the characteristic angiographic pattern while also having other well-recognized associated conditions are categorized as having moyamoya syndrome.[3]

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Received: 20/01/2022 | Accepted: 05/06/2022 | Published online: 01/10/2022 | Published: 01/10/2022

Cases of moyamoya with extracranial involvement have been described both in adults and children.[5-7] Some of these have been proposed to be in fact a manifestation of fibromuscular dysplasia.[5,8,9] Fibromuscular dysplasia is defined as a non-inflammatory non-atherosclerotic stenosing arteriopathy, classically described as having a cerebral-renal distribution,[8,10] although cases have been reported in almost every arterial bed.[9,11]

We describe a case of an infant presenting with the moyamoya syndrome associated with extensive extracranial involvement and hypertension as part of a clinical picture of a probable fibromuscular dysplasia, in coincidence with a (3;5) (q25.1;q22) translocation and features suggestive of blepharophimosis, ptosis and epicanthus inversus syndrome.

Case Report

A 6-month-old boy presented to our emergency department with a history of a sudden onset of irritability, persistent crying, and diminished movement of the right arm. The mother's description was consistent with a pulled elbow. An upper respiratory tract infection had been diagnosed one month before.

Past medical history was positive for mild supra-valvular pulmonary stenosis and complex eye malformations (bilateral iris hypoplasia, sclerocornea and microcornea and congenital right cataract). He presented distinctive facial characteristics (bilateral ptosis, blepharophimosis and epicanthus inversus) but was otherwise a healthy child and was appropriately immunized for his age.

After orthopedic surgeon evaluation, he was discharged home. On the following day, he was readmitted due to generalized tonic-clonic movements and conjugated gaze deviation. He was afebrile and physical examination was unremarkable apart from right-sided hemiparesis.

Computed tomography (CT) scan revealed a recent ischemic lesion in the territory of the left middle carotid artery (Fig. 1). Electroencephalogram showed diffuse lentification of electrogenesis at the left hemisphere. Laboratorial evaluation revealed no elevation of inflammatory markers, normal coagulation tests, normal kidney and liver function tests and no electrolyte disturbances. Blood cultures were negative. Cerebrospinal fluid analysis and culture were negative.

He was admitted in our pediatric intensive care unit, continuing to present convulsive phenomena despite appropriate anticonvulsant therapy. Aminosalicylic acid was initiated. Consistently high blood pressure values were observed, and captopril was started. Head CT scan was repeated, with no new or worsening radiological findings. Cardiac ultrasonography revealed only the previously known anomalies. A carotid Doppler-ultrasound showed no abnormalities. Magnetic resonance confirmed an ischemic lesion at the territory of the left anterior and middle cerebral arteries and magnetic resonance angiography revealed a suboclusive stenosis of the supraclinoid segment of both internal carotid arteries, suggestive of a moyamoya pattern.

Cerebral angiography confirmed pre-obliterative stenosis of both internal carotid arteries, and the presence of collateral circulation originating from posterior cerebral arteries bilaterally, configuring a moyamoya pattern. Infectious, autoimmune / inflammatory, hematological, and metabolic causes of stroke were excluded.

Due to the risk of malignant transformation and the potential need for neurosurgical intervention he was transferred to a tertiary care center. Although he showed clinical improvement, he was not considered a surgical candidate for reperfusion techniques, due to the severity and extension of arterial stenosis, so he was transferred back to our ward.

During admission, he maintained persistent severe hypertension, later confirmed by 24-hour continuous blood pressure monitoring. Plasma renin activity was abnormally high, although this test was not reliable since he was on captopril. Aldosterone dosing was normal. Doppler-ultrasound of the renal arteries showed no abnormalities.

Regarding investigation of his multiple congenital anomalies, microarray-based comparative genomic hybridisation, revealed no abnormalities, while karyotype showed a translocation: 46XY t(3;5) (q25.1;q22).

He was discharged after 30 days, with a residual right hemiparesis.

Two months later, he presented to our emergency department with lethargy and clonic movements of the left hemicorpus. Head CT-scan revealed a recent ischemic stroke in the territory of the right middle cerebral artery. He was transferred to the tertiary care center he had been previously referred to for neurosurgical consultation, where he remained clinically stable. Head magnetic resonance imaging and cerebral angiography confirmed the ischemic stroke in the right middle cerebral artery territory. A diffuse moyamoya-like pattern remained apparent (Fig. 2). Revascularization procedures were again not an option due to the severity of the disease and the absence of appropriate donor arteries.

After returning to our hospital, he continued to present a hypertensive profile, despite multiple dosage adjustments of captopril. An abdominal computed tomography angiography scan was then performed, showing generalized diminished caliber of all the main

abdominal vessels (abdominal aorta, common iliacs, celiac trunk and renal arteries bilaterally). A renal infarct was also noted (Figs. 3 and 4).

The patient recovered from this second event with right hypoacusis as the only new sequela. After two years of follow-up, he has not presented any new ischemic event and recovered from the right hemiparesis, displaying hypoacusia and a global developmental delay. A genetic investigation is currently underway. Molecular analysis of the *RNF213* gene, associated with moyamoya disease and fibromuscular dysplasia, has not identified any pathogenic variant. Blepharophimosis, ptosis and epicanthus inversus syndrome, although clinically confirmed by the ophthalmology team, has not been genetically confirmed yet.

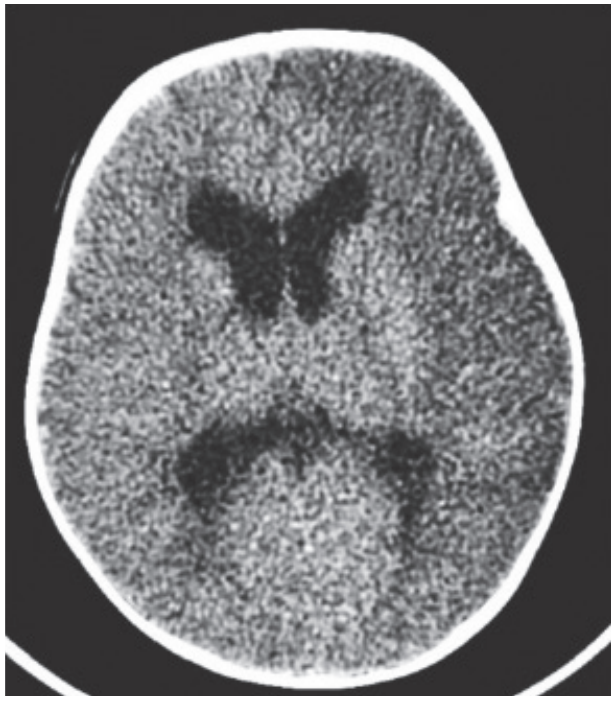


Figure 1. Non-contrast head computed tomography scan from first ischemic stroke. An extensive left cortico-subcortical fronto-insulo-temporo-parietal hypodense lesion is visible, corresponding to a recent ischemic lesion of the territory of the left middle cerebral artery.

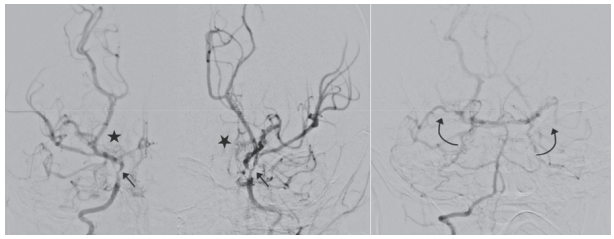


Figure 2. Cerebral angiography after the second ischemic stroke shows critical stenosis of both supraclinoid internal carotid arteries (black arrows), and dilated perforant arteries defining a moyamoya pattern ("puff of smoke", stars). The vertebro-basilar arteries compensate both internal carotid arteries territories through posterior communicating arteries and leptomeningeal collaterals (curved arrows).

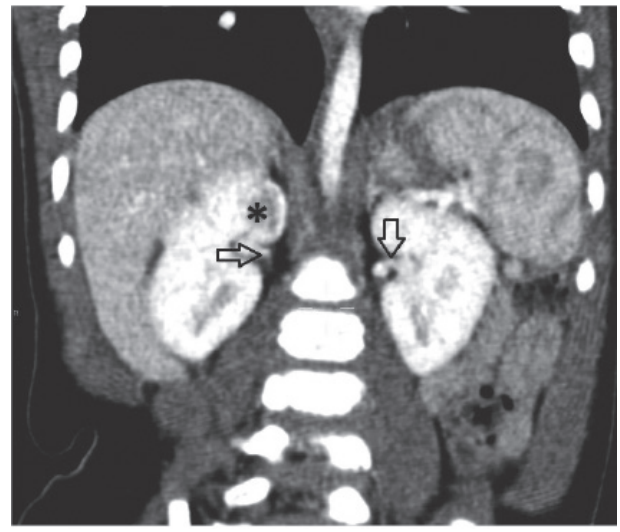
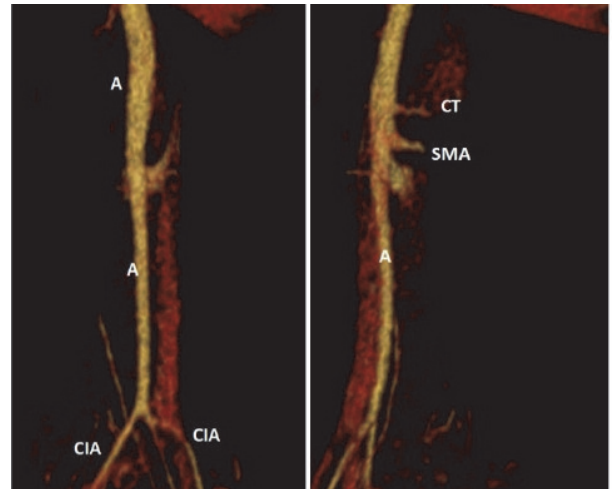


Figure 3. Abdominal computed tomography angiography (coronal view). Diminished caliber of both renal arteries (arrows) and a hypodense nodule (asterisk), corresponding to an infarct in the right kidney, are noted.



A - aorta; CIA - common iliac arteries; CT - celiac trunk; SMA - superior mesenteric artery.

Figure 4. Three-dimensional reconstruction of the main abdominal vessels (anterior and sagittal views). Note the much larger caliber of the inferior vena cava (red) in comparison with the descendant aorta (yellow). Progressive narrowing of the aorta and a diminished caliber of the celiac trunk in comparison to superior mesenteric artery are visible. Narrowing of the common iliac arteries is also evident.

Discussion

In the case, an apparently healthy infant presented with a sudden onset of a neurological deficit that was first misinterpreted as a pulled elbow, hence the 24-hour delay in diagnosis. According to the literature, this delay is common in pediatric stroke,[12] especially in infants and young children, due to its nonspecific clinical presentation (*eg* seizures, lethargy and focal weakness) and inability to verbalize complaints in this group.[3]

Head-CT scan showed the expected findings in ischemic stroke.[13] The various image methods further helped in defining the extension of the ischemic lesion and in characterizing the cerebral vasculature.[2,4,13]

Infectious and inflammatory etiologies did not seem likely in our patient based on the initial investigation, even though the exuberant presentation could have suggested a generalized central nervous system vasculitis. This hypothesis was put aside after secondary investigation. Moyamoya arteriopathy was proposed as the diagnosis in this patient based on some of the classical angiographic findings of the disease that were present, such as bilateral stenosis of the supraclinoid internal carotid arteries and development of collateral circulation.[3,4] However, it seemed to be in a disproportionate stage of severity[3] relative to our patient's age and time of onset of the disease. Some odd angiographic aspects were noted: the posterior circulation also showed stenosis and the main collaterals originated here, instead of originating from the superficial cortical vessels.

After a second episode and a second angiography, moyamoya disease was considered the primary diagnosis. However, an exceedingly difficult-to-treat hypertension was a worrying feature and it did not seem to fit in classical moyamoya disease. We hypothesized that the child could have extracranial involvement, namely of the renal arteries, which would explain a renovascular hypertension.[6,14,15] However, his two normal renal artery Doppler-ultrasounds did not confirm this. This could be explained by the fact that the child was highly agitated on both exams, so accuracy was compromised. On the occasion of his second stroke, a refractory hypertension was again evident, and the CT angiography finally confirmed a multivessel disease, affecting the aorta, celiac trunk and both renal arteries. Although cases of Moyamoya have been described in association with renal arteriopathy and hypertension,[5-7,14,15] such an extensive extracranial involvement has rarely been described.[9]

Contrarily to moyamoya disease, fibromuscular dysplasia is defined as a multivessel disease.[10,11] In adults, there is a female predominance and a multifocal angiographic pattern is frequently seen, which has been shown to be pathologically correlated with medial fibroplasia, with a common cerebral-renal association.[8,10,16] In children, there seems to be no gender difference, and focal stenosis is the most frequent finding, especially younger children, the histological analysis of which analysis seldom shows intimal fibroplasia.[8] While in adults fibromuscular dysplasia is a cause of less than 1% of hypertensive disease, in children it may be the cause of hypertension in 8%-25% in the age-group of 1-10 years.[9] In a systematic review of fibromuscular dysplasia and childhood stroke, moyamoya syndrome was formally diagnosed in 33% of pathologically proven fibromuscular dysplasia cases. Renal arteriopathy was present in 56% and systemic arteriopathy beyond cranio-cervical and renal arteries was documented in 76% of cases.[8]

Although we could not make a formal diagnosis of fibromuscular dysplasia, it seems plausible to attribute our patient's clinical picture to this disease.

In fact, moyamoya disease and fibromuscular dysplasia, described as two separate diseases, have been proposed to be the same, meaning moyamoya disease may be the intracerebral manifestation of a pathological process of fibromuscular dysplasia.[5,8] Also the progressive stenosis of the carotid arteries in fibromuscular dysplasia may lead to the angiographical appearance of moyamoya disease and the histopathological abnormalities in moyamoya closely resemble those seen in fibromuscular dysplasia.[8]

Both entities are thought to have a genetic component in their origin, although its exact contribution remains unclear.[3,10,16] Familial cases have been reported in both.[17,18] Moyamoya disease has been associated with mutations in multiple genes, namely on chromosomes 3, 6, 8 and 17.[3,19] Gene *RNF213*, located on 17q25, has been one of the most consistently reported genes in this disease, especially in early-onset presentation,[19] as is our case. Although less is known about fibromuscular dysplasia associated genetic variants, a recent systematic review has also reported an association with this gene,[18,20] although there seems to be great genetic heterogeneity.[20]

The molecular analysis of *RNF213* was normal in our patient. The patient had a translocation between chromosomes 3 and 5 at regions (q25.1; q22). His facial characteristics, that led us to pursue a genetic screening in the first place, are typical of blepharophimosis, ptosis and epicanthus inversus syndrome.[21] This syndrome has been consistently linked to a wide range of mutations in the *FOXL2* gene,[22,23] located at 3q21-24.[21] Mutations that occur outside the gene, in neighboring regulatory regions, can also be responsible for the syndrome.[23] We found no reports of the association of this syndrome neither with fibromuscular dysplasia nor moyamoya disease in the literature.

A genome-wide association study has recently identified 10 novel susceptibility loci for moyamoya disease and one of these is locus 3q25.1, where *TSC22D2* (transforming growth factor β-stimulated clone 22 domain family, member 2) gene is located.[19] This corresponds to the location of our patient translocation. We hypothesize

that this gene might be affected but this should only be confirmed through detailed gene molecular analysis. Treatment and secondary prevention of stroke with aminosalicylic acid alone is validated both for moyamoya disease[3,4] and fibromuscular dysplasia[16] but is has been shown to not be effective in slowing moyamoya disease progression.[3] In moyamoya disease, surgical revascularization is usually proposed,[3,4,24] but this does not seem to be a viable option in our patient's case, as decided by the neurosurgical team. On the same note, percutaneous angioplasty of the renal arteries to manage hypertension, a procedure done successfully in some cases,[15,25] was deemed too risky due to the extensive vascular involvement. In our patient, partial control of hypertension was achieved using oral antihypertensive agent.

We believe this case report might help to shed some light on the complexity of the relationship between these two entities. Finding a cause for the extraordinarily rare presentation of our patient might also be useful in drafting a prognosis and planning future therapeutic options for him. Besides the genetic analysis, biopsy of an affected vessel might prove useful.

Author Contribuitions

JMM and CL participated in the study conception or design. JMM and JGV participated in acquisition of data. JMM, JGV and CL participated in the analysis or interpretation of data. JMM and CL participated in the drafting of the manuscript. JMM, JGV and CL participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

Funding Sources

There were no external funding sources for the realization of this paper.

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

Consent for publication was obtained.

Acknowledgments

The authors would like to express their sincere acknowledgments to Dr. Sérgio Ferreira for helping with image acquisition and interpretation and to all the professionals of the neuroradiology, neurosurgery and neuropediatrics teams that were involved in the case.

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Síndrome de Moyamoya ou Displasia Fibromuscular?
Um Caso Complexo de Acidente Vascular Cerebral Pediátrico

Resumo

A doença de Moyamoya e a displasia fibromuscular são duas arteriopatias que podem ser causa de acidente vascular cerebral na idade pediátrica. Tem-lhes sido proposta a mesma base patológica e os casos de doença de moyamoya com envolvimento extracraniano têm características clínicas sobreponíveis às observadas na displasia fibromuscular. Acredita-se que um componente genético heterogéneo tem algum papel nas duas situações e demonstrou-se que alguns genes estão associados às duas doenças. Alguns aspetos da abordagem clínica também são semelhantes. Relatamos o caso de uma criança de 6 meses com uma doença multiarterial rara e extensa que se apresentou inicialmente como acidente vascular cerebral isquémico e hipertensão grave e refratária. Uma translocação cromossómica e características faciais distintas também estavam presentes. A investigação genética está em curso e pode ajudar a adaptar o tratamento e a definir o prognóstico.

Palavras-Chave: AVC Isquémico/etiologia; Diagnóstico Diferencial; Displasia Fibromuscular; Doença de Moyamoya/complicações; Doença de Moyamoya/diagnóstico; Doença de Moyamoya/genética; Isquemia Encefálica/etiologia; Lactente