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Moyamoya Angiopathy with Dolichoectatic Internal Carotid Arteries, Patent Ductus arteriosus and Pupillary Dysfunction: A New Genetic Syndrome?

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Key Words
Cerebral artery stenosis · Dolichoectasia · Moyamoya disease · Patent ductus arteriosus · Pupillary abnormality

Abstract
We report on 2 children with moyamoya angiopathy and bilateral dolichoectatic internal carotid arteries in combination with iris hypoplasia with bilateral fixed dilated pupils and a history of patent ductus arteriosus. Both were symptomatic with moyamoya angiopathy and underwent bilateral extracranial-intracranial (EC-IC) bypass operations for cerebral revascularization. This is the first report on moyamoya angiopathy and bilateral dolichoectatic internal carotid arteries with simultaneous occurrence of ocular and cardiovascular malformations. There have been descriptions of cerebral vascular abnormalities in combination with either congenital heart disease or ocular abnormalities but not with both presenting together. The combination of these separate congenital developmental defects may not be purely coincidental: we propose that the 2 probands are affected with a not yet recognized clinical syndrome of probably genetic etiology.

Introduction

Moyamoya disease or angiopathy (moyamoya disease and moyamoya syndrome) is a cerebrovascular malformation angiographically diagnosed and defined by the presence of bilateral stenosis of the intracranial internal carotid arteries (ICAs) at the level of the carotid bifurcation, accompanied by abnormal vascular networks at the base of the brain [1–4]. This condition is most prevalent in Japan and Asian countries; incidence and prevalence in Europe are estimated to be only around one tenth of that in eastern Asia [2, 3, 5]. The etiology of moyamoya angiopathy is unknown. From the present literature to date the typical neuroradiological findings of moyamoya angiopathy may be present in other acquired systemic diseases or genetic conditions, such as Down syndrome and sickle cell anemia, or may be present additionally to other cerebral vascular pathologies like arteriovenous malformation, aneurysms or cerebral arterial dolichoectasia as listed in table 1 [2]. In a part of them, especially the more frequent ones, the co-occurrence may be by chance. If occurring in combination with other, especially rarer congenital defects, it should be termed moyamoya syndrome in contrast to idiopathic or isolated moyamoya disease. The reason of this differentiation is that, just as with other

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Table 1. Diseases occurring in combination with moyamoya angiopathy

1	Alagille syndrome
2	Autoimmune disease Sjögren syndrome, Graves disease
3	Cardiac disorders Cardiomyopathy, *patent ductus arteriosus*
4	Drug abuse Phenobarbital, oral contraceptives with or without smoking
5	Eosinophilic granuloma
6	Gastrointestinal disorders Perforation of the small intestine
7	Genetic/chromosomal disorders Neurofibromatosis (von Recklinghausen disease), tuberous sclerosis, Down syndrome, Turner syndrome, retinitis pigmentosa, Hirschsprung disease, osteogenesis imperfecta
8	Growth failure
9	Harlequinism
10	Hematological disorders Sickle cell anemia, Fanconi anemia, thalassemia, aplastic anemia, lupus anticoagulant, anti-Ro/SS-A and anti-La/SS-B antibody, anti-DNA antibody, antinuclear antibody, thrombotic thrombocytopenic purpura
11	Eosinophilic granuloma
12	Infectious disease Leptospirosis, meningitis (tuberculous etc.), arteritis, nephritis, tonsillitis
13	Metabolic disorders Hyperlipoproteinemia (type 2A), glycogen storage disease (type 1), lipohyalinosis, pseudoxanthoma elasticum, hyperthyroidism, impaired NADH-CoQ reductase activity
14	Myopathies Progressive myopathy of late onset type
15	Neoplasm Sellar and parasellar tumor (craniopharyngioma, optic glioma), Wilms tumor
16	Ophthalmological disorders Morning glory papilla, *pupillary dysfunction*
17	Trauma Cranial trauma
18	Vascular disorders Renal artery stenosis, fibromuscular dysplasia, cerebral aneurysms (saccular, dissecting), arteriovenous malformations, *cerebral arterial dolichoectasia*

Italics emphasize the disorders (3, 16 and 18) accompanying the moyamoya angiopathy in our 2 patients.

Modified from [2].

rare congenital developmental defects, the etiology is likely to be different and mostly genetic. The prevalence of syndromic moyamoya disease is not well known. It is our impression that in contrast to idiopathic moyamoya angiopathy, syndromic moyamoya disease is more frequent in Europe versus Japan. These 2 cases additionally presented with (1) dolichoectasia of bilateral ICAs, (2) pupillary dysfunction and (3) patent ductus arteriosus. This combination of 4 presumably etiologically related but pathogenetically independent organ affections might constitute a new syndrome featuring moyamoya angiopathy as the most striking component of its syndromic pattern.

Case Presentation

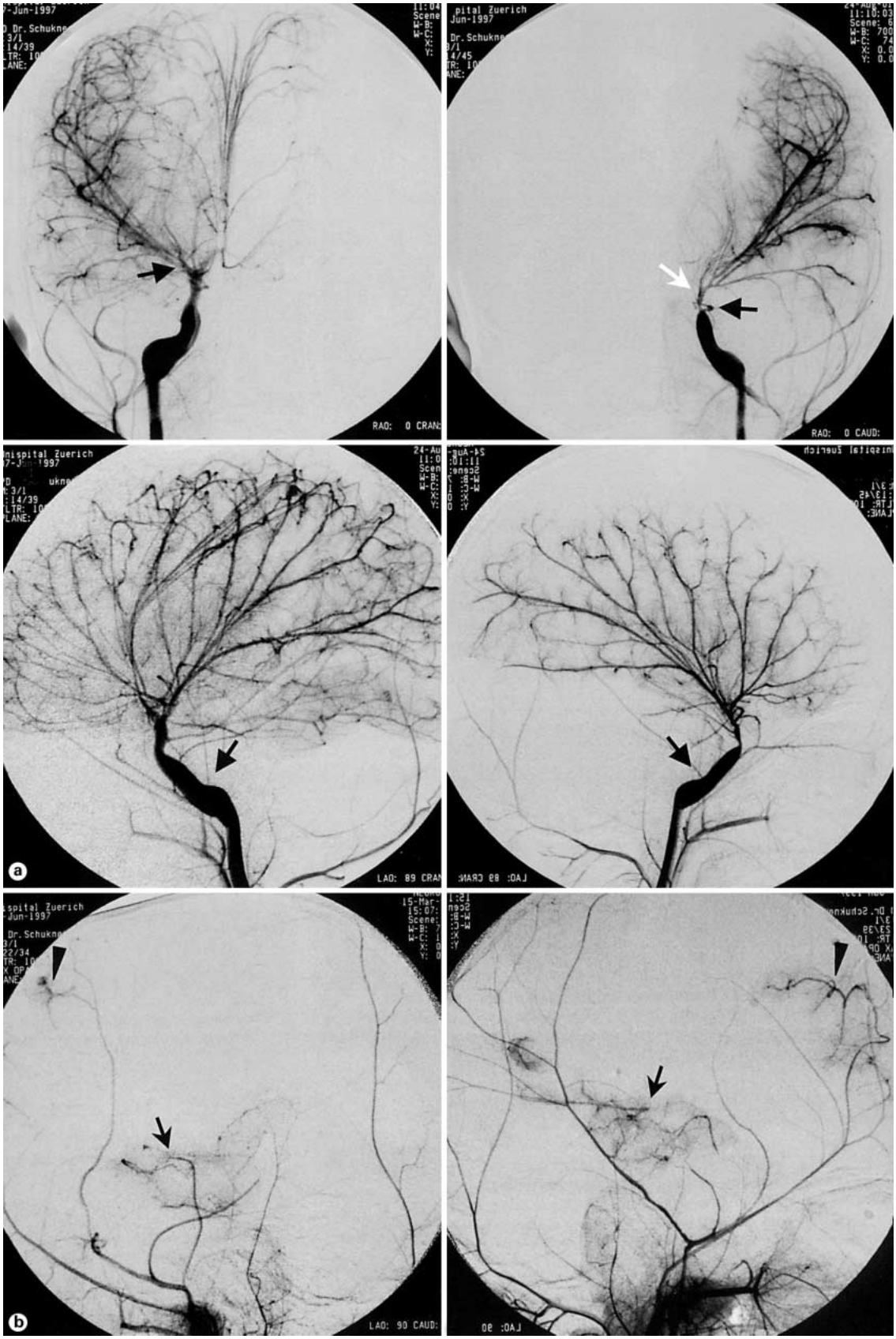
Case 1: Patient S.M.

This presently 4-year-old Caucasian girl born to nonconsanguineous parents suffered at the age of 2 years from 2 episodes of cerebrovascular insults with transient right-sided hemiplegia. Antenatal and birth history as well as postnatal development were unremarkable. Birth weight was 4,230 g at 36 weeks of gestation. At the age of 8 months, surgery for a patent ductus arteriosus was performed. On admission, clinical examination showed mild psychomotor retardation and bilaterally fixed pupils with absence of direct and consensual pupillary light reflexes as a consequence of bilateral iris hypoplasia. A brain CT scan demonstrated bifrontal infarcts in the territory of the anterior cerebral artery (ACA).

Angiography revealed <50% stenosis of the right ICA at the level of the bifurcation and a >50% stenosis of the ICA at the C2 segment of the left ICA along with absence of the ACA on the left side. The right ICA was dilated from the beginning of its intracranial course in the petrous bone to the bifurcation into the small-calibered medial cerebral artery (MCA) and the ACA, which supplied both ACA territories. The left ICA also showed similar fusiform dilatation in the pars petrosa. There was no abnormal moyamoya vascular network in the basal ganglia. The vertebral arteries were normal with leptomeningeal collaterals to the MCA territories (fig. 1a). $H_2{}^{15}O$ PET examination revealed decreased perfusion reserves in the left hemisphere and in the right parietotemporal region. The child received bilateral direct superficial temporal artery (STA) to MCA bypasses as well as bilateral indirect frontal arteriosynangiosis for cerebral revascularization (fig. 1b).

Case 2: Patient C.D.

This presently 6-year-old Caucasian boy born to nonconsanguineous parents at 36 weeks gestation weighing 3,110 g suffered at the age of 5 years from a transient left-sided hemiparesis and complained of recurring headaches with tinnitus. Antenatal, birth history and early postnatal development were unremarkable. At the age of 20 days, he had undergone surgery for a patent ductus arteriosus. On admission, there were no neurological deficits apart from bilaterally fixed pupils with absence of direct and consensual pupillary light reflexes, ophthalmologically diagnosed as bilateral hypoplasia of the iris. Because of hyperactivity, impulsiveness and poor concentration he was referred to a special school. Brain MRI showed multiple small ischemic lesions in the right frontal white matter. Cerebral angiography showed bilateral stenosis of the supraclinoidal part of the ICA at the level of the C2 segment and bilateral fusiform dilatation of the ICA in the petrosal part. There was a <50% stenosis of the left MCA and aplasia of the left ACA. No lenticulostriatal or thalamoperforator collaterals were seen. Leptomeningeal collaterals from the posterior cerebral artery (PCA) to the ACA distribution were present (fig. 2a).



$H_2{}^{15}O$ PET examination revealed decreased perfusion reserves in the right parietal and temporal regions and the left frontal regions. A bilateral direct STA-MCA bypass and bilateral indirect frontal durasynangiosis were performed for cerebral revascularization (fig. 2b).

Discussion

This is the first report on 2 patients with bilateral intradural stenosis of the ICA with additional dolichoectasia of bilateral ICAs combined with both ocular *and* cardiovascular malformations. There have been a number of reports on progressive stenosis of the cerebral vasculature, either in association with cardiovascular or with ocular abnormalities, but not both presenting together [6–11].

The presence of additional dolichoectatic cerebral vessels in combination with moyamoya angiopathy is a rarity but is not unknown. This presence of moyamoya angiopathy and dolichoectatic vessels has been reported previously in the literature [12, 13]. Structural congenital heart diseases such as coarctation of the aorta, atrial and ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot or aortic and mitral valve stenoses have been reported in combination with moyamoya angiopathy [8, 9, 14].

The exact etiology of this simultaneous occurrence of moyamoya disease and congenital heart disease is not known. Ganesan and Kirkham [14] describing moyamoya disease and Noonan syndrome suggested a common embryonic disturbance leading to cardiac, cerebrovascular and other systemic vascular anomalies.

The combination of moyamoya disease and cavitary optic disk malformations (optic nerve pit, morning glory disk anomaly, optic nerve dysplasia) has been presented in the literature [6, 10, 11, 15] suggesting that the occurrence of such associations may not be purely coincidental. The most common ocular abnormality known to occur with moyamoya angiopathy is the morning glory disk anomaly [10, 15]. The latter is characterized by a congenital excavation of the peripapillary fundus, enlargement of the optic disk, anomalous peripapillary glial tissue and a complex pattern of retinovascular anomalies associated with a profound retinovascular dysgenesis. Its association with moyamoya disease further points to the presence of a tendency towards a common intracranial vascular dysgenesis. Congenital mydriasis as seen in our patients is an extremely rare condition [16–19]. Combination of this disease with patent ductus arteriosus has previously been observed in 3 cases [20, 21]. In these publications, a receptor defect leading to dysfunction of the smooth muscles of both the eye (ciliary muscle and the iris sphincter) and media of the ductus arteriosus has been proposed as the most likely etiology.

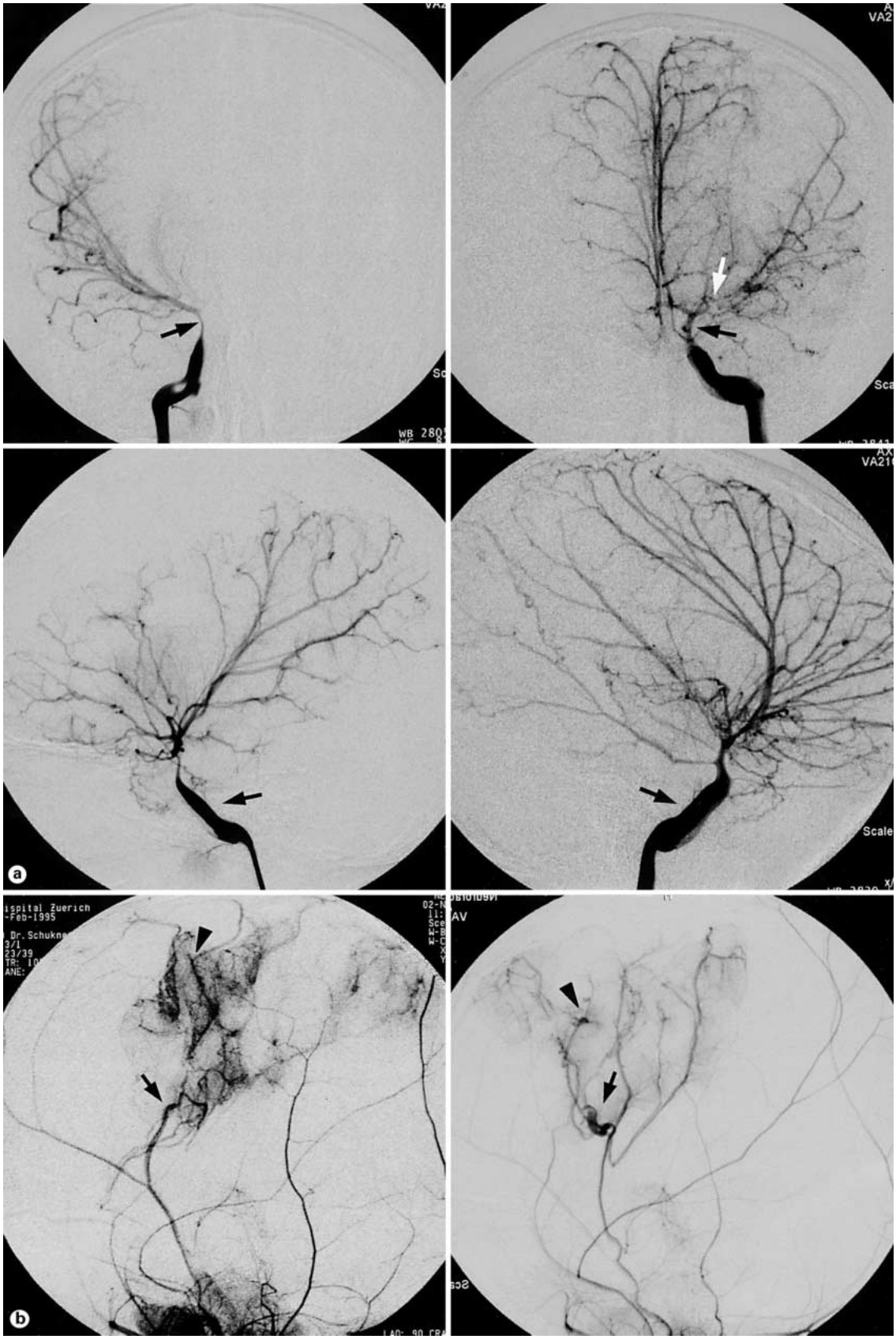
Epidemiological data for moyamoya disease indicate a polygenic or multifactorial inheritance pattern [4, 22–24] with possibly a minority of cases due to single gene mutations: predominantly sporadic occurrence, excess of female sex of the patients, different incidences in different populations, rarely occurrence in siblings and more remote relatives, linkage to different loci on different (3, 6, 19) chromosomes [22–24].

The combination of a specific cerebral angiopathy with, more or less, specific ocular anomalies and a specific heart malformation presumably indicates a common etiology. This could be genetic as well as environmental although the latter seems less likely. One possible genetic etiology could be a single – dominantly or recessively acting – gene mutated in the patients. As the phenotypic expression of pleiotropic genes is mostly very variable, it could be that other mutated patients have another spectrum of congenital anomalies ranging from e.g. only moyamoya angiopathy to a spectrum even severer than that found in our 2 patients.

Fig. 1. a Case 1: preoperative angiography of the ICA (anteroposterior and lateral projections) showing <50% stenosis of the right ICA at the level of bifurcation (anteroposterior projection, arrow) and a >50% stenosis of the ICA at the C2 segment of the left ICA (anteroposterior projection, arrow) along with absence of the ACA on the left side (anteroposterior projection, white arrow). Fusiform dilatation of both ICAs is seen from the beginning of the intracranial course in the petrous bone to the bifurcation (lateral projection, arrows). **b** Case 1: postoperative angiography of the external carotid artery (lateral projection), showing the arterial filling of the temporal branches of the MCA after a direct STA-MCA bypass (arrows) on both sides. Arterial filling in the frontal region is also seen after indirect frontal arteriosynangiosis on both sides (arrowheads).

Fig. 2. a Case 2: preoperative angiography of the ICA (anteroposterior and lateral projections) showing bilateral stenosis of the ICA at the level of the C2 segment (anteroposterior projection, arrows) and bilateral fusiform dilatation of the ICA in the petrosal part (lateral projection, arrows). A <50% stenosis of the left MCA and absence of a left ACA are also seen. **b** Case 2: postoperative angiography of the external carotid artery (lateral projection), showing the arterial filling of the frontal and temporal branches of the MCA after a direct STA-MCA bypass (arrows) on both sides. Arterial filling in the frontal region is also seen after indirect frontal durasynangiosis on both sides (arrowheads).

(For fig. 2 see next page.)



Another possibility is that our patients have a contiguous gene syndrome, i.e. that their findings are caused by deletion of more than 1 gene causing moyamoya angiopathy and another or 2 others causing ocular and heart anomalies. In this case, the gene(s) locus could be at one of the loci mentioned above as showing linkage to the disease in moyamoya patients. Even if this is the case, the same microdeletion might not necessarily cause a similar combination of congenital anomalies in all patients with similar extent of the deletion. However, lack of any developmental delay or mental retardation in the 2 probands would be rather unusual for a contiguous gene syndrome as most of them go along with mental retardation.

In summary, we report the 2 patients in order to draw the attention of colleagues potentially aware of similar cases to the combination of moyamoya angiopathy with ocular anomalies and patent ductus arteriosus.

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