



Case of Familial Moyamoya Disease Presenting 10 Years After Initial Negative Magnetic Resonance Screening in Childhood

Jiro Aoyama, Tadashi Nariai, Maki Mukawa, Motoki Inaji, Yoji Tanaka, Taketoshi Maehara

Key words

- Encephaloduroarteriosynangiosis
- Moyamoya disease
- RNF213
- Screening

Abbreviations and Acronyms

- ASL:** Arterial spin-labeling
CBF: Cerebral blood fluid
MRA: Magnetic resonance angiography
MRI: Magnetic resonance imaging

Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan

To whom correspondence should be addressed:

Tadashi Nariai, M.D, Ph.D.

[E-mail: nariai.nsrq@tmd.ac.jp]

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INTRODUCTION

Moyamoya disease is an acquired progressive obstruction of the cerebral blood vessels, primarily in the circle of Willis.¹ Both genetic and environmental factors are considered to contribute to the disease onset,²⁻⁶ but the exact mechanism has not been clarified. Furthermore, the typical time course of the progression to vessel occlusion has not been demonstrated, even in the genetically high-risk population. Here, we report a case of moyamoya disease with familial history who was diagnosed 10 years after the initial negative magnetic resonance angiography (MRA) screening in childhood.

CASE REPORT PATIENT

A 21-year-old female's major complaint was transient numbness of left upper and lower extremities and dysarthria. Her younger (by 2 years) sister was diagnosed with moyamoya disease at the age of 6 due to infarction onset. The sister had undergone bilateral encephaloduroarteriosynangiosis⁷

■ **BACKGROUND:** Both genetic and environmental factors are considered to contribute to the onset of moyamoya disease, but the exact mechanism has not yet been clarified. Furthermore, the typical time course of progression to vessel occlusion has not been established, even in the genetically high-risk population.

■ **CASE DESCRIPTION:** We present the case of a 21-year-old female with familial history of moyamoya disease. She underwent screening for moyamoya disease 10 years prior, but no abnormalities in magnetic resonance imaging or magnetic resonance angiography were found. She presented to our hospital for transient numbness of the left upper and lower extremities and dysarthria at the age of 21. She was diagnosed with moyamoya disease and underwent bilateral encephaloduroarteriosynangiosis. Gene analysis on the point mutation of *RNF213*, p.R4810K, was conducted for this patient, her younger sister with moyamoya disease, and their nonsymptomatic parents. A rare variant (p.R4810K) was positive in these sisters and their mother.

■ **CONCLUSION:** We show a case of familial moyamoya disease diagnosed 10 years after the magnetic resonance imaging screening in childhood. We must carefully consider when, how, and for whom screening for moyamoya disease should be performed, taking into account familial history of the disease.

at our hospital. Three years later, when the sister had totally recovered, her parents asked for a screening of her elder sister. Screening with MRI and MRA was performed at our hospital (GE SIGNA 1.5T) when the patient was 11. At this time, no abnormalities on magnetic resonance imaging (MRI) or MRA were detected (Figure 1A). Ten years later when the patient was 21, she developed transient numbness of the left upper and lower extremities with dysarthria. She visited a medical clinical and was examined by MRI (Philips Achieva 3T, Harvey, Illinois, USA). There were no ischemic lesions on MRI, but the MRA study clearly depicted bilateral occlusion of the terminal portion of internal carotid arteries (Figure 1B). She was referred to our hospital for treatment. Digital subtraction angiography (DSA) performed at our hospital also confirmed the diagnosis of moyamoya disease (Figure 2A and B). Arterial spin labeling (ASL) imaging with MRI (GE SIGNA 3T) showed reduced cerebral blood flow (CBF) in the

bilateral frontoparietal sensorimotor cortex (Figure 3A). An antiplatelet therapy using aspirin 100 mg daily was initiated. As her hemodynamic impairment was symmetric, we decided to treat her by bilateral encephaloduroarteriosynangiosis in single anesthesia as we have shown that indirect bypass surgery against the area with hemodynamic ischemia that was proved by reliable neuroradiologic technique works well both in child and adult patients with moyamoya disease.⁸⁻¹⁰

After the operation, rapid amelioration of cerebral blood flow was observed and her ischemic symptoms totally disappeared. The postoperative ASL study that was performed 10 days (Figure 3B) and 3 months (Figure 3C) after the operation depicted rapid improvement of CBF beneath the craniotomy site. The antiplatelet therapy was stopped after we confirmed disappearance of ischemic symptoms and amelioration of hemodynamic condition.

Gene analysis on point mutation of *RNF213*, p.R4810K, was conducted on this

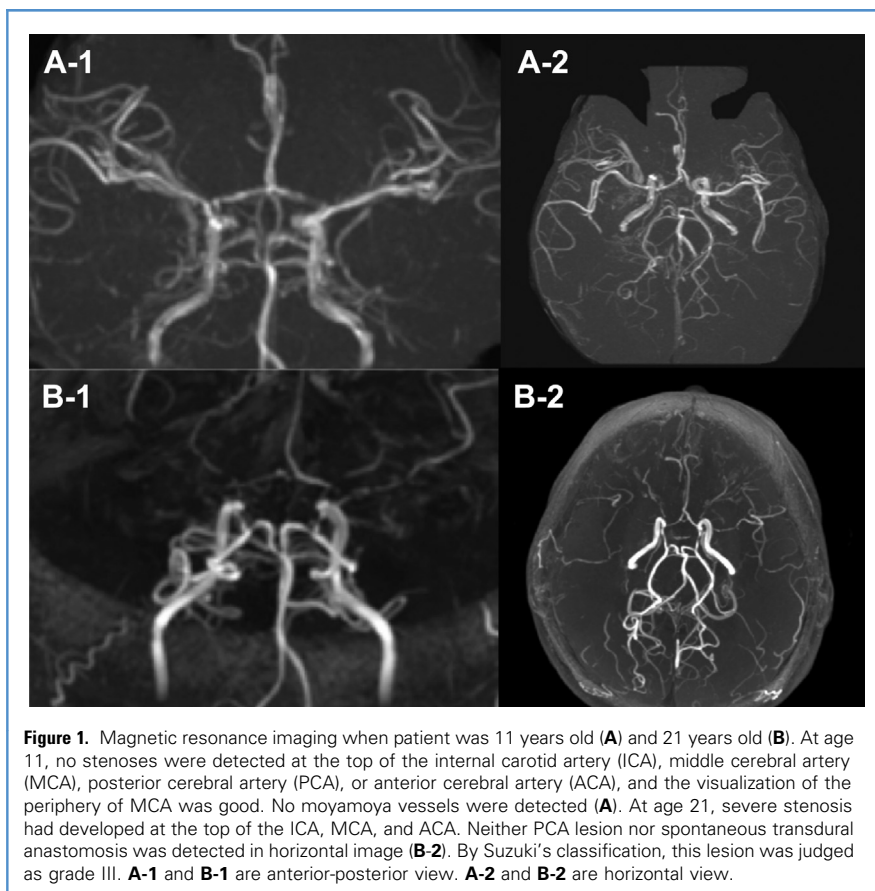


Figure 1. Magnetic resonance imaging when patient was 11 years old (A) and 21 years old (B). At age 11, no stenoses were detected at the top of the internal carotid artery (ICA), middle cerebral artery (MCA), posterior cerebral artery (PCA), or anterior cerebral artery (ACA), and the visualization of the periphery of MCA was good. No moyamoya vessels were detected (A). At age 21, severe stenosis had developed at the top of the ICA, MCA, and ACA. Neither PCA lesion nor spontaneous transdural anastomosis was detected in horizontal image (B-2). By Suzuki's classification, this lesion was judged as grade III. A-1 and B-1 are anterior-posterior view. A-2 and B-2 are horizontal view.

patient, her younger sister with moyamoya disease, and their nonsymptomatic parents. A heterozygous variant of *RNF213* (p.R4810K) was detected in these sisters and their mother.

DISCUSSION

Screening of Moyamoya Disease

In the guideline for moyamoya disease published in the United States,¹¹ screening

for moyamoya disease in nonsymptomatic patients is briefly mentioned. Specifically, the guideline says that a screening examination may be considered in selected populations, particularly in the setting of symptoms suggestive of cerebral ischemia. Select populations would include patients with moyamoya syndrome—associated conditions such as NF1, Down syndrome, congenital cardiac anomaly, renal artery stenosis, hyperthyroidism, and so on. On the other hand, the guideline suggests that the benefit of screening for patients with no symptoms or familial history are limited. Narisawa et al¹² reported that if asymptomatic patients are followed up with MRI/MRA every 6 months, they tended to have good outcomes from revascularization surgery due to the early detection of hemodynamic compromise such as ischemic events or progression in disease stage.

Familial moyamoya disease accounts for about 12%–15% of all cases,^{13,14} and recently, more asymptomatic moyamoya patients have been discovered because of widespread use of MRI.¹⁵ In a previous paper from our department,¹⁶ we reported that familial cases tend to be more severe than sporadic cases in terms of the occurrence rate of cerebral infarction, mental retardation, and occlusion of the posterior cerebral artery. Patients and their families sometimes hope to undergo screening examinations for moyamoya disease, being anxious about the possibility of a familial etiology, since screening may find the disease at an early stage. If detection of the disease before the onset of symptoms can lead to the prevention of ischemic brain damage by performing early revascularization surgery, such screening should be recommended.

Several points raise questions about the benefits of a screening scan. First, even if we could detect subtle stenosis of the intracerebral artery, revascularization surgery may not confer any benefit to the patients because both direct and indirect bypass surgery cannot provide good collateral flow when the cerebral perfusion pressure does not decrease significantly. Therefore in such situations, neurosurgeons generally cannot help but take a wait-and-scan strategy. The timing of surgery may not be different between the

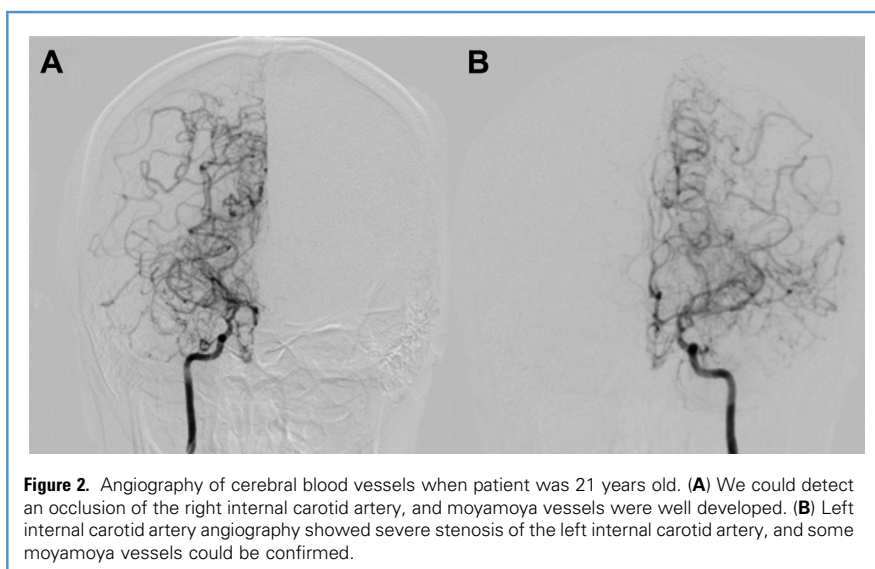
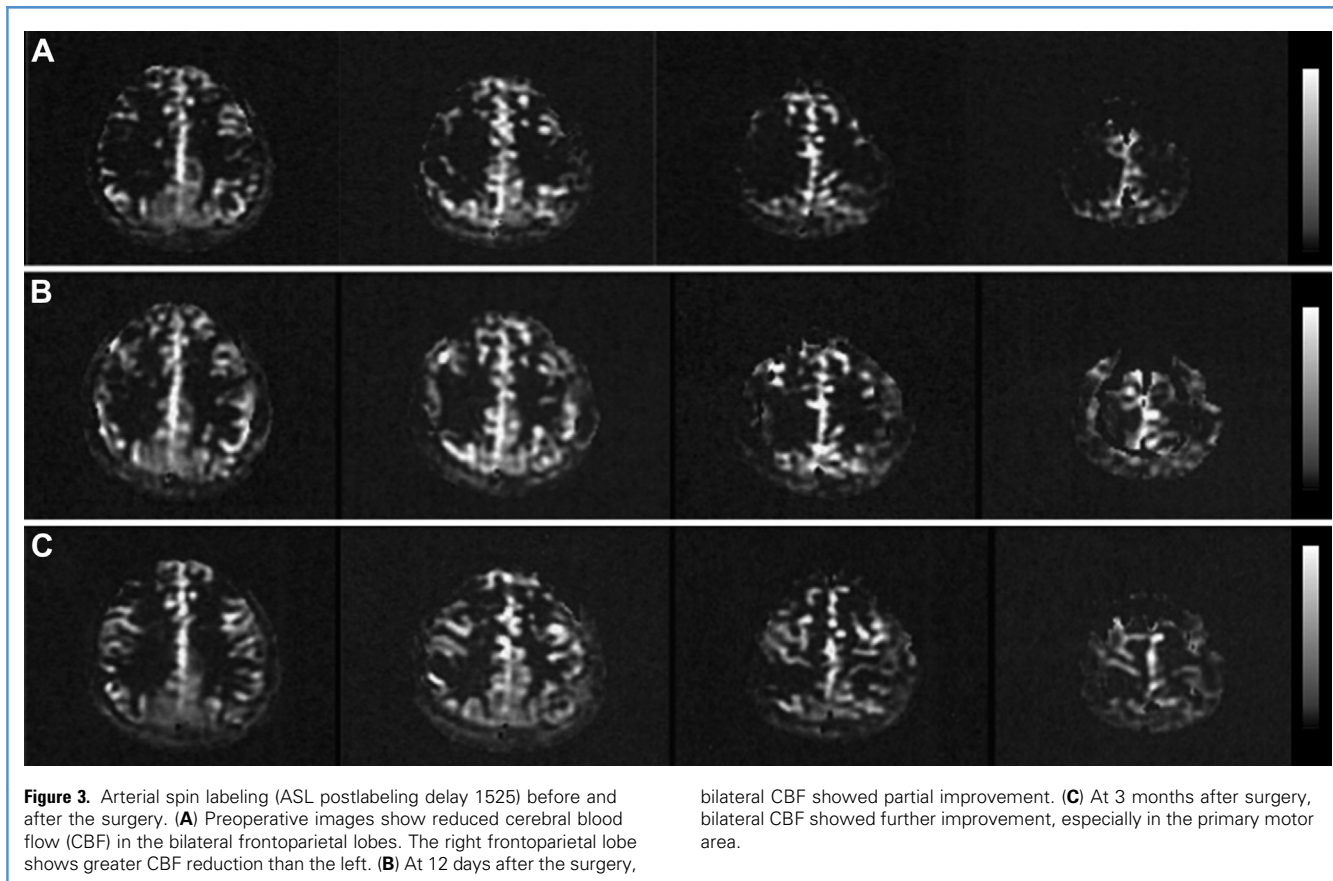


Figure 2. Angiography of cerebral blood vessels when patient was 21 years old. (A) We could detect an occlusion of the right internal carotid artery, and moyamoya vessels were well developed. (B) Left internal carotid artery angiography showed severe stenosis of the left internal carotid artery, and some moyamoya vessels could be confirmed.



detection of disease progress after such a wait-and-scan protocol and the first scan after a patient presents the first transient ischemic attack symptom. Second, the drawbacks of a screening MRI scan for small children who need sedation for examination may outweigh the benefits of the scan. We must always consider the balance of risks and benefits of screening scans in children.

Our present case report may raise a third issue related to the benefits of screening scans. Our patient displayed a normal MRA at the age of 11 but was diagnosed with typical bilateral moyamoya disease at the age of 21. In the past, we assumed that vessel occlusion of moyamoya disease progressed more rapidly in early childhood and stabilized in adolescence.¹⁷ However, such a concept established in the previous era of angiographic technology might simply be anecdotal. In the present MRA age, even in adult patients, we have experienced disease progress of patients who were accidentally diagnosed while

asymptomatic.¹⁴ We are not yet sure when in the lifespan vessel stenosis due to moyamoya is most likely to appear and reach severe stenosis and occlusion. Tashiro et al¹⁸ reported a newly developed moyamoya disease shown in an adult patient with the RNF213 variant. As the present case report and Tashiro's case suggest, the development pattern may be individual to each patient.

Mutation and Familial Moyamoya Disease

Our present case report also raises a question about the benefit of genetic analysis. RNF213, p.R4810K was reported in 2013 as a susceptibility gene of moyamoya disease^{2,3}; polymorphism of that gene was reported as present in 72%–89% of all Japanese patients with moyamoya disease.^{2,4,19} On the other hand, 1.4%–2.4% of the overall Japanese population has this gene polymorphism^{2,4,19}; therefore the penetration rate of this gene mutation is considered rather low. The present case report may provoke an interesting but complex problem

regarding screening for an RNF213, p.R4810K gene polymorphism. If de-novo appearance of moyamoya disease as presented in this paper is not uncommon, the exact penetration rate of the gene polymorphism may not be clarified by only 1-time screening. Also, if someone who is positive for the rare variant gene was diagnosed with a normal MRA in the initial screening, we cannot guarantee that this subject will not present with moyamoya disease at another time. Considering these problems, we conclude that there may be little benefit in screening with MRA and gene mutation studies while subjects are asymptomatic.

Such problems may arise simply because there is insufficient knowledge on the time course of the cerebral vessel occlusion process in moyamoya patients. We may need to accumulate a greater amount of data on such de-novo cases from the national or possibly even the global level to reveal the natural course of moyamoya disease and clarify the correlation between gene mutation and disease onset.

CONCLUSION

We show a case of familial moyamoya disease diagnosed 10 years after a negative MRI screening in childhood. We must carefully consider when, how, and for whom screening for moyamoya disease is performed, taking into account familial history.

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