

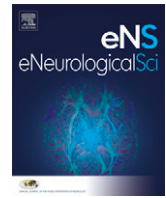
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Evolution into moyamoya disease in an infant with internal carotid artery aneurysms

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## Case report

# Evolution into moyamoya disease in an infant with internal carotid artery aneurysms



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## ABSTRACT

**Introduction:** Moyamoya disease (MMD) is characterized by progressive stenosis and occlusion in the terminal portion of both internal carotid arteries (ICAs) and the formation of an abnormal vascular network. Because of the fragile structure of the collateral vessels, MMD is frequently accompanied by intracranial aneurysms that are mainly located within the abnormal basal network or the circle of Willis. However, the association between MMD and aneurysms of the ICAs has never been reported previously.

**Case report:** A 1-month-old infant presented with a decreased level of consciousness and arterial infarction in the right frontal and temporal lobes. Brain computed tomography angiography results showed aneurysms in both ICAs and occlusions of the distal part of the aneurysms without moyamoya collateral vessels. Aspirin therapy was initiated, and his clinical status stabilized. At 12 months of age, collateral networks of small vessels were found in the distal part of both ICAs, and MMD had evolved. At 24 months of age, he remains on aspirin therapy, and no further ischemic events have occurred.

**Conclusions:** This is the first report of MMD in which ICA aneurysms and occlusions developed bilaterally in early infancy without moyamoya collateral vessels. Our case indicates that angiogenesis at the base of the brain may occur following extracellular matrix remodeling at the terminal portion of the ICAs.

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## 1. Introduction

Moyamoya disease (MMD) is characterized by progressive stenosis and occlusion in the terminal portion of the bilateral internal carotid arteries (ICAs) and the formation of an abnormal vascular network. Pathological analysis has shown that arterial occlusion results from a combination of hyperplasia of smooth muscle cells and luminal thrombosis. Whereas, smooth muscle cells of the collateral vessels are decreased, resulting in a thinner media [1]. Because of the fragile structure of the collateral vessels, probably along with hemodynamic stress, MMD is frequently accompanied by intracranial aneurysms that are mainly located within the abnormal basal network or the circle of Willis [2]. However, the association of MMD with aneurysms of the ICAs has never been reported previously.

Here we describe a rare case of a 1-month-old infant with early-onset arterial infarction and bilateral cerebral arteriopathies, including occlusion and large saccular aneurysms of both ICAs, which subsequently evolved into MMD. Repeated magnetic resonance angiography

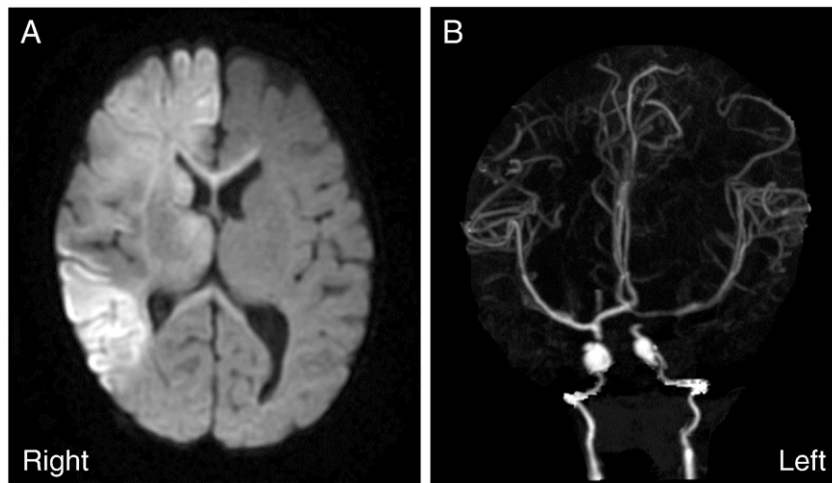
(MRA) enabled us to monitor the progression of occlusive changes in the ICAs and the formation of an abnormal vascular network.

## 2. Case report

A 1-month-old male infant presented with recurrent tonic seizures and a decreased level of consciousness. There was no history of trauma and no family history of MMD or thrombosis. His blood tests, including coagulation tests and antinuclear antibody tests, showed normal results. Brain computed tomography (CT) scan showed hypodensity and loss of the cortical ribbon in the right frontal and temporal lobes, and diffusion-weighted magnetic resonance imaging (MRI) scan demonstrated abnormal high signal intensity in the same areas (Fig. 1A). Brain CT angiography results showed aneurysms in both ICAs and occlusions of the distal part of the aneurysms (Fig. 1B). MRA findings demonstrated a loss of flow signal in both terminal ICAs without moyamoya collateral vessels (Fig. 2A). Results of <sup>99m</sup>Tc-ethyl-cysteinate-dimer single-photon emission CT (<sup>99m</sup>Tc-ECD SPECT) showed poor perfusion in the right frontal lobe; however, the other areas appeared normal (Fig. 3A). The intra-cerebral vessels were considered perfused with blood from the external carotid arteries or vertebral arteries.

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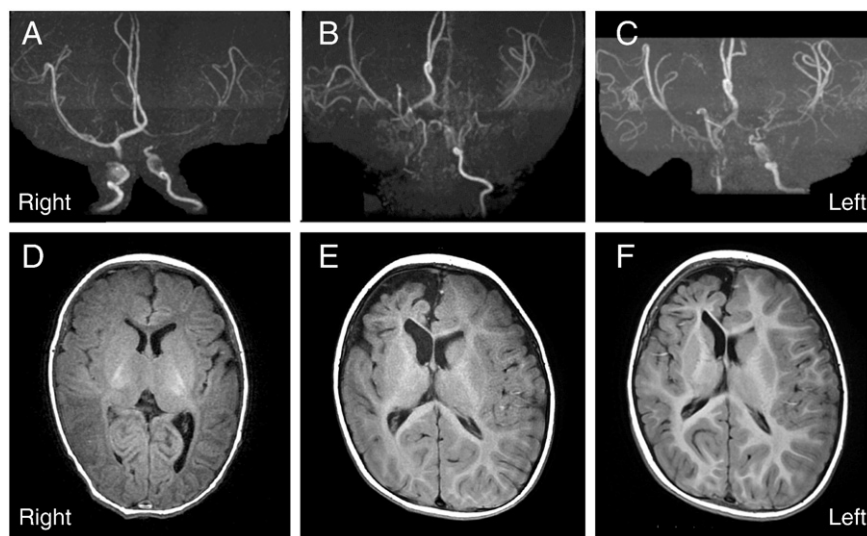
**Fig. 1.** Diffusion-weighted magnetic resonance imaging (A) and computed tomography angiogram (B) at the onset of arterial infarction of the right frontal and temporal lobes in a 1-month-old infant. Large saccular aneurysms in both internal carotid arteries and occlusions of the distal part of the aneurysms were observed (B).

Thereafter, aspirin therapy was initiated, and his clinical status stabilized. At 12 months of age, he manifested mild left hemiparesis. Brain MRI findings showed moderate hypoplasia in the right frontal, parietal and temporal lobes (Fig. 2E). The right ICA was no longer visualized on MRA examination (Fig. 2B). At that time, collateral networks of small vessels were found in the distal part of both ICAs, and MMD had evolved. At 24 months of age, he could run and climb stairs unaided, although he was uncoordinated with his left hand, and his speech development was normal. He remains on aspirin therapy, and no further ischemic events have occurred. Maximal diameter of the left ICA aneurysms at the ages of 1, 12, and 24 months were 8.9 mm, 8.8 mm, and 7.9 mm, respectively (Fig. 2A, B, and C). During follow-up,  $^{99m}\text{Tc}$ -ECD SPECT showed decreased perfusion in the right frontal lobe, however the other areas maintained normal levels of perfusion (Fig. 3B, C). These serial results of SPECT appeared to reflect his developmental profile in psychomotor functions. Genetic analysis of *RNF213*, the gene identified as a susceptibility gene for MMD [3], showed wild type at nucleotide 14576. We consult with the neurosurgeon to determine the optimal timing for surgery.

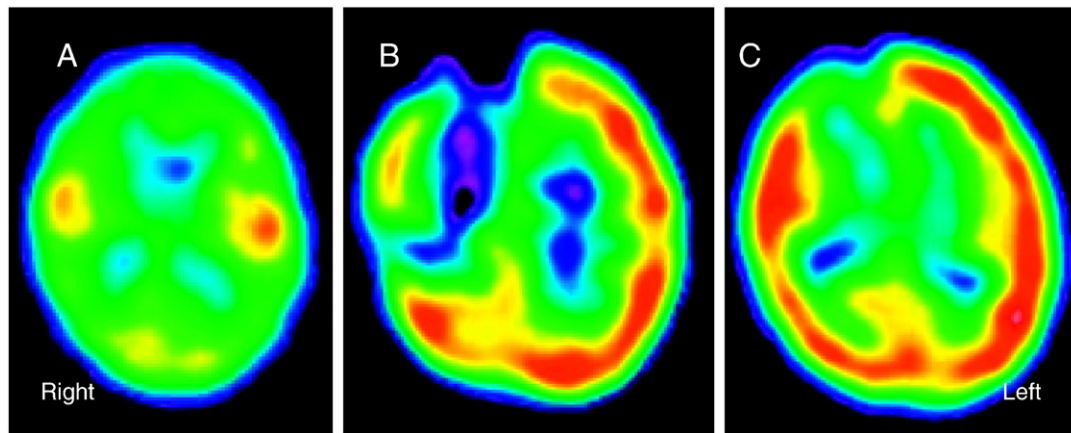
### 3. Discussion

The present case demonstrated serial changes of vasculopathy in an infant who initially presented with occlusions and large aneurysms of both ICAs before moyamoya collateral vessels developed. The c.14576G>A variant of the *RNF213* gene could be a good DNA biomarker for predicting the severe type of MMD [3]. However, it is important to note that there are reports of identical twins with only one affected sibling, supporting the possibility that non-genetic factors also contribute to the pathogenesis of this disease [4]. Haplotype analysis in this patient showed wild type at nucleotide 14576 of *RNF213*. Therefore, our case suggests that other genes or environmental factors may have a role in the pathogenesis of ICA aneurysms and MMD vasculopathy.

Recent studies have shown the importance of extracellular matrix (ECM) remodeling in the pathogenesis of cerebral aneurysm and MMD vasculopathy. Serum levels of matrix metalloproteinase (MMP)-9, a proteinase that is involved in the ECM degradation and promotes the progression of cerebral aneurysm, were reported to be significantly higher in patients with MMD than in healthy controls [5,6]. MMP-9 is



**Fig. 2.** Serial changes of vasculopathy in an infant with occlusions and large aneurysms of both internal carotid arteries before the development of moyamoya collateral vessels. Magnetic resonance angiography images at 1 month of age (A), 12 months of age (B), and 24 months of age (C); T1-weighted magnetic resonance images at 1 month of age (D), 12 months of age (E), and 24 months of age (F).



**Fig. 3.** Serial changes of cerebral blood flow in an infant with occlusions and large aneurysms of both internal carotid arteries before the development of moyamoya collateral vessels.  $^{99m}\text{Tc}$ -ethyl cysteinate dimer single-photon emission computed tomography ( $^{99m}\text{Tc}$ -ECD SPECT) at 1 month of age (A), 12 months of age (B), and 24 months of age (C).

secreted as an inactive precursor, proMMP-9, and is activated at specific sites by proteinases *in vivo*. The tissue inhibitor of metalloproteinase-1 (TIMP-1), a tissue inhibitor of MMPs, is an inhibitor of MMP-9, which participates in controlling the local activities of MMP-9 in tissues. TIMP-1 is mainly expressed by smooth muscle cells in aneurysmal walls [7]. In this patient, bilateral arterial occlusions and aneurysms occurred at the particular location in the terminal portion of the ICAs. Thus, imbalance between MMP-9 and TIMP-1 in the terminal portion of the ICAs may be one of the potential mechanisms underlying this rare association between MMD and ICA aneurysms. Our case further indicates that angiogenesis at the base of the brain may occur following ECM remodeling due to several factors that affect the terminal portion of the ICAs, however, those presumptions need further investigation.

This is the first report of MMD in which ICA aneurysms and occlusions developed bilaterally in the early stage of the disease. The temporal profile of vasculopathy in such a case may contribute to elucidating the underlying mechanism of the development and progression of MMD.

#### Conflict of interest

The authors declare that there are no conflicts of interest.

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