

## Case Studies

## Postpartum Ischemic Stroke in Moyamoya Disease Associated with Protein Z Deficiency—A Case Report

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The authors describe herein the first adult case with moyamoya disease associated with protein Z deficiency. A 41-year-old woman was admitted to our hospital due to sudden onset of dysarthria and left extremity weakness 6 days after the delivery of her first baby. Previously, she repeated early fetal losses and was diagnosed with protein Z deficiency. Laboratory examination showed that the plasma concentration of protein Z was .73  $\mu\text{g}/\text{ml}$ , being lower than the control. Radiological examination demonstrated typical findings of moyamoya disease with advanced stage on both sides. She successfully underwent surgical revascularization on both sides and was free from any cerebrovascular events during a follow-up period of 2 years. In addition to hemodynamic compromise, protein Z deficiency and hypercoagulation state after delivery might cause ischemic stroke in this case.

**Key Words:** Moyamoya disease—ischemic stroke—protein Z deficiency—delivery.

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### Background

Moyamoya disease is an uncommon cerebrovascular disorder that is characterized by progressive occlusion of the supraclinoid internal carotid artery (ICA) and its main branches within the circle of Willis. This occlusion results in the dilation of perforating arteries at the base of brain (moyamoya vessels).<sup>1,2</sup> In this report, the authors

describe the first case with moyamoya disease associated with protein Z deficiency.

### Case Presentation

A 41-year-old woman was referred to our hospital due to sudden onset of dysarthria and left extremity weakness 6 days after the delivery of her first baby. She had the past history of repeated spontaneous abortion and was diagnosed with protein Z deficiency, but had experienced no cerebrovascular events. Neurological examination on admission revealed mild dysarthria and weakness of the left extremities. Laboratory examination showed that the plasma concentration of protein Z was .73  $\mu\text{g}/\text{ml}$ , being lower than the control ( $2.9 \pm 1.0 \mu\text{g}/\text{ml}$ ).<sup>3</sup> Diffusion-weighted magnetic resonance imaging demonstrated multiple small infarctions in the right frontal and parietal lobes (Fig 1, A). Cerebral angiography showed the occlusion of the right cervical ICA (Fig 1, B). The supraclinoid portion of the left ICA was also occluded, and the intracranial branches were opacified via the ethmoid moyamoya vessels (Fig 1, C). On the axial images of three-dimensional constructive

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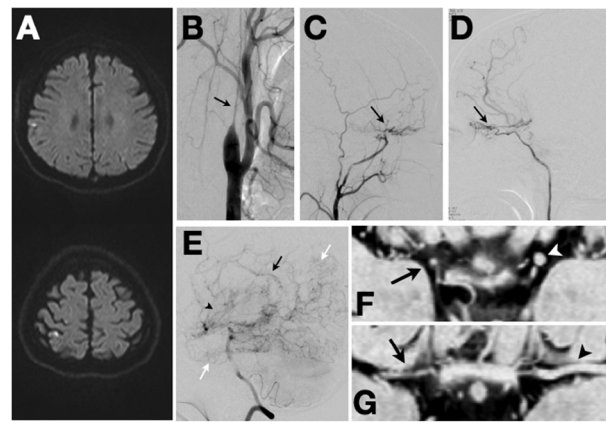
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interference in steady state (3D-CISS), the outer diameter of the supraclinoid ICA was 1.1 and 2.2 mm on the right and left sides, respectively. The values were abnormally smaller than the control ( $3.4 \pm .8$  mm, Fig 1, D).<sup>4,5</sup> Likewise, the outer diameter of the horizontal portion of the middle cerebral artery was .7 and 1.5 mm on the right and left sides, respectively. The values were also smaller than the control ( $2.7 \pm .4$  mm, Fig 1, E).<sup>4,5</sup> Therefore, she was diagnosed with ischemic stroke due to moyamoya disease associated with protein Z deficiency. Cerebral blood flow (CBF) measurements demonstrated markedly reduced CBF and cerebrovascular reactivity to acetazolamide on both sides.<sup>6</sup> She underwent surgical revascularization on both sides, as reported previously.<sup>7</sup> Postoperative course was uneventful. She was discharged without any neurological deficits. She is free from any cerebrovascular events for the last 2 years.

## Discussion

This is the first case with moyamoya disease associated with protein Z deficiency, although there are several case reports to describe moyamoya disease comorbid with protein C or S deficiency.<sup>8</sup> It is sometimes difficult to diagnose a moyamoya disease in patients with advanced stage because of a lack of basal moyamoya vessels. According to recent studies, however, the shrinkage of the involved arteries is highly specific for moyamoya disease.<sup>4,5</sup> Based on the findings on 3D-CISS (Fig 1), this case could be diagnosed as moyamoya disease.

Protein Z is a vitamin-K-dependent plasma glycoprotein and inhibits the activation of factor X by serving as a cofactor to a plasma proteinase inhibitor.<sup>3</sup> Protein Z deficiency has recently been reported in women with unexplained early fetal losses. Protein Z is also known to increase up to 120% of the control from the first trimester to delivery and decrease 6-12 weeks after delivery.<sup>9</sup> Therefore, the plasma concentration of protein Z was considered quite low in this case. Protein Z deficiency often causes arterial and venous thrombosis.<sup>10</sup> Furthermore, coagulation state is known to dramatically increase during the second and third trimesters and during the first postpartum week.<sup>11</sup> In general, cerebral infarction often develops in the watershed zone due to hemodynamic insufficiency in moyamoya disease.<sup>2</sup> However, the findings on diffusion-weighted imaging were atypical as watershed zone infarction. In addition to hemodynamic insufficiency, therefore, artery-to-artery thromboembolism through the collateral pathways due to protein Z deficiency and hypercoagulation state after delivery was also involved in the occurrence of ischemic stroke in this case (Fig 1, A). This speculation can be supported by the "washout" theory proposed by Caplan and Hennerici.<sup>12</sup>



**Figure 1.** Radiological findings of a 41-year-old woman with moyamoya disease associated with protein Z deficiency. (A) Diffusion-weighted magnetic resonance imaging demonstrated multiple small cerebral infarctions in the right frontal and parietal lobes. (B) Right common carotid angiography revealed a marked collapse of the right ICA (arrow). (C) On cranial portion of right common carotid angiography, the right ICA is not opacified, indicating its complete occlusion in the cervical portion. Note the abnormal collateral circulation through the right middle meningeal artery (arrow). (D) Left internal carotid angiography showed the occlusion of the supraclinoid ICA with the collateral circulation through ethmoidal moyamoya vessels arising from the ophthalmic artery (arrow). (E) Left vertebral angiography showed multiple and rich collateral pathways through the posterior pericallosal artery (black arrow), pial anastomosis (white arrows), and the perforators arising from the posterior communicating artery to the thalamus (arrowhead). (F) 3D-CISS imaging shows the shrinkage of the supraclinoid ICA on the right (arrow) and left sides (arrowhead). (G) 3D-CISS imaging shows the shrinkage of the horizontal portion of middle cerebral artery on the right (arrow) and left sides (arrowhead). Abbreviations: 3D-CISS, three-dimensional constructive interference in steady state; ICA, internal carotid artery.

## References

1. Suzuki J, Takaku A. Cerebrovascular moyamoya disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 1969;20:288-299.
2. Kuroda S, Houkin K. Moyamoya disease: current concepts and future perspectives. *Lancet Neurol* 2008;7:1056-1066.
3. Miletich JP, Broze GJ Jr. Human plasma protein Z antigen: range in normal subjects and effect of warfarin therapy. *Blood* 1987;69:1580-1586.
4. Kuroda S, Kasihwazaki D, Akioka N, et al. Specific shrinkage of carotid forks in moyamoya disease: a novel key finding for diagnosis. *Neurol Med Chir (Tokyo)* 2015;55:796-804.
5. Yamamoto S, Koh M, Kashiwazaki D, et al. Is quasi-moyamoya disease a uniform disease entity? A three-dimensional constructive interference in steady state imaging study. *J Stroke Cerebrovasc Dis* 2016;25:1509-1516. [Epub ahead of print].
6. Kuroda S, Houkin K, Kamiyama H, et al. Long-term prognosis of medically treated patients with internal carotid or middle cerebral artery occlusion: can acetazolamide test predict it? *Stroke* 2001;32:2110-2116.
7. Kuroda S, Houkin K, Ishikawa T, et al. Novel bypass surgery for moyamoya disease using pericranial flap: its impact on cerebral hemodynamics and long-term outcome. *Neurosurgery* 2010;66:1093-1101.

8. Bonduel M, Hepner M, Sciuccati G, et al. Prothrombotic disorders in children with moyamoya syndrome. *Stroke* 2001;32:1786-1792.
9. Quack Loetscher KC, Stiller R, Roos M, et al. Protein Z in normal pregnancy. *Thromb Haemost* 2005;93:706-709.
10. Pardos-Gea J, Ordi-Ros J, Serrano S, et al. Protein Z levels and anti-protein Z antibodies in patients with arterial and venous thrombosis. *Thromb Res* 2008;121:727-734.
11. Donaldson JO, Lee NS. Arterial and venous stroke associated with pregnancy. *Neurol Clin* 1994;12:583-599.
12. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Arch Neurol* 1998;55:1475-1482.