Posterior cerebral artery involvement and pediatric moyamoya disease

To The Editor: We read with great interest the article by Funaki et al. (Funaki T, Takahashi JC, Takagi Y, et al: Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease. Clinical article. J Neurosurg Pediatr 12:626–632, December 2013), which clearly showed that preoperative stenoocclusive lesions in the posterior cerebral artery (PCA) and infarctions before surgery were two independent risks that predicted future impairment of the postoperative long-term (average 15 years) clinical and social outcomes (long-term outcomes) in pediatric moyamoya disease.

The authors speculated on two possible reasons why preoperative PCA involvement and infarction were independently associated with unfavorable long-term outcomes in the multivariate analysis, although preoperative PCA involvement was reported to be associated with infarction.6,9

We completely agree with the authors’ speculation that preoperative PCA involvement represents “overall progression.” In moyamoya disease, occlusive changes initially affect the internal carotid artery (ICA) system, followed by PCA involvement mostly in its proximal segment, and therefore preoperative PCA involvement indicates a more advanced stage owing to the “aggressive nature” of pediatric moyamoya, which may affect the long-term outcomes. Indeed, homozygous c.14576G>A variant, ring finger protein 213 (RNF213), was recently discovered in patients with moyamoya disease with early onset and PCA involvement.5 Such patients with early onset and PCA involvement were already known as having an “aggressive type” of pediatric moyamoya in the literature.6 If the hypothesis is indeed the case, we also presume that the aggressive nature of this disease may cause further progression of PCA changes postoperatively as well as involvement in the anterior circulation as described in the literature,3,8 which should lead to unfavorable long-term outcomes as well. However, we are not sure if this overall progression theory could well explain why preoperative PCA involvement was associated with long-term outcomes independently of the severity of infarction, because we suspect that “overall progression” of this disease would cause further progression of ICA and PCA lesions and lead to development of infarctions accordingly.

Another speculation of the authors is that decreased cerebral blood flow (CBF) in the medial part of the hemisphere or the area supplied by the anterior cerebral artery (ACA) may result in unfavorable long-term outcomes. We can agree with this hypothesis, given that there are two kinds of leptomeningeal collaterals from the PCA to the anterior circulation, with territory-specific perfusion patterns, which we have previously proposed: 1) deep leptomeningeal collaterals through the posterior pericallosal artery from the proximal PCA that mainly perfuse the medial part of the hemisphere or the area supplied by the ACA, and 2) superficial leptomeningeal collaterals from the more distal PCA branches that mainly perfuse the lateral part of the hemisphere, including the middle cerebral artery (MCA) and its adjacent anterior and posterior watershed areas.7

Indeed, recent evidence has shown that, in patients without PCA involvement, cerebrovascular reserve capacity was exhausted with resultant decreased CBF in the lateral part of the hemisphere or the MCA and its adjacent anterior and posterior watershed areas, while there was no such decrease in the medial part of the hemisphere or the ACA territory with relatively preserved CBF.10 We believe that this insufficient compensation in the lateral part of the hemisphere was due to the lengthy and retrograde route of the superficial leptomeningeal collaterals from the distal PCA to the MCA territory and its adjacent watershed zones.7 The anterior watershed would be the distribution farthest from the heart. Indeed, in patients with and without PCA involvement, the anterior watershed is most commonly involved in this disease by infarction.9 Moreover, infarctions in the MCA, the adjacent anterior and posterior watershed areas, and the PCA territory showed a significant positive relationship to the severity of PCA lesions.8 In other words, infarctions tend to be distributed in the anterior watershed in less-advanced PCA cases, whereas in more-advanced PCA cases, lesions are additionally found posteriorly in the MCA area and the posterior watershed area. We postulate that decrease in superficial leptomeningeal collaterals owing to the advancement of PCA changes is closely related to development of cerebral infarctions in the lateral part of the hemisphere.9 Thus, we postulate that preoperative infarctions found in the study by Funaki et al., specifically large corticosubcortical infarctions, might have been caused by this mechanism or uncompensated superficial leptomeningeal collaterals, which could lead to unfavorable long-term outcomes with neurological deficits.

In contrast, preoperative infarctions were least common in the medial part of the hemisphere or the ACA territory, and their prevalence did not show significant correlation to the severity of PCA lesion.9 This may be explained by relative preservation of CBF there. In patients without PCA involvement or even in patients with PCA involvement, this region would receive relatively ample blood supply from the proximal PCA via the deep leptomeningeal collaterals and via the moyamoya vessels of the PCA (PCA moyamoya), including enlarged medial
posterior choroidal arteries that are known to have frequent anastomoses with the posterior pericallosal artery.\(^7\) The PCA moyamoya might gradually increase as the stenoocclusive PCA involvement advances until it becomes extremely severe, whereas the superficial leptomeningeal collaterals consistently decrease.\(^9\) Additionally, development of transdural collaterals from the ophthalmic artery or from the external carotid artery system could also contribute to the supply of the medial part of the hemisphere or the ACA territory. Thus, the ischemia would not be so severe as to cause infarction in this region even in patients with PCA involvement. As the stenoocclusive PCA involvement further advances to an even more severe degree, however, the PCA moyamoya and the deep leptomeningeal collaterals would decrease, with resultant decrease in CBF also in the medial part of the hemisphere or the area supplied by the ACA. This may in turn cause deterioration of neuropsychological functions and lead to unfavorable long-term outcomes as Funaki et al. speculated, irrespective of the severity of preoperative infarction. Thus, we suspect that such sequential changes in CBF pattern associated with evolving PCA involvement, including development of superficial and deep leptomeningeal collaterals from the PCA, might affect the long-term outcomes independent of preoperative infarction.

Since first described in the 1980s,\(^4\) PCA involvement has been described in several reports, but it is still generally disregarded in the literature. However, we believe that PCA lesions and the resulting decreased leptomeningeal collaterals from the proximal and distal PCA are closely related to the development of ischemia and infarction and affect long-term outcomes, which in turn affect the therapeutic strategy for pediatric patients with moyamoya disease.

**Disclosure**

The authors report no conflict of interest.

**References**


**Response:** We thank Drs. Mugikura and Takahashi for their thoughtful interpretation of our results from a radiographic perspective. Their comments address two points. First, they show that the association between PCA involvement and social outcome—which we revealed was independent of infarction—cannot be explained by the overall progression theory that PCA involvement might represent the overall progression of a stenoocclusive lesion in moyamoya disease. They referred to their recent work revealing that PCA involvement is associated with infarction in the cortical areas.\(^8\) We agree with their finding of 2011 because the senior author had already reported this discovery in the 1980s.\(^7\) In practice, however, we sometimes encounter cases of PCA involvement in which MRI reveals minimal infarction. In such cases, activities of daily life are well preserved because these patients have not experienced a major stroke. A PCA lesion might progress relatively slowly in such cases, allowing for sufficient development of other collaterals such as transdural anastomosis. Most of these patients, however, suffer from social adaptation problems as a result of cognitive impairment. Recently, Karzmark et al. demonstrated that cognitive impairment in moyamoya disease occurs in the absence of ischemic stroke as manifested on MRI.\(^3\) Long-standing cerebral hypoperfusion might be a cause of such impairment. In any event, PCA involvement might more accurately represent overall disease progression. As they postulated in the recent report,\(^9\) and as the senior author already demonstrated conceptually in the 1980s,\(^7\) progression of moyamoya disease should be staged according to involvement of the ICA as well as that of the PCA.

Second, it seems Drs. Mugikura and Takahashi question our speculation that decreased blood flow in the medial frontal lobe may cause unfavorable social outcome in patients with PCA involvement. They postulate that the medial frontal lobe is less affected even in patients with PCA involvement on the grounds that they found no increased prevalence of infarction in the ACA territory in cases with PCA involvement.\(^7\) We agree, in part, with
their findings because the senior author obtained the same results previously.² It is obvious, however, that CBF in this area is usually decreased in patients with involvement of both the ICA and PCA because collaterals via the posterior pericallosal artery, which they call “deep leptomeningeal collaterals,” are lost in the early stage of PCA involvement; the posterior pericallosal artery usually arises within the quadrigeminal cistern, from the PCA,³ and involvement of the PCA starts initially from the quadrigeminal segment of the PCA.⁴ Matched hypometabolism attributable to cortical neuron loss might be one reason that infarction in this area is less common in spite of decreased CBF. In the medial frontal area, decreased CBF is compensated for by several specific collaterals including trans–ethmoidal artery anastomosis (ethmoidal moyamoya).¹³ While this compensation might prevent critical ischemia resulting in infarct, longstanding mild ischemia might cause cortical neuron loss. Recently, Nakagawara et al. revealed that longstanding mild ischemia in moyamoya disease could lead to cortical neuron loss in the medial frontal lobes, as detected with [¹²³I]iomazenil SPECT, and that such neuron loss in bilateral medial frontal lobes was correlated with cognitive dysfunction.¹¹ In our latest study, frontal lobe dysfunction detected through several frontal lobe evaluation tasks was strongly associated with difficulty with social independence in moyamoya disease.¹ From these more recent findings, we can logically speculate that decreased CBF in the medial frontal lobe is one possible cause of unfavorable social outcome in patients with PCA involvement.

Generally, we agree with Mugikura and Takahashi’s theory that the PCA can supply two types of collaterals—leptomeningeal collaterals and those via the posterior pericallosal artery—and this view is common among those treating moyamoya disease in clinical practice. However, the theory alone does not fully explain the independent association between PCA involvement and social outcome. Although the senior author first reported the clinical importance of PCA involvement in moyamoya disease in the 1980s,⁵ this phenomenon has been disregarded for many years, as Mugikura and Takahashi pointed out. We welcome the recent revival and flourishing discussion of PCA involvement²–⁴,⁸,¹⁰ and hope that further discussion and investigation of this unique phenomenon will promote understanding of the pathophysiology of moyamoya disease.

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References

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