Editorial Commentary

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Twig-like middle cerebral artery: Embryological persistence or secondary consequences?

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We would like to comment on twig-like middle cerebral artery (MCA) in relation to the interesting article "Hemorrhagic events associated with unfused or twig-like configuration of the middle cerebral artery: A rare vascular anomaly with clinical relevance." by Dr. Viso et al.1 in the April issue of our journal. In this article, the authors reported on twig-like MCAs identified in 9 patients (0.088%) and 62.5% of them were hemorrhagic.

Introduction

MCA arises normally from internal carotid artery (ICA) as a single artery. Anomalies of MCA are found less frequently than those of the other major intracranial arteries.[2] MCA anomalies such as accessory MCA, duplicated MCA, and fenestration of MCA might be found in humans.[2,3] Recently, there are several reports describing unfused or twig-like MCA, in which the proximal trunk of MCA has not been found and it is accompanied by the plexiform arterial network.[4–7] Development of accessory and/or duplicated MCA are understood as an anomalously early ramification of the branches of MCA.[8] Thus, they are branching variations, and embryological vessels do not remain as their original configuration. At present, the pathogenesis of twig-like MCA is not yet elucidated.

Twig-like MCA

Twig-like MCA is reported as a rare vascular anomaly characterized by re-constitution of the M1 segment of MCA by a plexiform network of small vessels.[5] Twig-like MCA was detected in 0.11%–1.17% of individuals who underwent diagnostic angiography.[4,5,9] Literature concerning twig-like MCA is limited to case reports and small case series. The twig is connected from the distal ICA to the distal horizontal portion of MCA while lenticulostriate arteries (LSAs) arise from the plexiform network of the affected M1 segment.[4,5] In 2005, Cekirge et al. reported a case of an occluded MCA trunk with collateral plexiform network and named this variation as embryonic unfused MCA.[7] Liu et al. in the same year reported two similar cases and named them as twig-like MCA.[4] In 2012, Seo et al. reported the largest series of 15 cases and named them as aplastic or twig-like MCA.[5] Seo et al. explained that twig-like MCA is a persistent primitive plexus of MCA. Shin et al. subsequently reported four cases in 2014.[5] Common angiographical features of these cases are as follows; 1) a steno-occlusive lesion at the unilateral MCA,[4,5,10,11] except for one bilateral case,[12] 2) plexiform arterial network replacing the proximal MCA trunk, 3) LSAs arising from the plexiform arterial network, 4) normal cortical branches beyond the affected MCA trunk with anterograde flow, and 5) compromised blood flow to the distal MCA with compensatory leptomeningeal collaterals from anterior and posterior cerebral arteries.[9] Almost half of the cases presented with intracranial hemorrhage, and few cases were found incidentally.

Recent review of the literature summarized 42 stroke patients with twig-like MCAs.[9] Their ages ranged from 10–83 years (mean 52.9 years old) and 29 patients (69%) were female. Their symptoms included subarachnoid hemorrhage or intracerebral hemorrhage in 24 patients (57%), cerebral infarct or transient ischemic attack in 6 (14%). In the remaining 12 patients, the lesion was incidentally discovered, or their clinical presentation was not detailed.

Embryology of middle cerebral artery

The developing prosencephalon is supplied by primitive ICA, which comprises of the cranial and caudal divisions. The terminal branch of the cranial division of primitive ICA constitutes primitive olfactory artery

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(POA). POA, from which ACA eventually develops, has the medial and lateral olfactory arteries. Lateral olfactory artery divides into lateral striate artery and primitive anterior choroidal artery (AchA). Just distal to primitive AchA, plexiform arterial twigs appear, which later develop into lateral striate arteries by fusion and regression.[13] A group of embryological lateral striate arteries, which supply the growing cerebral hemispheres and basal ganglias, become MCA and perforating arteries to the basal ganglia.[14] Finally at the 40 mm stage of the embryo, MCA attains the approximate adult configuration.[13] Although there is no consensus about pathogeneses of MCA variations to date, accessory MCA, duplicated MCA, and MCA fenestration are presumed to be a failure in normal fusion/regression of primitive arterial network (group of lateral striate arteries).[14]

Pathogenesis of twig-like MCA

Although pathogenesis of twig-like MCA has not been fully understood, it is generally believed that it is a developmental anomaly due to unknown mechanism or ischemic insult *in utero*. That is, twig-like MCA is regarded as a "persistent" arterial network of primitive MCA due to regression failure.[5,10,11] Although this hypothesis seems to be reasonable,[5] it is difficult to prove that twig-like MCA is congenital, persistent anomaly. It seems unlikely that such embryological arterial network persists as it is until late adulthood (mean 52.9 years old) and retains angiographical twig-like configurations which we come across in the adult patients. Seo et al. illustrated the evolutional process of primitive MCA transformed into the adult form.[5] However, the size of a fetus and an adult are obviously not the same. At least 40 times difference in size exists between them. Their illustration is unacceptable because the scale size had not been considered. Currently, we believe there is no definitive evidence to support the hypothesis that twig-like MCA is the persistent embryonal arterial network.

Aneurysm formation

Aneurysm formation is a known complication of twig-like MCA. Aneurysms may arise at twigs,[6] distal ICA[5] or the A1-A2 junction of the anterior cerebral artery,[15] suggesting that they are flow-related aneurysms.[9] It is reported that intracranial hemorrhage occurred in up to 40% of twig-like MCA cases.[5,9] It has occurred from rupture of an aneurysm, but many were presumably non-aneurysmal intracranial hemorrhages. The primitive arterial walls are considered to be vulnerable to hemodynamic stress.[5] If flow-related aneurysms are formed on embryologically persistent vessels, it is strongly postulated that they rupture at younger ages. The fact that twig-like MCA has been reported primarily in adult population implies that this is not an embryonal anomaly.

Moyamoya disease

Differential diagnoses of twig-like MCA include moyamoya disease (MMD) or syndrome, and the other steno-occlusive disorders of the arterial circle of Willis including MCA. Pathogenesis of twig-like MCA is supposed to be different from MMD in which normal MCA becomes progressively stenotic at the ICA terminus and/or proximal MCA bilaterally.[11] In twig-like MCA, steno-occlusion is almost exclusively found unilaterally, and LSAs arise from the plexiform network of the affected M1 segment. The difference of the locations of steno-occlusive changes does not necessarily mean two diseases are different. While MMD progresses, twig-like MCA was recognized to be non-progressive during the reported short periods. However, because there is no report of long-term follow up, it remains to be elucidated whether twig-like MCA progresses or not.

R4810K polymorphism in the gene encoding RNF213 at chromosome 17q25.1 is the strongest genetic susceptibility factor for MMD in East Asian population.[16] R4810K variant was also associated with non-MMD disorders, such as intracranial atherosclerosis and systemic vasculopathy.[17] Recently, a case with a ruptured aneurysm of twig-like MCA was reported from Japan.[18] The genetic screening revealed that this patient carried a heterozygous mutation of RNF213 (c.14429G>A, p.R4810K). Further genetic investigation may provide insights on the underlying common pathogenesis of MMD and twig-like MCA.

Embryologically persisted or secondarily acquired lesion?

Twig-like MCA consists of a plexiform network of small vessels or twigs replacing the proximal M1 segment. Intraoperative findings were reported in the limited cases. One was a network of small tortuous vessels without an original main trunk of MCA,[4] and the other was abnormal network exhibiting whitish, calcified degeneration in the place of normal M1 portion.[12] Although absence of proximal M1 portion would lead us to consider this segment had never developed, this is not correct. Even in patients with twig-like MCA, ICA and MCA should be formed initially similar to ICA agenesis, rete mirabile, and MMD, where ICA and MCA are formed normally. Otherwise, the cerebral hemisphere of the affected side would never develop normally. We would consider that isolated anomalous change of the M1 segment and concomitant normal development of the distal MCA are unlikely embryologically.

In the literature, most twig-like patterns were found at the proximal M1, but the similar morphological changes occur at the distal MCA (Figure 1).

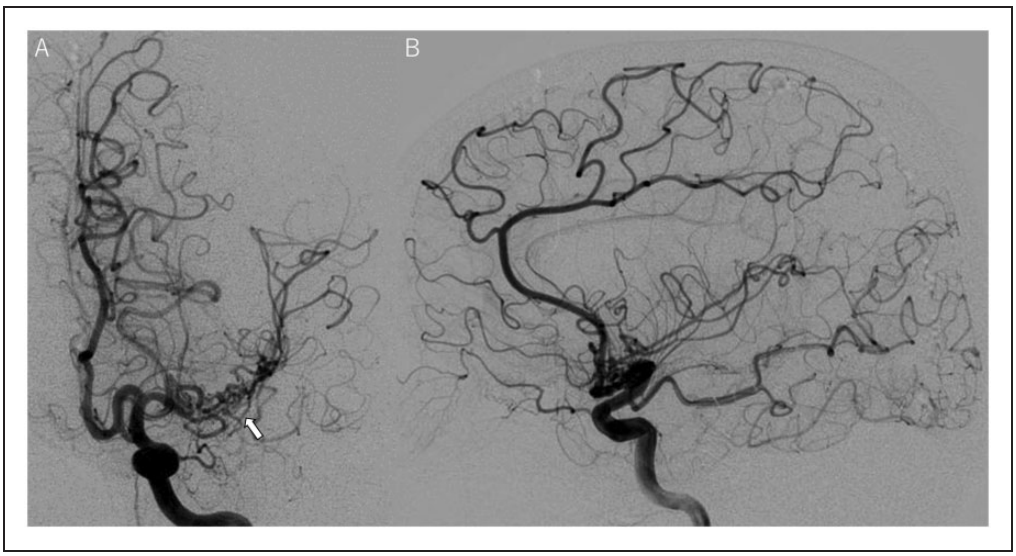

Figure 1. Left internal carotid artery angiography ((a) AP view and (b) lateral view) showing normal proximal M1 and plexiform network of the distal M1 (arrow), and antegrade compromised blood flow to the distal MCAs.

Although there are few cases with angiographical twig-like configurations at the distal M1 or M2 in the literature,[15,18] this can be partially attributable to a lack of exact definition of twig-like MCA and its underdiagnosis in the clinical scene. The common angiographic findings discussed herein (unilateral M1 proximal, no progression, normal distal MCA) are not the evidence that twig-like MCA is a persistent embryological arterial network.

As we discussed in this commentary, it is probably rational to consider twig-like MCA as a secondary collateral after segmental steno-occlusive change of the proximal MCA, and this twig-like configuration may occur in the distal MCA or other arteries. Because its natural history is unknown, patients with twig-like MCAs should be followed clinically and radiologically, and informed of the potential risks and complications.

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