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Case Report

De novo formation of twig-like middle cerebral artery: An illustrative case

Michihide Kajita[1], Kiyoyuki Yanaka[1], Sho Hanai[1], Hitoshi Aiyama[1], Nobuyuki Takahashi[2], Shinji Saiki[3], Eiichi Ishikawa[4]

Departments of [1]Neurosurgery and [2]Radiology, Tsukuba Memorial Hospital, Departments of [3]Neurology and [4]Neurosurgery, University of Tsukuba, Tsukuba, Ibaraki, Japan.

E-mail: Michihide Kajita - aquas_jersey@me.com; Kiyoyuki Yanaka - kyanaka@ybb.ne.jp; Sho Hanai - gnt871@gmail.com; Hitoshi Aiyama - jinaiyama@hotmail.com; Nobuyuki Takahashi - nbyktakahashiodn@yahoo.co.jp; Shinji Saiki - ssaiki@md.tsukuba.ac.jp; *Eiichi Ishikawa - e-ishikawa@md.tsukuba.ac.jp

***Corresponding author:**
Eiichi Ishikawa,
Department of Neurosurgery,
University of Tsukuba, Tsukuba,
Ibaraki, Japan.

e-ishikawa@md.tsukuba.ac.jp

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ABSTRACT

Background: Twig-like middle cerebral artery (T-MCA) is a rare vascular abnormality characterized by the replacement of the M1 segment of the middle cerebral artery (MCA) with a plexiform arterial network of small vessels. T-MCA is generally regarded as an embryological persistence. Conversely, T-MCA may also be a secondary sequela but no reports of cases of *de novo* formation exist. Here, we report the first case describing possible *de novo* T-MCA formation.

Case Description: A 41-year-old woman was referred to our hospital from a nearby clinic because of transient left hemiparesis. Magnetic resonance (MR) imaging revealed mild stenosis of the bilateral MCAs. The patient then underwent MR imaging follow-ups once a year. MR imaging at the age of 53 showed a right M1 occlusion. Cerebral angiography revealed a right M1 occlusion and formation of a plexiform network consistent with the occlusion site, leading to the diagnosis of *de novo* T-MCA.

Conclusion: This is the first case report describing possible *de novo* T-MCA formation. Although a detailed laboratory examination did not confirm the etiology, autoimmune disease was suspected to have precipitated this vascular lesion.

Keywords: Anomaly, Autoimmune disease, Etiology, Middle cerebral artery, Twig

INTRODUCTION

Twig-like middle cerebral artery (T-MCA) is a rare vascular anomaly characterized by the replacement of the M1 MCA segment with a plexiform network of small vessels.[27] T-MCA was reported in 0.11–1.17% of individuals who underwent diagnostic angiography[6,13,18] and approximately 70% of these patients will develop hemorrhagic stroke while 20% develop ischemic stroke and few remain asymptomatic.[23] The most important differential diagnosis is moyamoya disease (MMD), which involves spontaneous progressive steno-occlusion of the internal carotid artery (ICA) and abnormal collateral blood channels (moyamoya vessels) in the basal ganglia.[12]

It is generally believed that the etiology of T-MCA results from an embryonic abnormality in proximal MCA development. Although some investigators have suggested that T-MCA may be acquired,[2,19,20] cases with *de novo* T-MCA formation have never been reported to support this theory. Therefore, the etiology of T-MCA remains controversial and unelucidated. In this article, we report the first case describing possible *de novo* T-MCA formation.

CASE DESCRIPTION

A 41-year-old woman presented to her primary care physician after experiencing one episode of left upper and lower extremity weakness lasting several minutes. Because her father had been diagnosed with MMD, the patient was referred to our hospital in 2011 for a close examination of her cerebrovascular system due to possible familial occurrence of MMD.

The patient was asymptomatic at the initial presentation. Based on initial magnetic resonance imaging (MRI), mild stenosis in the bilateral MCA was suspected but there was neither stenosis in the ICA and no evidence of moyamoya vessels [Figure 1]. There were also no abnormalities in the brain parenchyma. General laboratory tests, including complete blood count, coagulation, and thyroid function data, were normal. In addition, 99m-Tc single-photon emission computed tomography (SPECT) showed stable cerebral hemodynamics without laterality [Figures 2a and b].

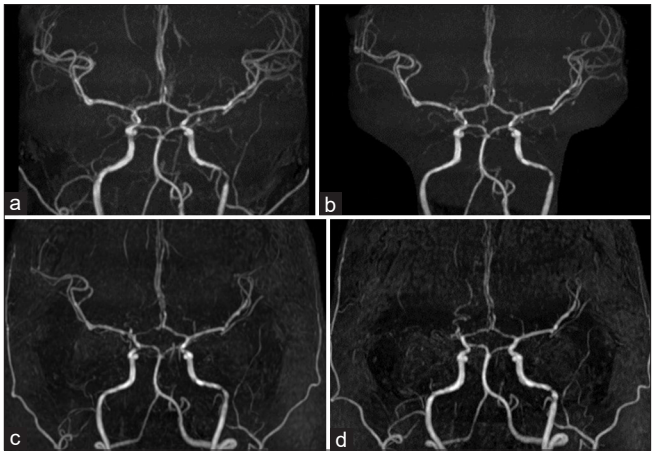

Figure 1: Magnetic resonance image at the age of 41 (a) shows mild stenosis of bilateral middle cerebral arteries (MCAs). At ages 45 (b) and 49 (c), there are no significant changes in the MCAs. At the age of 53 (d), there is an occlusion of the right MCA.

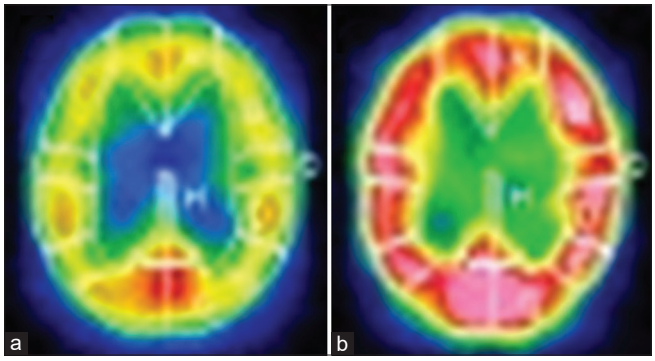

Figure 2: 99 m-Tc single-photon emission computed tomography (SPECT) images at the age of 41 show no differences in cerebral blood flow (CBF) at rest (a) and no hemodynamic compromise after acetazolamide challenge (b).

Since the patient was asymptomatic and had no significant imaging abnormalities, an annual MRI follow-up was performed. There were no imaging changes over approximately 10 years but MRI performed at the age of 53 showed a signal loss in M1 and its distal portion, suggestive of the right M1 occlusion [Figure 1]. No other vascular changes were found and there was no cerebral infarction [Figure 3]. In addition, 99mTc-SPECT imaging showed a subtle decrease in resting cerebral blood flow in the right compared to the left hemisphere and imaging after acetazolamide challenge showed hemodynamic compromise in the right cerebral hemisphere [Figure 4].

Digital subtraction angiography (DSA) revealed occlusion of the right M1 segment and a plexiform vascular network around the occluded segment [Figure 5]. The vessel diameter of the M2 segment was nearly normal. There was no stenosis in the anterior cerebral artery (ACA) or the ICA terminus. Furthermore, there was no transdural anastomosis with the external carotid artery and no abnormalities in the ICA or the vertebrobasilar artery system.

Several laboratory tests were performed to distinguish the etiology. Repetitive blood tests showed that blood counts, thyroid, and renal function were within normal ranges and various items associated with collagen-related disease were negative. In addition, there were no coagulation abnormalities (prothrombin time: 11.2 s, activated partial thromboplastin time: 28.6 s, and D-dimer: 0.5 μg/dL) and cerebrospinal fluid analysis was normal (cells: 1/μL, protein: 37 mg/dL, glucose: 67 mg/dL, and oligoclonal bands: Negative). The antinuclear antibody (ANA) test was positive and showed high antibody titers (ANA test was positive at 1:640, speckled and nucleolar staining patterns were positive at 1:640, and the homo pattern was positive at 1:80). However, test for all other disease-specific antibodies, such as antibodies to double-stranded deoxyribonucleic acid, ribonucleoprotein, Sm, SS-A/Ro, SS-B/La, Scl-70, Jo-1, ribonucleic acid polymerase III, myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA), and proteinase3-ANCA, was all negative. Although a definitive diagnosis was not reached, the immunological data strongly suggested autoimmune disease involvement.

Bypass surgery was considered due to progression on angiographic findings and hemodynamic deterioration. However, since the patient had been asymptomatic to this point and had without cerebral infarction, conservative follow-up was chosen with strict management of risk factors for atherosclerosis, administration of an antiplatelet drug, and periodic MRI. The patient has remained asymptomatic ever since.

DISCUSSION

T-MCA is a rare vascular anomaly characterized by a replacement of the M1 segment of the MCA by a webbed network of small vessels.[27] T-MCA is often misdiagnosed as MMD or other MCA degenerative steno-occlusive

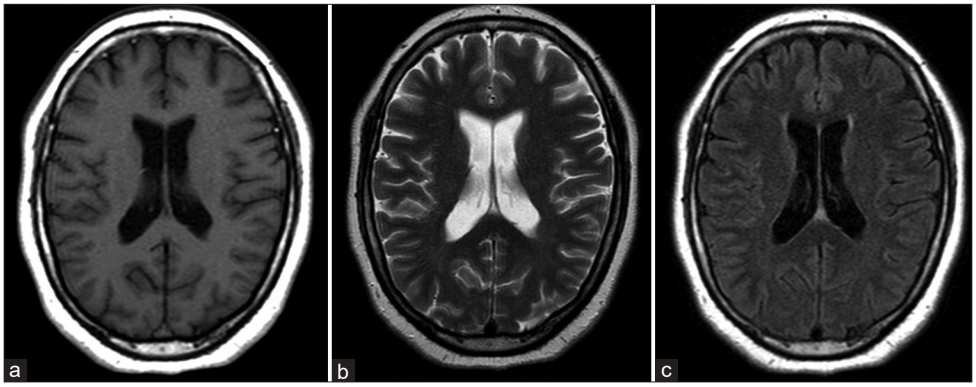

Figure 3: T1-weighted (a), T2-weighted (b), and fluid-attenuated inversion recovery (c) magnetic resonance imaging at the age of 53 show no abnormalities in the brain parenchyma.

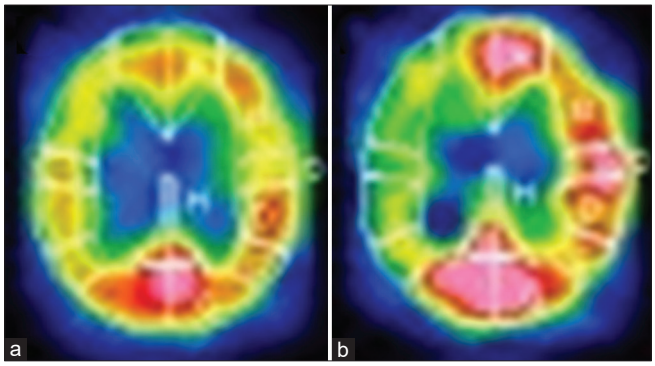

Figure 4: SPECT images at the age of 53 show a subtle decrease in CBF in the right compared to the left hemisphere at rest (a) and hemodynamic compromise after acetazolamide challenge (b).

diseases, which are the most common differential diagnoses. Because of the similar vascular structure, it is challenging to differentiate T-MCA from MMD, especially in the case of unilateral MMD. This case showed a steno-occlusive lesion limited to the MCA and the plexiform arterial network at the same site, but the ICA was unaffected. Furthermore, there was no collateral vessel development and no atherosclerotic degeneration. Considering these findings, MMD and degenerative steno-occlusive disease could be safety eliminated as differential diagnoses. Meningitis, brain tumor, radiation therapy, neurofibromatosis Type I, Down's syndrome, sickle cell disease, and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome may lead to the development of a proximal MCA collateral network with a web-like pattern.[1,12,18] However, none of these diseases were present based on physical examination, various laboratory tests, and neuroimaging. Therefore, this case was diagnosed as T-MCA rather than other conditions that may cause MCA-like abnormalities.

The etiology of T-MCA is not well understood but it is generally believed that T-MCA is a congenital abnormality resulting from anomalous MCA embryonic development.[25] In normal cerebrovascular development, a web of small vessels known as the plexus or twigs first forms from the primitive distal ICA as the fetal arterial circuit. Subsequently, the twigs evolve through fusion and regression into the adult configuration of the ACA and MCA.[6] Fusion arrest or a lack of coalescence is thought to create the absence of a typical, fully developed M1 trunk with twig-like arterial network retention.[14] T-MCA has also been reported under other names, such as unfused MCA, MCA aplasia, and ICA atresia, and aplastic or twig-like MCA, all of which suggest developmental abnormalities.[3,21,22] On the other hand, there is also a theory that T-MCA is an acquired abnormality for the following reasons: 1) Normal cerebral hemisphere development requires the normal formation of the ICA and MCA. However, patients with T-MCA have isolated abnormal changes in the M1 segment but typically develop cerebral hemispheres and a distal MCA.[19] 2) Most twig-like patterns are found only in the proximal M1 but similar morphological changes have also been reported in the distal MCA.[5,7] 3) If T-MCA were a congenital anomaly, there would be many pediatric cases but such reports are rare.[2,16] These facts make it difficult to assume that the embryonic arterial network persists into late adulthood. Ota and Komiyama suggested that the T-MCA may be acquired as collateral circulation after partial steno-occlusive changes in the proximal MCA[19,20] but no cases or evidence of acquired T-MCA formation have been reported. In the present case, the acquired formation of the plexiform arterial network was observed with occlusion of the MCA, which was not initially occluded and this has not been previously reported. This case indicates that acquired factors may be involved in the pathogenesis of T-MCA and may shed light on the natural history of T-MCA. This vascular abnormality has also been referred to as aplastic or twig-like MCA, among the several names previously mentioned. However, as in this case, the term "aplastic" may be inappropriate because it does not necessarily involve a

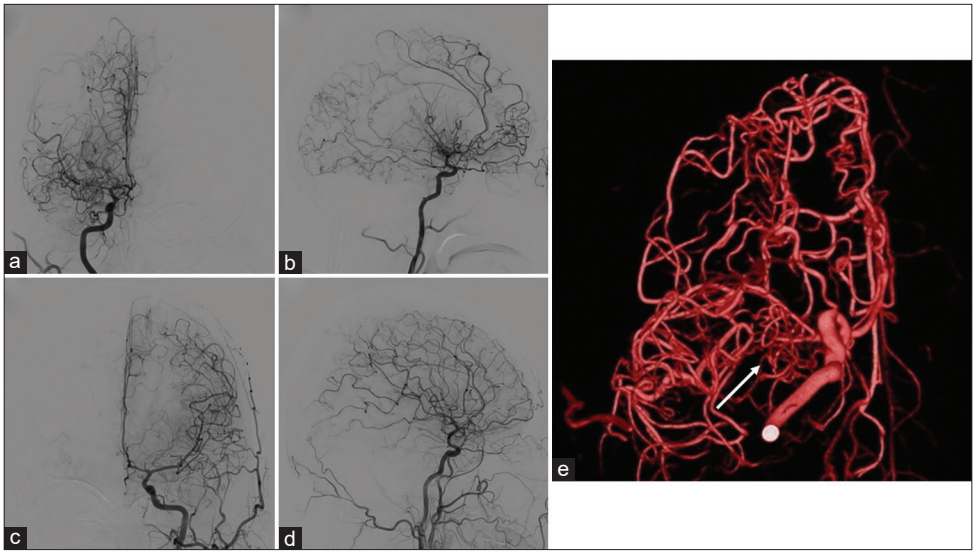

Figure 5: Digital subtraction angiograms at the age of 53 show occlusion of the right middle cerebral arteries and the abnormal vascular network around the occluded segment. The vessel diameter of the M2 segment is almost normal. There is no stenosis in the supraclinoid portion of the internal carotid artery (a: Anterior-posterior [A-P] view, b: Lateral view). Left carotid angiogram in normal (c: A-P view, d: Lateral view). (e) Rotational angiograms clearly show a plexiform network formation replacing the M1 occlusion (arrow).

developmental abnormality. Therefore, it may be better to call it a "twig-like MCA" demonstrating only morphological changes. In addition, this patient required an extended follow-up of about 10 years from the first suspected anomaly to T-MCA formation. Thus, the long time required for full pathogenesis of the T-MCA and the accompanying long follow-up period required to detect it may be why there are no reported cases of acquired T-MCA.

The previous reports have shown that approximately 70% of patients with T-MCA develop hemorrhagic stroke whereas 20% develop ischemic stroke.[23,24] It is unclear why ischemic cases are common in MMD but less common in T-MCA.[8] We have previously reported on the effectiveness of bypass surgery for hemorrhagic and ischemic T-MCA.[23,24] In that paper, we speculated that the reason why T-MCA is less likely to develop ischemia is that it is considered to be a developmental abnormality and therefore likely to be angiographically non-progressive.[4,24] It has also been reported that T-MCA has no hemodynamic difference between the affected and healthy sides.[8] However, this patient progressed radiologically on magnetic resonance angiography and developed hemodynamic compromise on the T-MCA side on SPECT. It is also possible that this patient will develop further disease featuring bilateral lesions and stenotic changes in the ICA. Thus, although this case cannot be diagnosed as MMD through imaging, the pathophysiology is very similar.

Since the observed ANA staining pattern is not unique to healthy individuals, it was speculated that some immune mechanism was causative.[15,26] On the other hand, since her father had been diagnosed with MMD, a genetic factor cannot be ruled out. Therefore, genetic studies may help to determine whether MMD and T-MCA, as seen in our case, are essentially within the same disease family. Although the Ring Finger Protein 213 (RNF213) polymorphism is a genetic susceptibility factor for MMD and is sometimes found in patients with T-MCA, the association between RNF213 polymorphism and T-MCA remains unclear and controversial.[9,10,17] The discrepancy between the RNF213 polymorphism retention rate and the actual prevalence of MMD in a healthy population indicates that this specific factor alone does not fully explain the development of MMD. Therefore, predisposing genes other than RNF213 may also be involved and further genetic studies may reveal common pathologies shared by MMD and T-MCA.

In this case, bypass surgery was initially planned because of the progression of angiographic findings and hemodynamic deterioration. However, conservative treatment was chosen since the patient had been asymptomatic for more than 10 years since the initial diagnosis. We previously repeated the efficacy of bypass surgery for T-MCA.[23,24] Bypass surgery has been shown to improve cerebral perfusion, reduce hemodynamic stress, and reduce the risk of future ischemic or hemorrhagic stroke in patients with MMD. Because MMD and T-MCA are similar in their propensity to induce ischemic or hemorrhagic strokes involving vulnerable collaterals, bypass surgery should also be effective for some cases of T-MCA. There are two groups of MMD: Rapidly

progressive and asymptomatic or slowly progressive groups. The rapidly progressive MMD group is treated aggressively with bypass surgery. However, clinical characteristics, prognosis, and treatment are unknown for asymptomatic MMD cases because of the small number of cases and short follow-up period.[11] Therefore, as with asymptomatic T-MCA patients, careful judgment must be exercised when choosing a treatment option.

CONCLUSION

We reported the first case report describing possible *de novo* T-MCA formation during long-term follow-up. This case demonstrates that T-MCA is not an embryological persistence but may develop secondarily in an acquired manner. Further case accumulation and diagnostic efforts are needed to understand the natural history of T-MCA.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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