Abnormal Embryonic Development of Cerebral Arteries as a Potential Cause of Moyamoya Disease

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OBJECTIVE: **Moyamoya disease (MMD) is a cerebrovascular disorder, currently defined as progressive stenosis of intracranial internal carotid artery and its main branches with secondary formation of netlike vessels. Its precise formation mechanism, however, is unknown. We propose that MMD is caused by abnormal embryonic development of the cerebral arteries and also propose a mechanism for MMD formation.**

METHODS: **The anterior, middle, and posterior cerebral arteries, anterior choroidal arteries (AChoA) and posterior choroidal arteries, and posterior corpus callosum arteries were analyzed separately for each patient with MMD to determine whether the arteries exhibited the following characteristics, which we regarded as remnants of primitive vessels: 1) plexiform arteries rather than normal artery trunks; 2) clustered arteries converging at locations of normal artery trunks; and 3) dilated AChoA.**

RESULTS: **We retrospectively analyzed 39 consecutive patients with MMD, of whom 30 had anterior cerebral arteries, 31 middle cerebral arteries, 10 posterior cerebral arteries, 30 AChoAs, 18 posterior choroidal arteries, and 20 posterior corpus callosum arteries and had the characteristics of primitive vessel remnants. Altogether, 82.05% of the patients had the remnants of primitive vessels.**

CONCLUSIONS: **MMD is more likely to be caused by abnormalities of cerebral artery development, which mainly occur in the embryonic period or postnatally. The abnormality developing processes include sprouting angiogenesis, vessel fusion, and pruning, which primarily affect cranial ramus of primitive internal carotid artery, may occasionally affect the caudal ramus of the primitive internal carotid artery, and rarely affect the vertebrobasilar artery system. So-called moyamoya vessels comprise unfused primitive small vessels; to compensate, enlarged AChoAs remain undegenerated but are not dilated.**

INTRODUCTION

Moyamoya disease (MMD) is a chronic cerebrovasculopathy of unknown etiology, characterized by progressive stenosis of the terminal portion of the internal carotid artery (ICA) and its main branches, with a compensatory collateral arterial network developing at the base of the brain.[1-5] Previously, we proposed that from an embryologic perspective, MMD should be classified into 2 main types: primitive ICA system MMD and primitive vertebrobasilar artery system MMD. Primitive ICA system MMD can be further divided into 2 subtypes: 1) MMD from the cranial ramus of the primitive ICA, mainly comprising the anterior cerebral artery (ACA), middle cerebral artery (MCA), and anterior choroid artery (AChoA); and 2) MMD from the caudal ramus of the primitive ICA, mainly comprising the posterior cerebral artery (PCA).[6]

After comparing the vasculature between patients with MMD and the embryo, we propose that MMD is caused by abnormalities of sprouting angiogenesis, vessel fusion, and pruning. More specifically, so-called "moyamoya vessels" are unfused primitive small vessels or capillary plexus. The occlusive or stenotic terminal portion of the ICA and its main branches (ACA/MCA/PCA) is caused by the failure of primitive vessel fusion and/or failure of sprouting angiogenesis. The commonly seen dilated AChoA on digital subtraction angiography (DSA) scans of patients with MMD

Key words
- Cerebral artery development
- Embryology
- Moyamoya disease

Abbreviations and Acronyms
ACA: Anterior cerebral artery
AChoA: Anterior posterior choroidal artery
DSA: Digital subtraction angiography
ICA: Internal carotid artery
MCA: Middle cerebral artery
MMD: Moyamoya disease
PCA: Posterior cerebral artery
PChoA: Posterior choroidal artery

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is an undegenerated remnant; the plexiform posterior corpus callosum artery also comprises an unfused remnant of embryonic primitive vessels, which is common in patients with MMD. Based on this hypothesis, we performed a retrospective study to analyze whether patients with MMD exhibit remnants of vessel development from the embryonic period.

METHODS

Patient Selection

To exclude the effects of atherosclerosis, we limited our analysis to patients younger than 30 years of age. From January 1, 2017, to May 31, 2018, we enrolled 39 patients who were diagnosed with MMD according to the guidelines for diagnosis and treatment of Moyamoya disease (spontaneous occlusion of the circle of Willis).[1] For all 39 patients, DSA Digital Imaging and Communications in Medicine data were available.

DSA Analysis

DSA data were analyzed retrospectively. All DSA scans included bilateral internal and external carotid arteriography and bilateral vertebral arteriography. Our analysis focused on the ACA, MCA, PCA, AChoA, PChoA, posterior corpus callosum artery, and ICA. Arteries with the following characteristics were referred to as remnants of primitive vessels: 1) plexiform arteries rather than normal artery trunks; 2) clustered arteries converging at the locations of normal artery trunks; 3) dilated AChoA, with or without surrounding plexiform arteries; and 4) hypoplasia of internal carotid artery, as is shown in Figure 1. All DSA analyses were performed by 2 neurosurgeons, who were blinded to each other and had more than 10 years' experience treating MMD. A third neurosurgeon who specialized in cerebral vascular disease was consulted when there was disagreement. This study was approved by the Peking University International Hospital Research Ethics Committee. We have received written informed patient consent to perform this study.

RESULTS

We retrospectively analyzed 39 consecutive patients with MMD who were admitted to our institution between January 1, 2017, to May 31, 2018; they comprised 19 males and 20 females, and 25 of them were younger than 18 years of age. There are 30 ACAs (15 right and 15 left), 31 MCAs (15 right and 16 left), 10 PCAs (6 right and 4 left), 30 AChoAs (11 right and 19 left), 18 PChoAs (10 right and 8 left), 20 posterior corpus callosum arteries (11 right and 9 left), and 14 ICAs (9 right and 5 left) with characteristics of primitive vessel remnants. Altogether, 82.05% (32/39) of the patients had the remnants of primitive vessels. Detailed characteristics of the patients are listed in Table 1.

DISCUSSION

MMD was first described as "hypoplasia of the bilateral internal carotid arteries."[2] Its etiology remains unknown, and treatment is unsatisfactory.[4,5] Recently, we have identified some patients

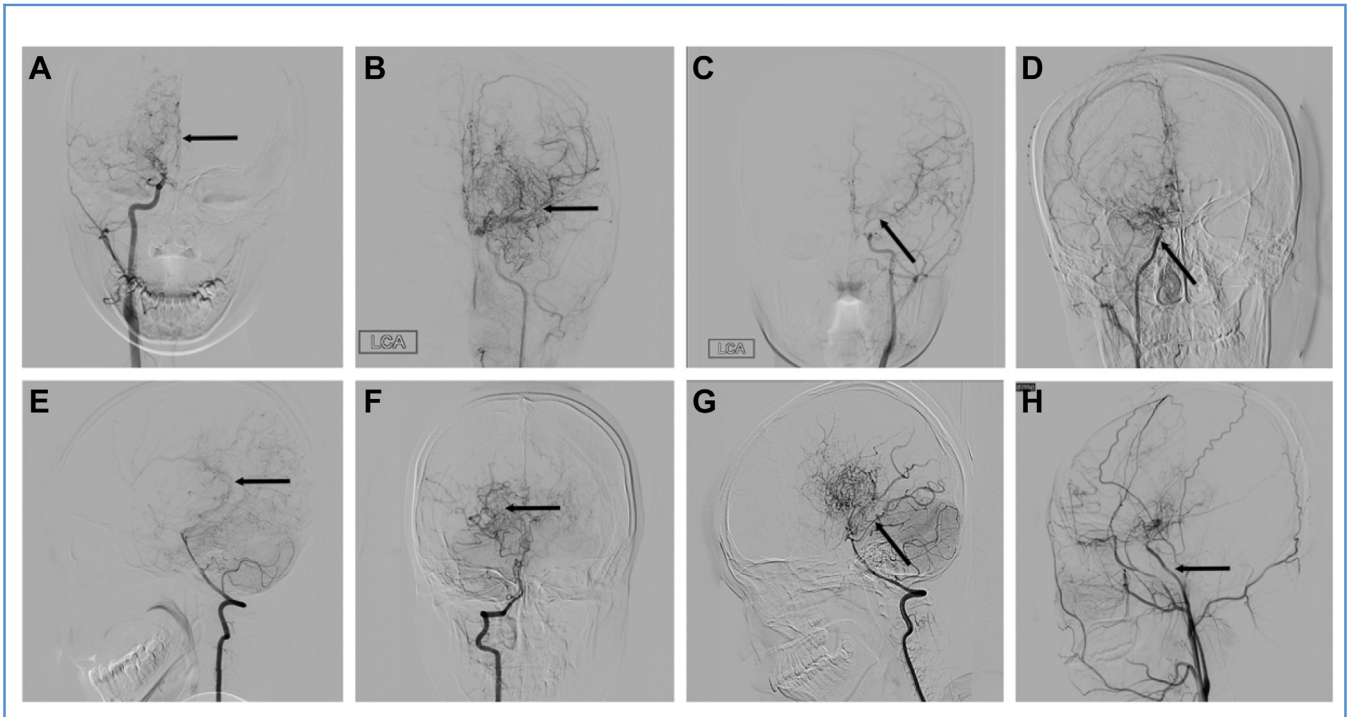

Figure 1. Illustration of arteries with the morphology of primitive remnants. (**A**) Plexiform anterior cerebral artery (*arrow*). (**B**) Plexiform middle cerebral artery (MCA; *arrow*) and un-degenerated anterior posterior choroidal artery (*arrowhead*). (**C**) Overpruning MCA (*arrow*). (**E**) Plexiform posterior corpus callosum artery (*arrow*). (**F**) Plexiform posterior choroidal artery (*arrow*). (**G**) Plexiform posterior cerebral artery (*arrow*). (**D** and **H**) Hypoplasia internal carotid artery (*arrow*).

Table 1. Detailed Characteristics of the Patients

General Information			Right Side								Left Side							
Patient No.	Sex	Age, years	ICA	ACA	MCA	AChoA	PChoA	PCCA	PCA	Summation	ICA	ACA	MCA	AChoA	PChoA	PCCA	PCA	Summation
1	M	11	1	o	o	1	1	0	o	3	1	o	o	1	1	0	o	3
2	M	7	1	s	o	1	1	1	s	4	1	o	o	1	1	1	o	4
3	M	23	0	o	o	o	0	1	1	2	0	s	o	0	0	0	o	0
4	M	14	0	s	o	0	1	1	0	2	0	s	o	1	0	1	0	2
5	F	10	0	1	1	1	0	1	0	4	0	1	o	1	0	1	0	3
6	M	5	0	s	0	0	0	0	o	0	0	0	0	0	0	0	0	0
7	M	8	1	o	o	1	0	0	o	2	0	1	0	1	1	1	0	4
8	F	11	0	s	s	0	0	0	0	0	0	s	o	1	0	0	0	1
9	M	30	0	1	0	0	0	0	0	1	0	s	1	1	0	0	0	2
10	M	30	o	o	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	F	23	0	1	o	1	0	0	o	2	0	o	o	0	0	0	o	0
12	M	19	0	0	o	0	0	0	0	0	0	0	0	0	0	0	0	0
13	F	10	0	o	1	0	0	1	0	2	0	s	s	1	0	0	0	1
14	M	11	0	1	1	1	1	0	0	4	0	1	1	1	0	1	0	4
15	F	11	1	o	o	0	1	1	1	4	0	1	1	1	1	1	1	6
16	M	17	1	o	o	0	1	0	0	2	1	o	0	0	0	0	0	1
17	F	10	1	o	0	0	0	1	1	3	0	1	1	1	0	0	0	3
18	F	11	0	1	1	0	0	0	0	2	0	1	1	0	0	0	0	2
19	M	7		1	1	1	1	1	1	7	1	1	1	1	1	1	1	7
20	F	19	0	o	o	0	0	0	0	0	0	1	1	0	0	0	0	2
21	M	9	0	1	1	0	0	1	0	3	0	1	1	1	0	1	0	4
22	F	8	0	0	1	0	0	0	0	1	0	o	o	0	0	0	0	0
23	F	16	1	1	1	1	1	1	0	6	o	o	o	o	1	1	0	2
24*	F	11	0	0	0	0	0	0	0	0	0	0	s	0	0	0	0	0
25	M	9	0	1	1	0	0	0	0	2	0	1	1	0	0	0	0	2
26	F	19	1	0	0	0	0	0	0	1	0	1	1	1	0	0	0	3
27	M	15	0	o	o	0	0	0	0	0	0	o	o	0	0	0	0	0
28†	F	14	0	o	0	0	0	0	0	0	0	o	0	0	0	0	0	0
29	M	28	0	o	o	0	0	0	0	0	0	o	o	0	0	0	0	0

30	F	13	0	1	1	0	0	0	0	2	0	1	1	1	0	0	0	3
31	F	26	0	1	1	0	0	0	1	3	1	1	1	0	0	0	1	4
32	F	10	0	1	1	1	0	0	0	3	0	1	1	1	0	0	0	3
33	F	8	0	s	s	0	0	0	0	0	0	1	1	1	1	0	0	4
34	M	28	0	1	1	1	1	0	0	4	0	o	1	1	1	0	1	4
35	M	18	0	1	o	0	0	0	0	1	0	o	o	1	0	0	0	1
36	M	28	0	o	1	0	0	0	0	1	0	0	1	0	0	0	0	1
37	F	6	0	1	1	1	1	0	1	5	0	o	o	0	0	0	0	0
38	F	28	0	0	0	0	0	0	0	0	0	0	s	0	0	0	0	0
39	M	17	0	o	o	0	0	0	0	0	0	s	s	0	0	0	0	0
No. of zeros			9	15	15	11	10	11	6	12	5	15	16	19	8	9	4	13

ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; AChoA, anterior choroidal artery; PChoA, posterior choroidal artery; PCCA, posterior corpus callosum artery; PCA, posterior cerebral artery; M, male; 1, have the characteristics of remnants of primitive vessels; o, occluded; 0, normal; s, stenosis; F, female.

*Case No. 24 is a primitive vertebrobasilar artery system moyamoya disease of which the vertebrobasilar artery shows the characteristic of remnants of primitive vessels.

†Case No. 28 shows a primitive trigeminal artery.

whose cerebral artery morphology resembles primitive vessels in different embryonic stages, as shown in Figure 2. As the embryo develops a primary vascular plexus through a process called vasculogenesis, additional blood vessels are generated by both sprouting and non-sprouting angiogenesis; these are progressively pruned and remodeled into the adult circulatory system.[7,8] During the fourth week of the embryonic period, the primitive carotid artery branches into cranial and caudal rami.

The AChoA is the first branch of the cranial rami; it is a relatively large artery at that stage and degenerates later. In the embryonic period, new vessel trunks differentiate out of the cranial capillary plexus. The proximal part of the ACA is formed from the primitive olfactory artery, its recurrent branch, and a cranially directed branch of the primitive olfactory artery. The portion of the ACA situated between the 2 cerebral hemispheres differentiates in situ from the general capillary plexus. The PCA is formed proximally from portions of the caudal ramus of the ICA; the intermediate portion is formed by the proximal portion of the original posterior choroid artery (PChoA), whereas the distal portion is formed by the lateral branch of the original PChoA.[9-12] The MCA comprises a fusion of several arterial twigs.[9]

MMD Is Caused by Abnormal Development of Cerebral Arteries

From the definition of MMD, we can conclude that a stenotic or occluded ICA and its main branches develop progressively from a normal ICA, which is the currently accepted theory.[1] The newly formed net-like vessels compensate for the ischemia caused by stenosis of the main arteries. This descriptive definition is only

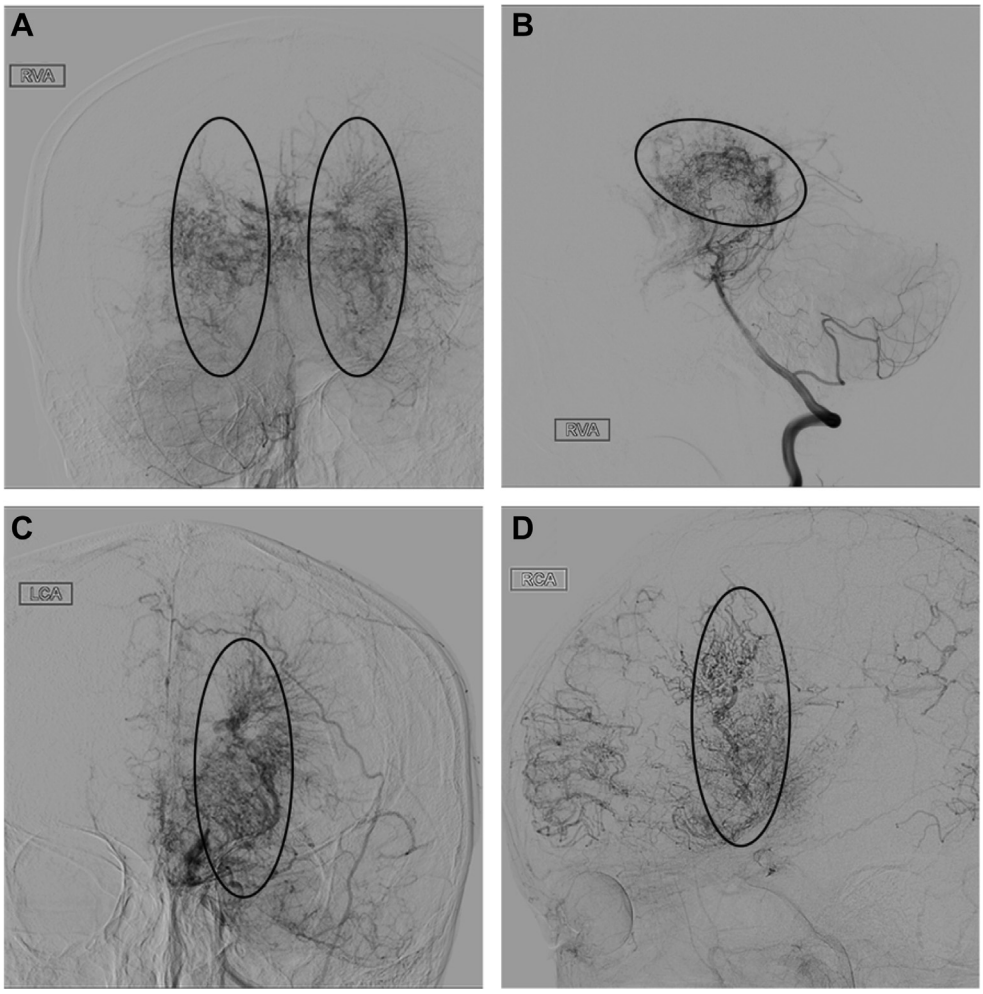

Figure 2. Digital subtraction angiography (DSA) of a patient with moyamoya disease (MMD) shows the vessels resemble the primitive vessels in the embryo. DSA scan of an 11-year-old male patient with MMD is shown. (**A** and **B**) Frontal and lateral view of right vertebrobasilar artery angiogram; (**C**) frontal view of left ICA angiogram; and (**D**) lateral view of right internal carotid artery angiogram. The vessels in the *ovals* are the so-called moyamoya vessels, which mimic the morphology of the undegenerated primitive vessels in the embryo. Small vessels are meant to fuse to form a vessel trunk, however, they ceased abnormally, leaving a cluster of small vessels to converge radially.

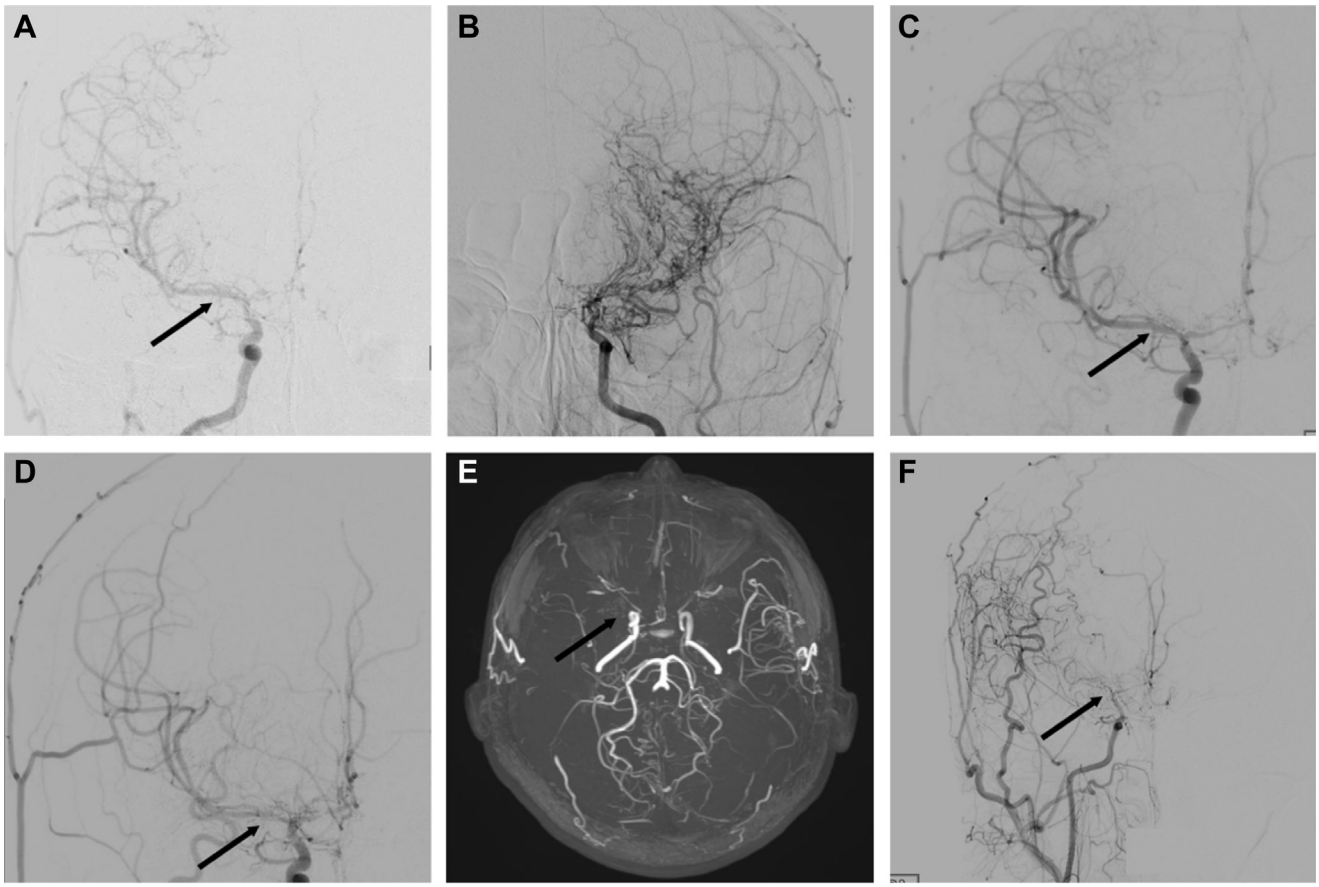

Figure 3. Progressive moyamoya disease (MMD) shows the overpruning process of the anterior cerebral artery (ACA) and middle cerebral artery (MCA). A 23-year-old male patient with MMD is shown. (**A** and **B**) Right and left sides of MCA of the initial diagnosis; *arrow* in (**A**) shows a relatively normal MCA. (**C**) ACA and MCA (*arrow*) 3 months later are still normal. (**D**) The proximal part of right MCA (*arrow*) shows mild stenosis 12 months later. (**E**) At 16 months later, the patient developed left-sided limb weakness. Magnetic resonance angiography shows occlusion of right ACA and MCA (*arrow*). (**F**) At 15 months later (3 months after the right side bypass surgery), digital subtraction angiography shows occlusion of the right-side ACA and MCA (*arrow*).

consistent with observations in a few patients, in whom the progress of stenosis can be detected. However, most patients are stabilized at the state of stenosis or occlusion.[13] In addition, there are many patients whose trunks of ACA, MCA, and PCA are replaced by a cluster of small vessels that mimics the unfused primitive vessel plexus. More typically, some patients exhibit a cluster of capillaries that converges radially toward the position of a normal vascular trunk, but without the formation of a normal trunk, as shown in **Figure 2**. The plexiform vessels are like remnants because of the abnormal fusion in the process of artery development. Thus, most stenotic or occluded vascular trunks in patients with MMD are likely to be caused by abnormal fusion or vasculogenesis but not progressive stenosis. The plexiform ACA, MCA, PCoA, and posterior corpus callosum artery, all of which are often observed in patients with MMD, can be better understood from the perspective of vessel development. The plexiform arteries (so-called moyamoya vessels) constitute unfused or undegenerated primitive vessels of the embryo. The result of our analysis shows most of patients with MMD have the remnants of primitive vessels.

Importantly, how progressive stenosis of the ICA and its main branches occur is unclear; the exact mechanism is unknown. This also can be interpreted from the perspective of vessel development, involving an important process in arterial maturation: pruning. The mechanisms of pruning include degeneration and shrinkage of vessels where tissue requires less blood, often via programmed cell death.[8] The maturation of the AChoA is an example of vascular pruning. Arterial maturation continues for several years after birth; previous studies have suggested that the vascular system does not mature until about 20 years of age.[7] Thus, in patients with MMD, the disturbance of vascular development also persists until adulthood. In rare cases, we may even find moyamoya lesions arising from a normal intracranial vascular system; this might also be caused by abnormal pruning. These kinds of cases often show few moyamoya vessels, because the primitive small vessels have already fused

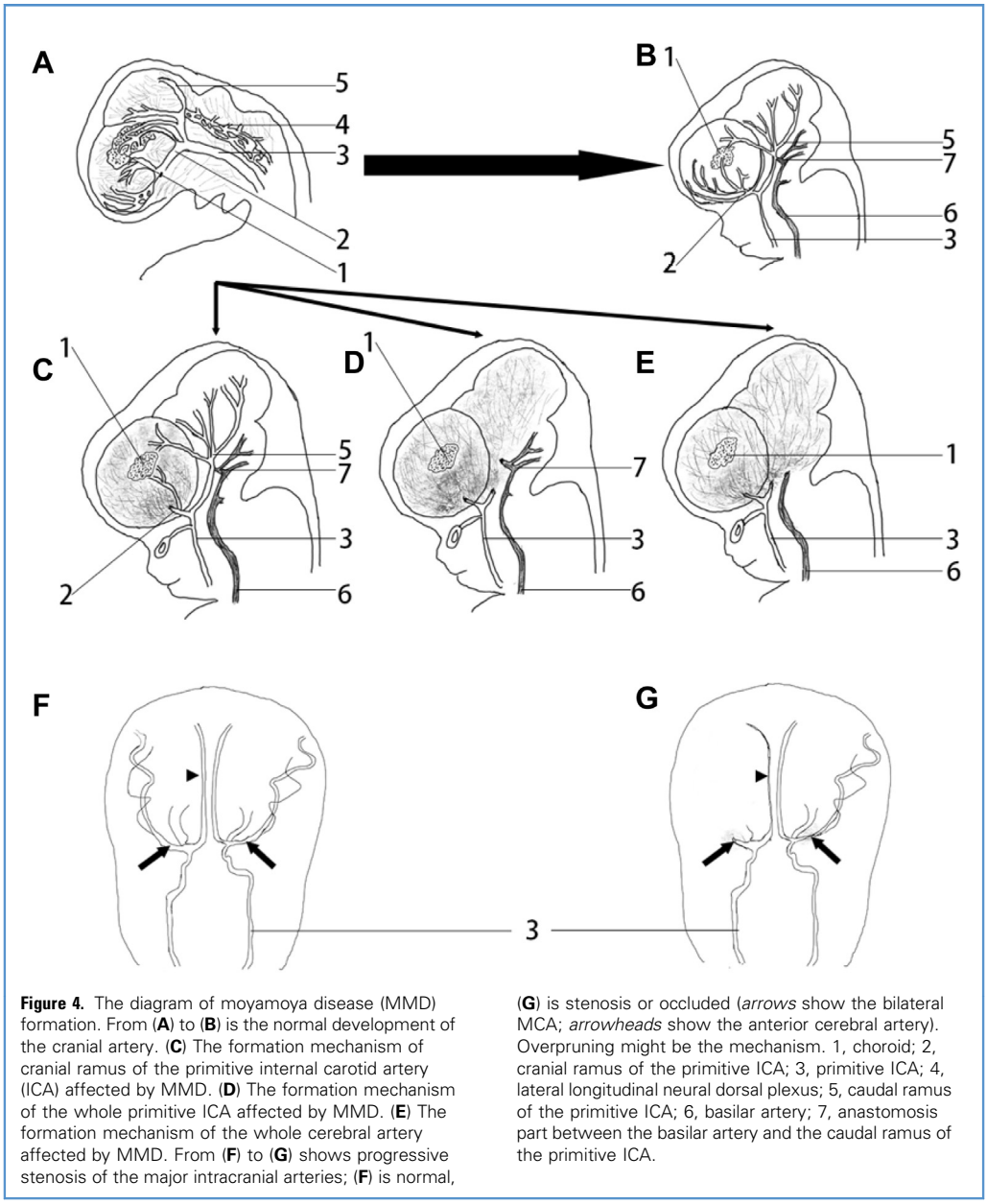

Figure 4. The diagram of moyamoya disease (MMD) formation. From (**A**) to (**B**) is the normal development of the cranial artery. (**C**) The formation mechanism of cranial ramus of the primitive internal carotid artery (ICA) affected by MMD. (**D**) The formation mechanism of the whole primitive ICA affected by MMD. (**E**) The formation mechanism of the whole cerebral artery affected by MMD. From (**F**) to (**G**) shows progressive stenosis of the major intracranial arteries; (**F**) is normal, (**G**) is stenosis or occluded (*arrows* show the bilateral MCA; *arrowheads* show the anterior cerebral artery). Overpruning might be the mechanism. 1, choroid; 2, cranial ramus of the primitive ICA; 3, primitive ICA; 4, lateral longitudinal neural dorsal plexus; 5, caudal ramus of the primitive ICA; 6, basilar artery; 7, anastomosis part between the basilar artery and the caudal ramus of the primitive ICA.

into main trunks or have degenerated (Figure 3). These observations suggest that progressive stenosis might be caused by a disturbance of vascular pruning: over pruning, the normal arteries were over pruned to be a stenotic one, sometimes even occluded. Previous studies have shown that pediatric moyamoya is more like to progress[14,15]; this may be further evidence of progressive stenosis caused by abnormal vascular pruning, which slows over time.

Source of Moyamoya Vessels

In the current definition of MMD, moyamoya vessels are described as secondary formations to compensate for ischemia after stenosis or occlusion of arterial trunks.[1] If moyamoya vessels form to compensate for ischemia, a proliferation of moyamoya vessels secondary to ischemia aggravation is likely over time. However, moyamoya vessels do not proliferate with increasing patient age or degree of ischemia. In contrary, moyamoya vessels might decrease over time, especially after revascularization surgery. Furthermore, the appearance of moyamoya vessels are different from the secondarily formed vessels, such as in MCA-occluded patients.[16] A previous study showed that moyamoya vessels differed from compensatory vessels that developed after bypass surgery.[17] In clinical cases, it is common to encounter pediatric patients with many moyamoya vessels, whereas adult patients exhibit few such vessels. A previous failed attempt to create a MMD model from ligation of the terminal portion of the ICA

showed that compensatory moyamoya vessels do not develop in this model.[18] Thus, we argue that moyamoya vessels constitute primitive small vessels that are not degenerated or fused normally. With the progress of brain development, the corresponding blood requirement increases dramatically. Therefore, primitive small vessels fuse to form larger vascular trunks, accompanied by angiogenesis to satisfy the blood requirement.[8,9] If errors occur during this period, the vascular trunk (such as ACA, MCA, PCA, AChoA, PChoA, and posterior corpus callosum artery) cannot form, and the primitive vessel remnants remain.

Manifested in the DSA are net-like vessels, or so-called moyamoya vessels, and stenotic or occluded terminal portions of the ICA and its main branches, sometimes the plexiform PCA or MCA (**Figure 4**). Some may argue that a pediatric patient with MMD has many moyamoya vessels because angiogenesis during that young age is strong. However, the fact is before birth in the embryo stage, the primitive small vessels already have formed. According to the "economic principle," moyamoya vessels should not re-develop after degeneration but remain undegenerated. Functionally, the undegenerated primitive vessels can compensate for the ischemia caused by the abnormal vascular trunk; we refer to this as "compensatory un-degeneration." The abnormal fusion and un-degeneration of primitive vessels is the initial lesion of MMD.

Additional evidence to support the inference of "compensatory un-degeneration" is the presence of a dilated AChoA in MMD. During embryonic development, the AChoA progressively degenerates.[11,12] In the very early stage of embryonic development, the primitive AChoA is a major branch of the caudal ramus of the ICA. The primitive AChoA degenerates as the cerebral hemisphere develops rapidly, whereas the ACA/MCA enlarges. If errors occur in this period, the degeneration might be incomplete. Occasionally, the ACA/MCA might not fully develop, and the primitive AChoA might be preserved to compensate the blood supply for the developing brain.

The Likely Mechanism for Bimodal Age Distribution of Onset

The MMD bimodal age onset phenomenon also can be better explained from the perspective of vessel development. Previous studies have shown that the first peak onset occurs at approximately 10 years of age and the second occurs near 35 years of age.[1] We speculate that the mechanism is as follows.

1. Before 2 or 3 years of age: moyamoya lesions have already formed during the development of the cerebral vasculature, early in the embryonic period. It will not be diagnosed unless the child can express their discomfort or show some symptoms that are sufficiently serious to warrant medical attention, such as limb seizures. Thus, in this period, only a few serious cases can be diagnosed.
2. The period of 3–12 years of age: With respect to the development of the child's cerebellum, this is a fast developmental period and requires great oxygen consumption. In a healthy child, the cerebral vasculature develops in a corresponding manner, allowing the developing cerebellum tissue to obtain sufficient oxygen. However, in the child with MMD, the cerebral vasculature cannot develop normally. In contrast, it is affected more severely over time. As a result, the abnormal vasculature cannot provide sufficient oxygen for the developing cerebellum, which may lead to transient ischemic attack or stroke. Therefore, several cases are diagnosed; the number of diagnoses increases with age in this period.
3. The period of 12–30 years of age: The development of the cerebellum slows or stabilizes in this period; the vasculature also becomes more stable. Notably, the development of the vasculature continues until adulthood. Considering these factors, relatively stable moyamoya vessels can provide appropriate oxygen for the cerebellum. However, compared with the healthy individuals, the cerebral vascular reserve capacity of patients with MMD has already been damaged, which might be observed in certain circumstances, such as tiredness; few patients will recognize relevant symptoms. As a result, few patients are diagnosed in this period.
4. The period of 30–50 years of age: Previous studies have shown that retrogression of the vasculature begins in the early 20s. Atherosclerosis also develops later in this period. For individuals without MMD, symptoms related to atherosclerosis and vascular retrogression are likely to emerge after 50 or 60 years of age. For potential patients with MMD who were previously asymptomatic, ischemia symptoms emerge much earlier (e.g., after 30 or 40 years of age) than in otherwise-healthy individuals. Thus, in adult patients, especially those who are 30–40 years of age, symptoms are caused primarily by vascular retrogression and atherosclerosis, on the basis of moyamoya lesions formed earlier in life, chiefly during the embryonic period.
5. The period after 50 years of age: Although retrogression and atherosclerosis continue to progress over time, the oxygen consumption of the cerebellum also decreases. Moreover, moyamoya lesions do not become severe in this period. Accordingly, the numbers of diagnoses decrease after 50 years of age.

In summary, the first peak age of onset occurs because the increasingly severe vascular lesions cannot provide sufficient oxygen to meet the increasing demand of the developing cerebellum; the second peak age of onset occurs because of degenerative vascular changes (including physiological and pathologic aspects, primarily related to atherosclerosis), combined with the basic pathologic changes of MMD.

Abnormal Development of Cerebral Arteries Mainly Caused by Genetic Factors

An increasing number of papers demonstrates that MMD is mainly caused by genetic and environmental factors. Recently, ring finger protein 213 was identified as a susceptibility gene among East Asian populations.[19] We agree with the previous researchers, and combined with our present research we further argue that the genetic factors start to work early during the embryonic period when the cerebral arteries begin to develop. In a few instances, the genetic factors might start to work after birth, which causes the progressive stenosis of main cerebral arteries. Obviously,

there is a long way to go to find the exact pathogenic gene and the pathways from gene to phenotype.

Obviously, this study has lots of limitations: first, we proposed this hypothesis based on the theory of embryology and the cerebral artery characteristics of patients with MMD, mainly based on the similarities of the appearance of primitive cerebral vessels and the cerebral vessels of patients with MMD; however, we did not have the fundamental experiment or animal model to prove it. Second, even if this theory is likely to be true, there is still a long way to go to find the treatment and the etiology of MMD. Third, this hypothesis can explain a lot of characteristics of MMD, but it does little with the prognosis. Above all, we think this hypothesis can provide an orientation for the future research, that we should pay more attention to the embryology of artery, which might help us find etiology and treatment.

CONCLUSIONS

In conclusion, we propose a hypothesis for the formation of MMD. MMD is caused by abnormalities of arterial development, primarily in the embryonic and postnatal period. In the embryonic period, if the primitive vessels do not fuse normally to form the trunks of the ACA, MCA, and PCA, or the primitive ICA has not sprouted normally, the ACA, MCA, and PCA will be observed as occluded or stenotic, sometimes in a plexiform manner. The unfused primitive small vessels will remain as "moyamoya vessels," which can be detected on DSA. Rarely, the aforementioned abnormality also will occur in the vertebrobasilar artery system. In some cases, the primitive AChoA will remain undegenerated to compensate for the ischemia caused by the failure formation of vascular trunk. Overpruning in the arterial maturation process might result in progressive stenosis or occlusion. This hypothesis provides a new orientation for MMD research. More attention to the embryonic of cerebral vessels will help discover the etiology and treatment for MMD.

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