

The collateral circulation in pediatric moyamoya disease

Gerasimos Baltasvias · Nadia Khan · Anton Valavanis

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Abstract

Purpose The descriptions of collateral circulation in moyamoya have so far been a mixture of topography-based and vessels' source-based analyses. We aimed to investigate the anatomy and systematize the vascular anastomotic networks in pediatric moyamoya disease.

Methods From a series of 25 consecutive complete angiographic studies of newly diagnosed children with moyamoya, 14 children had moyamoya disease and 11 were diagnosed with moyamoya syndrome, i.e., moyamoya angiopathy with some additional concomitant systemic disease. We retrospectively analyzed the arterial branches supplying the moyamoya anastomotic networks, their origin, course, location, and connections with the recipient vessels.

Results We describe four types of anastomotic networks in children with moyamoya disease, two superficial-meningeal and two deep-parenchymal. As superficial-meningeal, we defined the leptomeningeal and the durocortical networks. Apart from the previously described leptomeningeal network observed in the convexial watershed zones, we report on the basal temporo-orbitofrontal leptomeningeal network. The second superficial-meningeal network is the durocortical network, which can be basal or calvarian in location. We define as deep-parenchymal networks the nonpreviously described subependymal network and the inner striatal and inner thalamic networks. The subependymal network is fed by the

intraventricular branches of the choroidal system and diencephalic perforators, which at the level of the periventricular subependymal zone, anastomose with medullary—cortical arteries as well as with striatal arteries. The inner striatal and thalamic networks are constituted by intrastriatal connections among striatal arteries and intrathalamic connections among thalamic arteries when the disease compromises the origin of one or more sources of their supply.

Conclusion The previously inexplicitly described “moyamoya abnormal network” in pediatric moyamoya disease can be described as a composition of four anastomotic networks with distinct angioarchitecture. A better understanding of the collateralization in moyamoya may help in defining a new staging system of the disease with clinical relevance.

Keywords Moyamoya vessels · Anastomotic network · Collateral network · Moyamoya disease · Pediatric

Introduction

Pediatric moyamoya is characterized by progressive, usually bilateral steno-occlusive changes of the intracranial carotid artery (ICA) centered at its bifurcation, with typical extension to the proximal middle cerebral (MCA) and anterior cerebral (ACA) arteries and possible extension into the posterior cerebral artery (PCA). These changes occur in parallel with the development of the so-called moyamoya abnormal vessels or anastomotic vessels or network (MAN). Most authors agree that basal moyamoya vessels are dilated perforating vessels or branches of the ICA, which ordinarily supply the optic nerves, pituitary gland, anterior perforated substance, dura mater, and other skull base structures, anastomosing to distal cortical branches through a collateral network as a response to the increasing hypoperfusion [1–4] although other descriptions

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G. Baltasvias (✉) · A. Valavanis
Department of Neuroradiology, University Hospital Zurich,
Frauenklinikstrasse 10, 8091 Zurich, Switzerland
e-mail: Gerasimos.Baltasvias@usz.ch

N. Khan
Moyamoya Center, University Children's Hospital Zurich, Zurich,
Switzerland

still refer to new anastomotic vessels [5] and true neoangiogenesis around the circle of Willis [6, 7].

Matsushima and Takahashi have previously proposed two distinct descriptions of the moyamoya collaterals. Matsushima et al. described six concentric collateral systems (A to T). The A system is the intracerebral anastomotic one connecting the medullary arteries with the basal perforators at the external angle of the lateral ventricle. The B system includes the circle of Willis and persistent carotid-basilar anastomoses. The C system is the cortical leptomeningeal anastomotic network. The D system consists of the dural arteries, which are anastomosed with each other and can eventually form anastomoses with the C system. The E system is the extracranial vascular network of the scalp and pericranial muscles, which is practically not involved in the MAN except if a skull opening (as craniotomy or burr hole) has taken place. The T system is described as the “transdural anastomosis,” which brings in contact the E and D systems with the C system. It probably arises at the regions where some soft tissue intervenes between the C system and the D and E systems, where the bridging veins enter the dural sinuses, where there are arachnoid villi, or where arteries or nerves bridge the dura mater and the brain [8].

According to the description of Takahashi, four systems are spontaneously involved in moyamoya. The first collateral pathway is known as basal moyamoya and includes abnormal dilatation of the lenticulostriate and thalamoperforating arteries in the basal ganglia and thalamus. The second pathway involves substantial dilatation of the anterior choroidal and posterior pericallosal arteries. The third pathway is known as ethmoidal moyamoya, which includes abnormal dilatation of the anterior and posterior ethmoidal arteries, mainly from the ophthalmic arteries to the ACA branches. The final pathway is a vascular network in the cranial vault that is responsible for the collateral flow from dural branches of the external carotid artery (ECA) to pial arteries (“vault moyamoya”) [2].

Both of the above descriptions and definitions are unsatisfactory and confusing for one basic reason: They mix purely topographical descriptions with descriptions linked to the nature of these networks. Namely, their definition of basal moyamoya includes only lenticulostriate and thalamoperforating arteries despite the fact that the branches of anterior choroidal artery are also basal in location together with the ethmoidal branches, which are dural in nature and do not belong to the same group with the other dural branches of the vault apparently due to their basal location. Moreover, the above descriptions fail to identify leptomeningeal networks in the so-called basal moyamoya and bring the anterior choroidal and posterior pericallosal arteries in the same group without appropriate justification and ignore the posterior choroidal arteries. Additionally, they differentiate the scalp network from the dural one although the latter constitutes the final common pathway of the former to the pial arteries. Eventually, this analysis was developed to explain the rational of the

encephalo-duro-arterio-synangiosis, which justifies partially the above description [8]. Another reason might be their purpose to describe the chronological sequence of network development as the disease progresses. In either case, the descriptions remain limited. In our present analysis based on high quality selective and superselective angiographies, we present a coherent angioanatomical description of the complex collateral system in moyamoya disease.

Materials and methods

From 2012 to 2013, 32 newly diagnosed patients with moyamoya disease and moyamoya syndrome underwent an angiographic investigation under general anesthesia. Twenty-five patients were children up to 16 years old; 14 children were diagnosed with moyamoya disease. A detailed analysis of their digital angiograms was undertaken; six of these patients with moyamoya disease were previously studied, which helped us to clarify aspects of the moyamoya angioarchitecture [9, 10]. The eight additional patients with moyamoya disease investigated in these 2 years have been added in the current report. There were six females and eight males. Ages ranged from 2 to 16 years with a mean of 7.5 years.

The English literature related to angiographic features of pediatric moyamoya disease as well as relevant anatomical and microsurgical reports were studied and correlated with the analyzed angiographic images. We focused our attention to the less precise yet widely accepted descriptions of the angiographic findings referred to the collateral systems in moyamoya, and we tried to provide and efficiently support our analysis and interpretation.

Results

The systems of collateral circulation can be grouped as follows:

1. The leptomeningeal system, which mostly consists of the anastomoses of the PCA-ACA branches and PCA-MCA branches at the watershed zones. This system also includes a leptomeningeal network fed by the uncal artery, a branch of the proximal anterior choroidal artery or distal ICA. This network extends over the temporal pole and retrograde through temporal branches, supplying the M1 segment of the MCA; connections to orbitofrontal branches of ACA have also been observed. An additional leptomeningeal network identified was the one fed by the hypophyseal artery(ies), which through known extraparenchymal anastomoses among the hypothalamic perforators supply the ACA at the anterior

communicating artery (Acom) level. One classic (A) and two nonclassic (B, C) examples of this system appear in Fig. 1.

2. The durocortical system, which consists of all dural branches of the ICA, ECA, and vertebrobasilar system such as the anterior and posterior ethmoidal, the artery of the falx, the tentorial branches of the ICA, the posterior meningeal branch of posterior inferior cerebellar artery (PICA) or vertebral artery (VA), the dural branches of anterior inferior cerebellar artery (AICA) and PCA and the middle meningeal artery (MMA). These branches, which irrigate the dura, may create or activate preexisting anastomoses with the pial arteries whenever there is a need to bypass steno-occlusive lesions, which cause distal hypoperfusion. Two classic (A, B) and one nonclassic (C) examples of this system are presented in Fig. 2. We have

not identified connections of dural branches with basal brain perforators.

3. The subependymal anastomotic network. This system includes the direct connections of striate arteries with the medullary arteries of the hemispheres, the septal transcalsal connections of the posterior choroidal arteries with the pericallosal arteries, and the connections of the anterior and posterior thalamoperforating arteries and anterior and posterior choroidal arteries with the medullary arteries either directly or indirectly through their anastomoses with distal segments of the striate arteries. Three examples of this system appear in Fig. 3.
4. The inner thalamic and striatal anastomotic networks. To this system belong the intrathalamic and intrastriatal anastomoses among thalamic and striatearteries respectively,

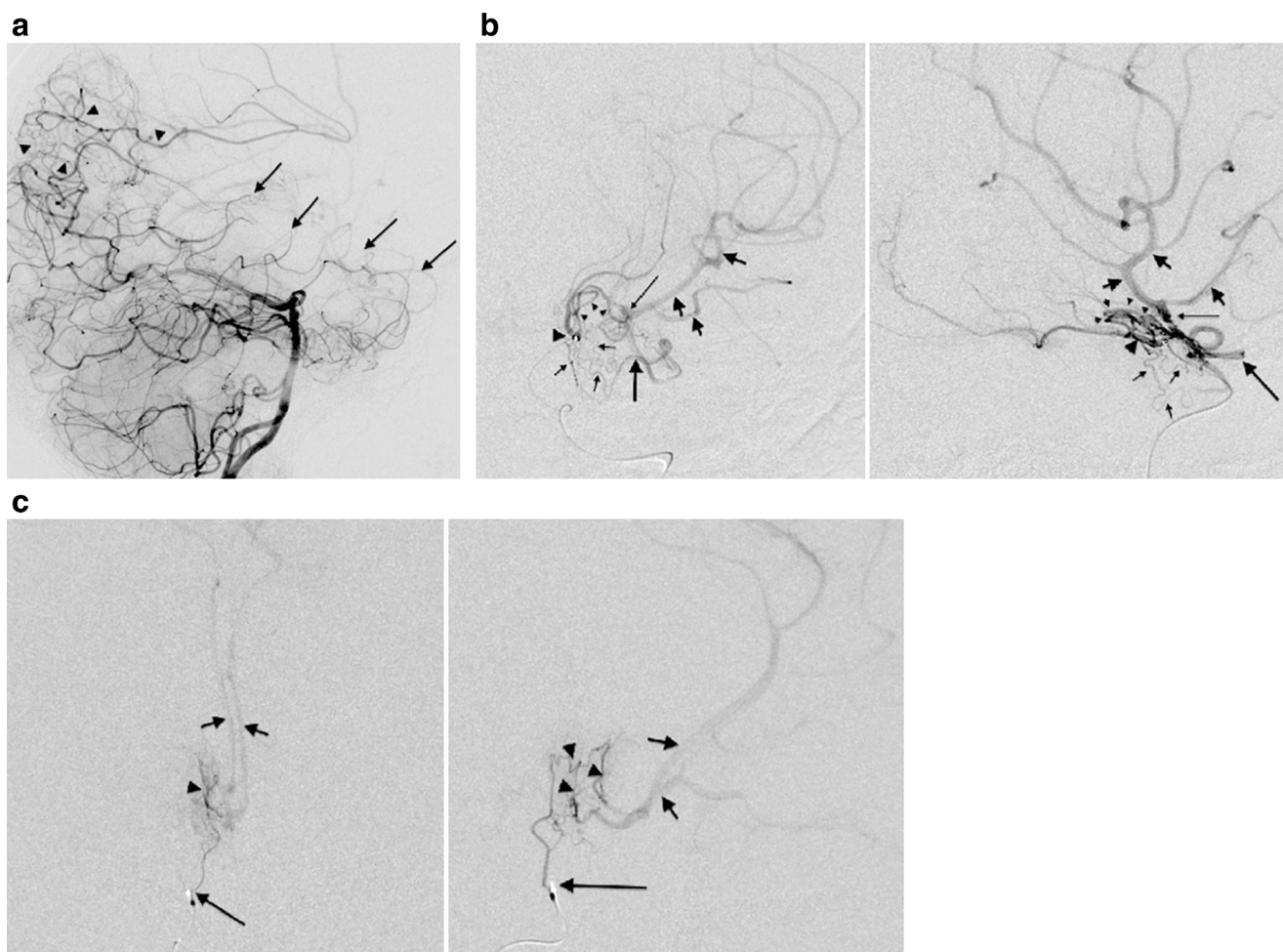


Fig. 1 **a** Lateral projection of a VA injection with the classic watershed collaterals of the PCA to both MCA (*arrows*) and ACA leptomeningeal distal branches (*arrowheads*). **b** AP and lateral projection of a superselective injection of the anterior choroidal artery (*arrowhead*) with origin of the rostral uncus artery just distal to the tip of the microcatheter with demonstration of its characteristic meandric collateral connection (*small arrowheads*) with the anterior temporal branch (*long arrow*) of the MCA (*short arrows*) and reconstruction of

the artery at the level of M1 segment (*long thin arrow*). Fine branches on the medial temporal pole also visible (*thin short arrows*). **c** AP and lateral projection of a superselective injection of a superior hypophyseal artery (*long arrow*). Superomedial course of the artery and anastomoses (*arrowheads*) with diencephalic perforators of distal A1 and reconstruction of both ACA (*short arrows*). Used with permission from Baltasavias et al. [9]

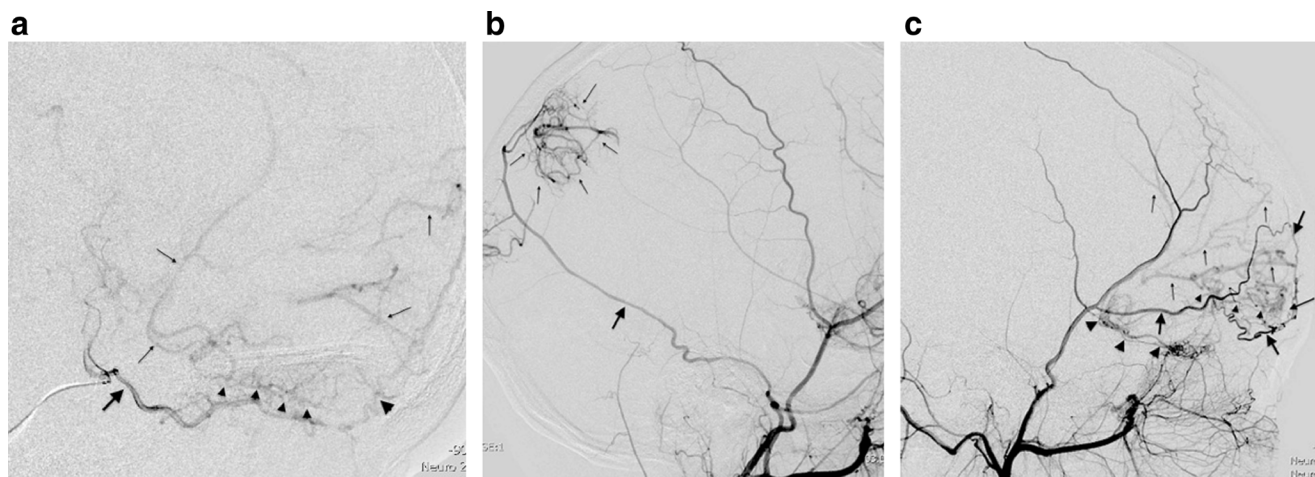


Fig. 2 **a** Lateral view of a superselective ophthalmic injection (*large arrow*) showing a classic ethmoidal network of collateral vessels (*small arrowheads*) reconstructing the ACA (*thin long arrows*). Used with permission from Baltasvias et al. [9]. **b** Lateral view of an ECA injection with demonstration of classic convexial collateral durocortical connections between MMA (*large arrow*) and MCA branches (*small arrows*). **c**

Lateral view of an ECA injection showing participation of the STA (*large arrows*) to the supply of the fronto-orbital cortex (*long thin arrows*) through trans-orbital connections to the anterior ethmoidal artery and artery of the falx branches (*small arrowheads*). Also notice the reconstruction of the orbitofrontal branch of the ACA (*large arrowheads*) through the sphenopalatine-septal branches of ECA

when the disease affects one or more arteries from each group. Two examples of this system(s) appear in Fig. 4.

The four collateral network systems with distinct arterio-arterial pathways identified in children suffering from moyamoya disease are presented in Table 1. Two systems (leptomeningeal and durocortical) are superficial-meningeal and the other two systems (subependymal and inner) are deep-parenchymal.

Discussion

Although Japanese experts have provided a more complete description of the moyamoya anastomotic networks [2, 8] and contributed a lot to our understanding of the collateral networks developing in pediatric moyamoya disease, there are still several questions about the nature and origin of the anastomotic vessels, the precise connections among arteries of these networks, their location, as well as differences between children and adults. Our description and definition of groups of collateral networks is mainly based on the nature of the vessels participating in the networks. This applies to the leptomeningeal, dural, and inner intrastriatal-intrathalamic networks regardless if the vessels are basal, superficial, convexial, or calvarian. The definition of subependymal network, which is an important component of our current analysis and a significant addition to previous descriptions, is based on location. The current study is a continuation and conceptualization of previous analysis of high quality selective and superselective angiographies of children with moyamoya disease [9, 10].

The leptomeningeal anastomotic network

It is clear that the leptomeningeal system plays the most important role in the collateral supply of the ischemic cortex of the ACA and MCA territory especially in the non-advanced phases of the disease. This is not related only to the PCA contribution, which remains active and robust as long as the disease does not affect the posterior circulation but also to leptomeningeal collaterals fed by branches of the ICA proximal to the steno-occlusive lesions. Such a local network is the one fed by the uncus artery, rostral branch of the anterior

Fig. 3 **a** AP and **b** lateral views of a superselective thalamoperforator injection (*arrow*) showing an extensive collateralization to distal MCA cortical branches (*large arrowheads*) with retrograde flow through medullary arteries (*thin arrows*) connected with the dilated thalamoperforator at the level of the angle of the lateral ventricular wall (*small arrowheads*). Used with permission from Baltasvias et al. [9]. **b** AP and lateral views of a superselective injection of a proximal Pcom hypothalamic perforator showing collateral supply to both ACA and MCA territory. The ACA is supplied at the level of Acom with retrograde flow through hypothalamic perforators connected with the injected perforator at the level of the wall the third ventricle. In contrary, the MCA territory is supplied by retrograde flow through the medullary arteries, fed by the distal branches of a striate artery, which is connected with the injected perforator at the level of the ventricular wall of the lateral ventricle. Used with permission from Baltasvias et al. [9]. **c** Anteroposterior and lateral views of a superselective injection of a left anterior choroidal artery (*long thick arrow*) with supply through its medial and lateral branches (*long thin arrows*) of medial striate arteries (*short thin arrows*) exiting to the M1 (*thick arrow head*) and A1 (*thick short arrow*). A very tortuous arterial branch (*thin arrowheads*) running laterally (anteroposterior view) and retrogradely opacified through the lateral intraventricular branch of the anterior choroidal is also exiting into the MCA at the M1-M2 level. Used with permission from Baltasvias et al. [9]

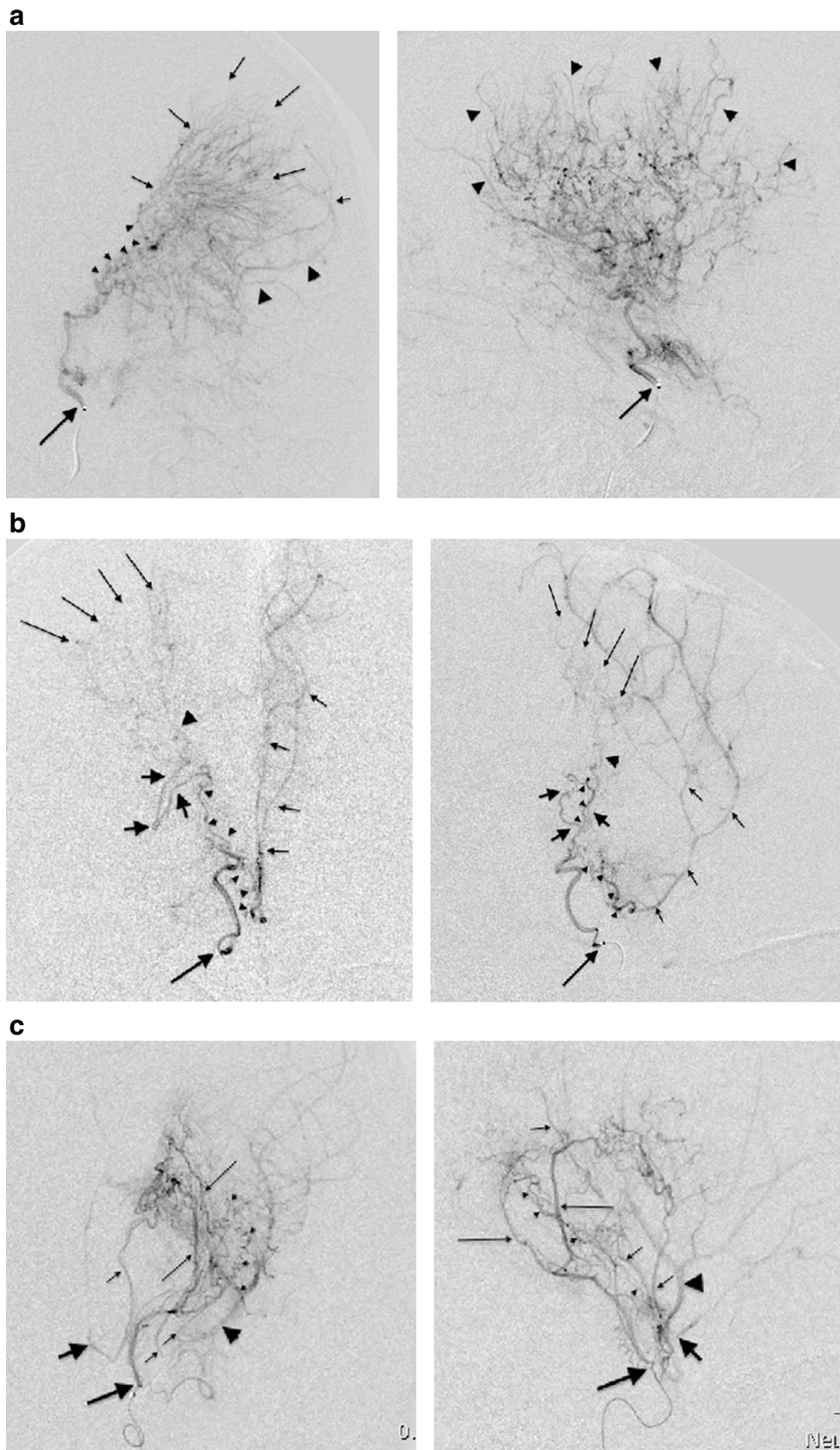
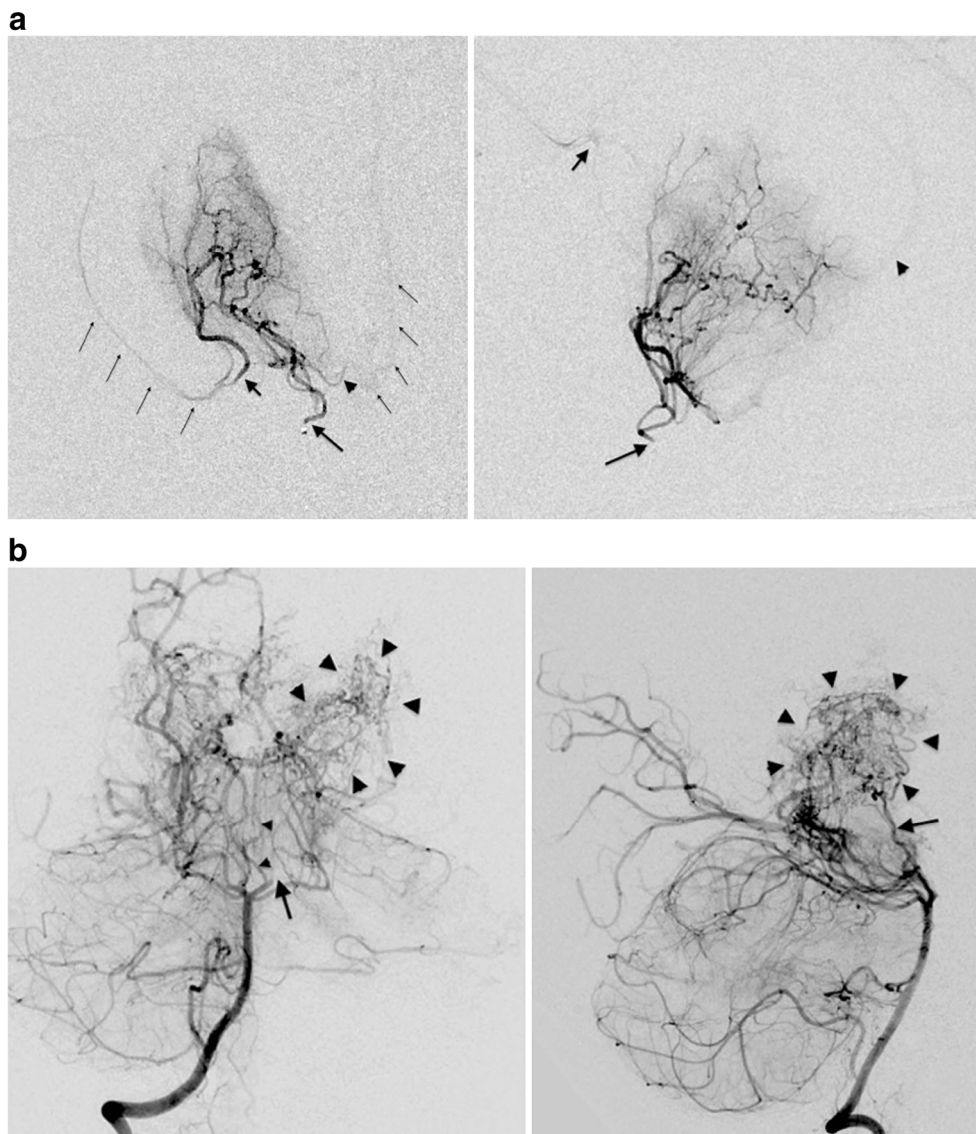


Fig. 4 a Anteroposterior view of a superselective injection of a medial striate artery (*arrow*) arising just proximal to the major stenotic site of the ICA bifurcation. An intrastriate network of vessels is opacified that fills retrogradely a lateral striate arteries, which exit (*short arrow*) at the MCA trunk (*thin arrows left*) distal to the level of the major stenosis as well as to a small medial striate branch of the ACA exiting at the level of the mid A1 (*arrowhead*) and opacifying the distal ACA (*thin arrows right*). Lateral view. The *arrowhead* indicates the ACA and the short arrow the MCA. Used with permission from Baltasvias et al. [9]. **b** Anteroposterior view of a vertebral injection which shows an intrathalamic network (*large arrowheads*) of dilated vessels supplied among other branches, by a left-sided thalamoperforator (*small arrowheads*) in a patient with occlusion of the ipsilateral PCA beyond the P2 segment. The same injection in lateral projection showing the mentioned thalamoperforator (*arrow*) connected with the intrathalamic network. Used with permission from Baltasvias et al. [9]



choroidal artery or the choroidal segment of the ICA, which constitutes a standard pathway for the reconstruction of the MCA at the level of M1 [11]. Another similar local network is the one fed mainly by the superior hypophyseal arteries, which through known leptomeningeal anastomoses [12, 13] among the diencephalic arteries supply the ACA at the level of the distal A1 and Acom. The latter network does not serve only to the collateral supply of the ACA cortical vessels but also to the irrigation of the anterior hypothalamus itself through the circuminfundibular network which later on and after severe proximal progression of the stenosis to the extradural ICA can be reconstructed through the posterior hypophyseal branch of the meningohypophyseal trunk of the ICA. This underlines the great collateral capacity of the brain in this area. One more known leptomeningeal collateral pathway connecting the posterior communicating artery (Pcom)

with the anterior choroidal artery can reconstruct the latter after occlusion of its origin [11].

The durocortical anastomotic network

This system is not a prerogative of the ECA branches simply because the blood supply of the dura matter is not their exclusivity. This means that the so-called ethmoidal moyamoya belong to the same system with the vault moyamoya as well as the collaterals developed from the dural branches of the ICA, or the transosseous dural branches of the occipital artery and other scalp arteries. Obviously, the ethmoidal durocortical collaterals grow relatively early in the course of the disease, presumably because the collateral supply through the leptomeningeal PCA-ACA system cannot be very effective for the coverage of the frontopolar and fronto-orbital territory.

Table 1 The vascular connections tabulated according to the collateral network they belong to

Network	Feeding vessels	Course	Recipient vessels
Leptomeningeal	Splenic artery	Retrosplenic	Pericallosal artery
	Parietoccipital PCA branches	Medial and convexial parietoccipital hemispheric surface	ACA distal cortical branches
	Temporal PCA branches	Inferior temporal hemispheric surface	MCA distal cortical branches
	Pcom perforators	Mesial temporal surface–cerebral peduncle	Anterior choroidal artery
	Anterior choroidal artery–uncal artery	Anterolateral to the temporal pole	Temporal MCA branches (possibly orbital branches too)
	Superior hypophyseal artery	Circuminfudibular plexus, diencephalic perforators	ACA at the A1 or Acom level
	Inferior hypophyseal artery	Circuminfudibular plexus, diencephalic perforators	ACA at the A1 or Acom level
	Prechiasmatal ophthalmic branches	Along the optic nerve, hypothalamus	Probably ACA
Durocortical	Posterior ethmoidal artery, anterior ethmoidal artery, artery of the falx	Lamina cribrosa and anterior falx	Orbital and frontopolar branches of ACA
	MMA	Durocortical connections	MCA, ACA cortical branches
	Occipital artery	Mastoid artery and other dural branches	MCA, ACA cortical branches
	STA	Supratrochlear, ophthalmic, ethmoidal arteries	Orbital and frontopolar branches of ACA
	Tentorial branches of ICA	Along the tentorium	Medial occipital and temporal lobe cortical branches
	Dural branches of PCA, SCA	Durocortical connections	Cortical branches
	Post. meningeal artery	Durocortical connections	Occipital and temporal cortical branches
	Subependymal	Anterior choroidal artery	Ventricular branches
Anterior choroidal artery		Ventricular branches	Medullary arteries and convexial cortical arteries
Anterior choroidal artery		Ventricular branches	M2 insular branches
Pcom perforators		Subependymal to the angle of the lateral ventricles	Medullary arteries and convexial cortical arteries
Thalamoperforators		Subependymal	Striate arteries
Thalamoperforators		Subependymal	Medullary arteries and convexial cortical arteries
Posterior choroidals		Choroid plexus, to septum, transcallosal	Pericallosal arteries
Posterior choroidals		Choroid plexus, subependymal	Striate arteries
Inner intrastriatal, intrathalamic	Medial striate arteries	Endostriatal network	Lateral striate arteries to M2
	Thalamoperforators	Intrathalamic network	Adjacent thalamic territories

ICA internal carotid artery, *MCA* middle cerebral artery, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery, *SCA* superior cerebellar, *STA* superficial temporal, *MMA* middle meningeal artery, *Pcom* posterior communicating artery, *Acom* anterior communicating artery; *A1*, *M1*, *M2* segments of ACA and MCA

As it has already been assumed, these durocortical connections probably arise at the regions where some soft tissue intervenes between the dural and pial arterial system, where the bridging veins enter the dural sinuses, where there are arachnoid villi, or where arteries or nerves bridge the dura mater and the brain [8].

It looks like all dural branches can be involved depending on the level of steno-occlusion. The example presented in our previous report, of the dural branch of the PCA, which supplied its distal cortical medial occipital territory to bypass an occlusion of the P2 segment, illustrates this potential. The case

with bilateral contribution of the accessory meningeal artery through unusual connections underlines also the capacity of the system [9]. How this system is activated and whether it represents a hypertrophied preexisting system or a newly developed and angiogenetically induced one is actually unknown.

The subependymal anastomotic network

In the past, it was believed that the cerebral arteries do not anastomose with each other once they pierce the brain

parenchyma [14]. Shellshear in 1920 reported that there are free capillary anastomoses among these arteries but not connecting arterial channels [15].

Van den Bergh [16] in 1969 described the centrifugal system of arterioles originating from subependymal arteries which are branches of the choroidal and the striatal arteries. Plets et al. [17] studied the ventriculofugal, irrigating branches of the thalamus arising from the choroidal arteries and reported that most of thalamic arteries have a subependymal course with branches distributed to the subependymal area. Similarly, De Reuck [18] described three types of periventricular border zones between medullary, perforating, and choroidal arteries. Handa and Handa [19] described that the cortical branches of MCA and ACA distal to the stenosed or occluded ICA bifurcation were reconstructed by intraparenchymal collateral precapillary network among perforating arteries of the brain, a concept supposedly supported by previous studies [20, 21].

Subsequently, Kuban [22] and later Gilles [23] in their studies described that the striatal capillary bed is continuous between the striatal and extrastriatal circulations but denied the model proposed by Van den Bergh and De Reuck as did Moody et al. [24] and Nelson et al. [25]. Later, Mayer et al. [26, 27] noticed that the existence of ventriculofugal arteries throughout the white matter is certain, though their significance in relation with the proposed border zone concept is speculative. In parallel, other studies by Nakamura et al. [28], Takahashi [29], and Saito et al. [30] supported the ventriculofugal-ventriculopetal arteries border zone concept. Marinković et al. [31] in their anatomic cadaveric study of adult brains described in detail subependymal arteries arising from the anterior and posterior choroidal arteries and irrigating the temporal and posterior horns, the atrium, and the body of the lateral ventricles. They perfused only partially the frontal horn, which was found to be perfused also by the Heubner artery, whereas the superior-callosal aspect of the ventricles was irrigated by penetrating callosal twigs of the pericallosal artery. The subependymal arteries supplied also the subependymal layer over the thalamus.

From the above short review, it is clear that the literature furnishes us completely discrepant information. According to our observations, which are based on several superselective injections of the lateral striate arteries done in the past, these arteries often present a distal ventriculofugal segment, which is undoubtedly opacified in the arterial phase (unreported data). However and regardless of this observation, it seems widely accepted that (1) there are capillary and/or precapillary anastomoses throughout the telencephalon [25] and (2) no anastomoses of a higher order exist between deep medullary, striatal, thalamic [17], and choroidal arteries since they are considered as end arteries. In other words, there must be a

border zone between their territories [24], regardless of the existence or not of ventriculofugal arteries. Accordingly, there must be a striatal/medullary border zone, a thalamo/striatal border zone, and a thalamo/medullary border zone. As a matter of fact and despite the contradictory reports about the existence of subependymal branches of the choroidal arteries irrigating some specific areas of the periventricular white matter, the participation of the intraventricular branches of the choroidal arteries in the developed collateral network in our cases of pediatric moyamoya disease is beyond any doubt. The selective and superselective injections enabled us to decompose complex angiographic images and distinguish connections between choroidal and striate arteries, choroidal and medullary arteries, striate and medullary arteries, thalamic and striate arteries, thalamic and medullary arteries, and hypothalamic with striate and medullary arteries. In all these cases, the connection was between peripheral segments of the arteries with one disputable case where a thalamoperforator seemed having a connection also to a proximal segment of a striate artery. With this one conceivable exception, the commonly identified location of all the above-described anastomotic connections was the periventricular subependymal white matter. Therefore, our findings support the idea of a periventricular subependymal territory acting as a meeting area for the medullary, striate, thalamic, hypothalamic, and choroidal arteries. The participation, connections, and distribution of these vessels are certainly not uniform and not random [32]. Presumably, it depends on the relation of their primary territory with the nearest ventricle wall as well as on the specific demand according to the stage and progression of the disease. Although no anastomoses have been reported between subependymal branches of the choroidal arteries and other arteries [31], such an ischemic condition, especially in children, can promote either the enlargement of preexisting precapillary anastomoses which then can be functional and capable to provide vital blood flow to ischemic zones or a kind of vascular reorganization process [24].

The inner thalamic and striatal anastomotic networks

Our study demonstrated that in pediatric moyamoya disease the medial striate arteries can anastomose with the lateral striates via connections of their (mostly) distal branches with retrograde flow through the latter to the M2 segment of the MCA. These anastomoses are triggered or used when the MCA is affected at the level of the origin of the lateral striates. They constitute an inner striatal anastomotic network.

The existence of a similar inner vascular anastomotic network, this time supplied by the thalamoperforators of the P1 segment, was observed in the thalamus when the parent vessel (PCA) was affected by steno-occlusive lesions at the level of the origin of other thalamic arteries (as thalamogeniculate or posterior choroidal). The pathomechanism for the induction or activation of such networks is unknown and its ultimate pathway could be the enhancement of the preexisting precapillary anastomoses triggered by the ischemic demand.

The accurate description of the collateral networks in pediatric moyamoya disease has not only been a purely anatomic interest without clinical relevance. Moreover, their definition cannot be primarily dictated by the need to support operative strategies. It is rather the other way around; the knowledge of the role, the territory, and the potential of each vessel in providing collateral supply can assist in the evaluation and prediction of the reserves of the anastomotic networks. Additionally, the elaboration of a more accurate classification of the available and potentially functional collateral pathways in pediatric moyamoya, where the disease is rapidly progressive in comparison to the adult angiopathy, can assist in defining the operative criteria in individual patients.

Conclusion

The anastomotic collateral network in pediatric moyamoya disease is composed of two superficial-meningeal systems, the leptomeningeal collateral and the durocortical system, and two parenchymal systems, the subependymal one and the inner system of striatum and thalamus. The so-called basal moyamoya is a composite of all the above systems; therefore, the designation “basal” as it appears in the literature is inaccurate since it includes under the same name different systems and at the same time excludes other basally located anastomotic networks. A more precise description and definition of the developed anastomotic networks in pediatric moyamoya disease can help in our better understanding of the disease.

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No Institutional Review Board vote for this retrospective study was necessary.