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ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ISCHEMIA

In vivo demonstration of blood-brain barrier impairment in Moyamoya disease

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Abstract

Background Moyamoya disease (MMD) is a cerebrovascular disorder characterized by fragile vascular system. Previous studies suggested that the blood-brain barrier (BBB) destabilizing cytokine angiopoietin-2 plays a critical role in increasing vascular plasticity and endothelial disintegration in MMD. The aim of this study was to assess cerebrovascular integrity in vivo in patients affected by MMD.

Methods We retrospectively analyzed 11 patients that underwent bypass for MMD (MMD group), 11 patients that underwent bypass for atherosclerotic cerebrovascular disease (ACVD—control group I), and 5 patients that underwent clipping for unruptured aneurysms (non-ischemic—control group II). Sodium fluorescein (NaFL) extravasation was evaluated during videoangiography when checking for bypass patency. A grading system (0, +, ++, +++) was used to define the extent of extravasation. Frequency and intensity of leakage was compared among different groups.

Results NaFL extravasation appeared in 10/11 (91%) patients with MMD and in 8/11 (73%) patients with ACVD during bypass procedures. Extravasation was observed in none of the patients undergoing clipping for unruptured aneurysms. Although both chronic ischemic patient groups showed a comparably high incidence of NaFL extravasation, the MMD group was characterized by a much greater intensity of NaFL extravasation (grade +++ in 82%) than the ACVD group (grade +++ in 27%, $p < 0.05$).

Conclusions We demonstrate blood-brain barrier impairment in MMD patients for the first time in vivo. This may be due to mechanisms intrinsic to the unique pathology of MMD, probably explaining the higher association with hemorrhage and post-operative hyperperfusion.

Keywords Blood-brain barrier · Bypass · Fluorescein angiography · Hyperperfusion · Moyamoya disease · Vascular disorders

Introduction

The blood-brain barrier (BBB) is one of the most important controllers of brain homeostasis. It is composed of endothelial cells sealed by extensive tight junctions, and reinforced by capillary basement membrane, end-feet of astrocytes, and pericytes [1]. The ways of passage through the neurovascular unit constituting the BBB are strictly regulated through different mechanisms, among which one of the most important is represented by the paracellular water way through the tight junctions, allowing the passage of hydrophilic substances of less than 180 Da molecular weight [4]. Its integrity is fundamental for normal function of the central nervous system, since it strictly limits the passage of molecules from the intravascular compartment into the brain, guaranteeing protection from toxic substances and maintenance of fluid balance as well as correct neurochemical environment around neurons. BBB can be altered by different mechanisms in several pathophysiological conditions, such as aging, hypertension, hyperglycemia, neurodegenerative diseases, malignancies, inflammation, trauma, and acute and chronic ischemia [1, 32].

In Moyamoya disease (MMD), impairment of cerebrovascular integrity with loss of BBB characteristics seems to play a critical pathophysiological role. Differently from chronic hemodynamic insufficiency due to atherosclerotic

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cerebrovascular disease (ACVD), in patients affected by MMD, there is evidence of an increased brain-specific vascular plasticity and fragility affecting mainly the pathologic collateral network that characterizes the pathology. This leads to a high incidence of strokes, either hemorrhagic or ischemic. In a recent paper published by our group [6], we demonstrated the upregulation of the pro-angiogenic cytokine angiopoietin-2 in Moyamoya vessels, but also the ability of serum from MMD patients to induce angiopoietin-2 overexpression and secretion by endothelium of cerebral vessels, with subsequent loss of endothelial integrity.

Based on this in vitro work, the aim of this study was to provide an in vivo evidence of our laboratory findings concerning endothelial disintegration and subsequent BBB impairment in MMD patients. Assessment of BBB permeability is commonly performed in animal models using tracers able to cross disrupted but not intact BBB, through the quantification of marker's extravasation into the brain parenchyma [30]. One of the main fluorophore used on this purpose is sodium fluorescein (NaFL). This low molecular weight dye (360 Da) represents in fact an established marker of BBB breakdown in animal models [14, 18, 19, 24, 33].

The peculiar characteristics of NaFL have recently promoted its clinical use in the field of neuro-oncology as tracer for intraoperative guidance during high-grade glioma resection [2, 3, 23]. NaFL has also been reported as valid alternative to indocyanine green (ICG) in the field of cerebrovascular surgery, since it represents a suitable dye for intraoperative videoangiography [16, 20–22, 25, 26, 29, 37].

In the present paper, we report our observations on BBB impairment in patients affected by MMD that underwent surgery for cerebral blood flow augmentation, through superficial temporal artery (STA) to middle cerebral artery (MCA) bypass, and undergoing NaFL videoangiography for intraoperative assessment of graft patency. This represents, to our knowledge, the first report on direct in vivo visualization of BBB characteristics, since ICG, the conventional dye utilized to assess graft patency does not pass through the BBB in MMD patients [36].

Material and methods

Patient population

We retrospectively analyzed our neurovascular database, surgical records, operative videos, and clinical data of 11 consecutive patients who underwent STA-MCA bypass for treatment of MMD (MMD group) in our Institution between March and July 2016. We compared the results with control groups composed by 11 consecutive patients that underwent STA-MCA bypass for ACVD (chronic hemodynamic impairment—control group I) and 5 consecutive patients that underwent clip ligation of unruptured anterior circulation aneurysms (non-ischemic—control group II). In total, there were 14 female patients and 13 male patients who ranged in age from 7 to 77 years (median 61 years).

All patients that underwent STA-MCA bypass received a diagnostic workup consisting of a neurologic examination, six-vessel digital subtraction angiography (DSA), magnetic resonance imaging (MR), and functional cerebral blood flow (CBF) studies with either single photon emission tomography (SPECT) or positron emission tomography (PET) with H_2O_{15} before and after acetazolamide administration. MMD was defined according to the guidelines of the Research Committee on Moyamoya Disease of the Ministry of Health and Welfare, Japan [13]. All patients that underwent STA-MCA bypass for ACVD fulfilled the criteria for hemodynamic cerebrovascular insufficiency [31] due to internal carotid artery occlusion or stenosis (*n*, 10) or MCA stenosis (*n*, 1). All bypass procedures were performed at least 6 weeks after the last neurological event. Post-operative DSA and/or computed tomography angiography (CTA) were performed to evaluate bypass patency.

Patient that underwent clip ligation for unruptured aneurysms (3 MCA bifurcation, 1 anterior communicating artery, 1 posterior communicating artery) received a clinical and radiological pre-operative evaluation through DSA, CTA, and/or magnetic resonance angiography (MRA). Post-operative CTA or DSA were performed for confirmation of aneurysm exclusion.

Surgical procedures

STA-MCA bypass was performed as previously described [31]. Briefly, patient position was supine with the head rotated contralaterally to the surgical side. Target point for bypass was detected using a specially designed template. After isolation of the STA branch, a 3 cm craniotomy was made, centered over the target point. After completing the anastomosis, control of bypass patency was performed in all cases through fluorescein videoangiogram. In MMD patients, the direct bypass was supplemented by indirect revascularization via encephalo-duro-synangiosis. In pediatric MMD cases, indirect revascularization was performed using both encephalo-duro-synangiosis and encephalo-myo-synangiosis. In aneurysm cases, patients underwent standard procedure for clip ligation, via lateral supraorbital craniotomy. We divided patients in three groups, according to the disease, in order to compare the extravasation of the dyes in different pathological entities.

Intraoperative videoangiography

For intraoperative angiography, we used a new commercially available microscope (Zeiss Opmi Pentero 900, Carl Zeiss Meditec, Oberkochen, Germany) equipped with a YELLOW

560 fluorescence filter module. In order to check for the patency of the established anastomosis, we administered a 500 mg bolus of sodium fluorescein (5 ml 10%—Akorn, Inc.) through a peripheral vein, switching the microscope to stimulus light for fluorescence visualization with the room lights switched off, as previously described [29]. As part of our clinical intraoperative videoangiography protocol, we recorded the fluorescently labeled bypass graft, anastomosis, and cerebrovasculature for a minimum of 2 min, to facilitate identification of early graft failure. This prolonged period of fluorescent videoangiography enabled us to detect early NaFL extravasation into the cortical parenchyma. White light stereomicroscopy sequences following this 2 min recording were used to rule out surgical trauma to the regions assessed for NaFL extravasation.

Grading system

We quantified NaFL extravasation using the semiquantitative grading system showed in Table 1 and Fig. 1. Since the observed pattern of extravasation was spot-like in both pathologies, we classified the spots according to their size, dividing them in *large* and *small*, depending on the involvement of 3 or less cortical capillaries. A grading score was assigned to each enrolled patient, according to the size and number of extravasation spots visualized. We subsequently proceeded to compare the results between the three groups. Two investigators (A.N. and Y.K.) reviewed the operative videos independently without knowledge of clinical information to assign an extravasation grade to each patient. When there was no agreement, the final decision was reached involving a third investigator.

Statistical analysis

Statistical analysis was performed using JMP7.0 software (SAS Institute, Cary, NC, USA). The statistical significance of intergroup differences was assessed through Pearson's test and ANOVA, as appropriate. If significance was obtained, we performed Turkey-Kramer multiple comparison test. $p < 0.05$ was considered significant.

Table 1 Grading system

Grade	Description
0	No extravasation
+	Less than 5 small spots, no large spots
++	5 or more small spots or 1 large spot, or both
+++	2 or more large spots

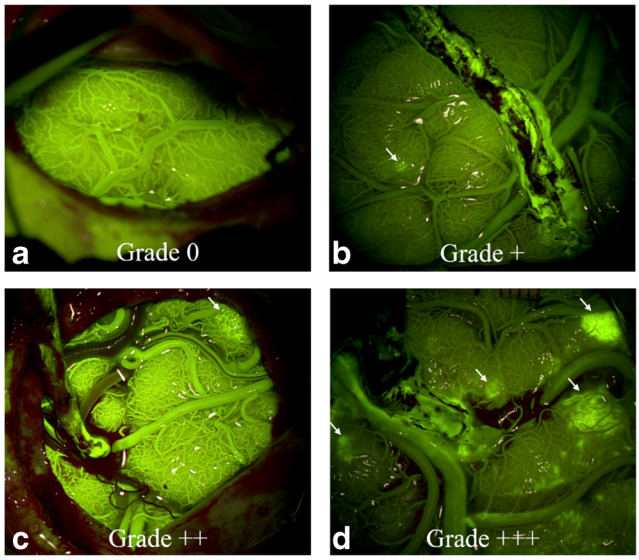

Fig. 1 **a**, **b**, **c**, **d** Grade examples. Extravasation spots are indicated with arrows

Results

During the 27 procedures, in all cases, NaFL videoangiography showed good graft patency in case of bypass and optimal aneurysm exclusion as well as good filling of perforating arteries in case of clip ligation. No adverse effects or allergy reactions related to NaFL administration were observed. The postoperative course was uneventful in all patients.

During NaFL videoangiographies, the extravasation of the dye appeared in 18/22 (82%) patients that underwent STA-MCA bypass procedure, approximately 10–15 s after the capillary phase (Fig. 2). Higher magnification provided more detail about the morphology of NaFL leakage (Fig. 3); firstly, it was evident that the staining involved superficial and also deeper cortical parenchyma; secondly, the extravasation was irregular and located within the perivascular space, without involving vessel walls that appeared darker compared to vessels without surrounding leakage (negative contrast); thirdly, in the vast majority of cases, extravasation seemed to involve post-capillary venules, and in some cases capillary segments. In none of the patients treated for unruptured aneurysms (non-ischemic—control group II), NaFL extravasation was detected.

In MMD, a minimum of 1 extravasation spot was evident in almost all cases (*n*, 10/11–91%). In ACVD group, NaFL extravasation was evident in 8/11 (72%) cases. The difference between the incidence of extravasation between two groups was not statistically significant. However, when we assessed the intensity of extravasation, our analysis revealed that in 9/11 (82%) cases in to MMD group a grade +++ extravasation was observed; in the ACVD group, by contrast, a grade +++ extravasation was observed only in 3/11 (27%) cases.

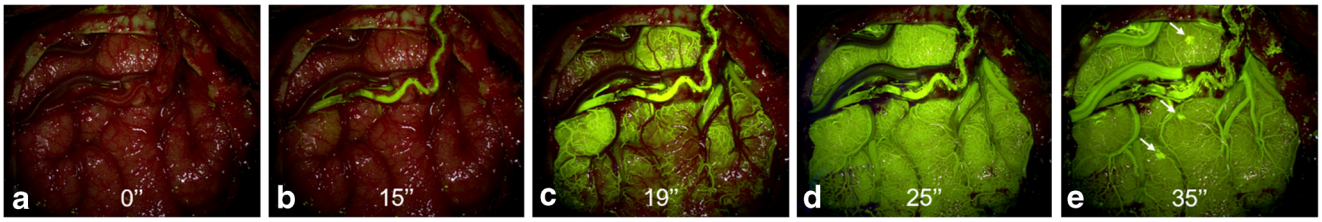

Fig. 2 **a**, **b**, **c**, **d**, **e** Intraoperative photographs showing time progression during sodium fluorescein videoangiography. Extravasation of the dye into the cortical parenchyma is usually observable 10–15 s after capillary phase (**e** arrows)

In only 18% (*n*, 2/11) of MMD patients we observed a grade inferior to +++ (*n*, 1 grade 0; *n*, 1 grade +); since the two patients belonging to grade 0 and + were pediatric, in no adult MMD cases an extravasation grade of less than +++ occurred.

The ACVD group presented a more balanced distribution between grades inferior to +++, with 27% of cases attributable to grade 0, 9% to grade +, and 36% to grade ++.

The difference of the median grade between MMD and ACVD groups was statistically significant ($p = 0.0460$).

Results are summarized in Table 2 and Fig. 4.

Discussion

The principal new finding of our study is the in vivo evidence of BBB breakdown in MMD patients, in which NaFL extravasation was observed in the vast majority of cases, and with greater intensity compared to ACVD group (Fig. 5). This important result confirmed the presence in such disease, beyond the chronic ischemic stress (common to both diseases), of additional mechanisms leading to superior vascular permeability and fragility, which is probably the main determinant of high incidence of strokes, either hemorrhagic or ischemic.

The different intensity of dye leakage observed between two groups of patients affected by chronic hemodynamic impairment (MMD and ACVD) deserves a detailed discussion on pathophysiological mechanisms underlying both diseases in correlation with BBB permeability.

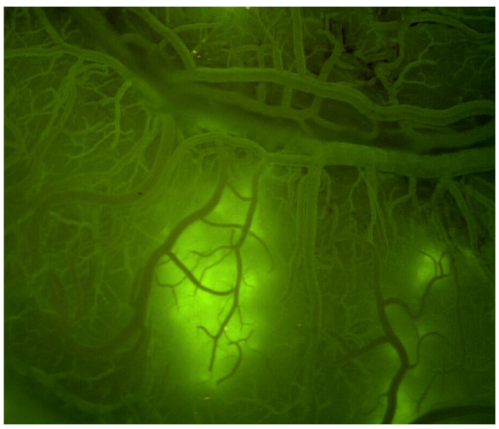

Fig. 3 Intraoperative photograph under higher magnification showing staining in deeper areas of cerebral cortex around post-capillary venular segment

BBB alterations in chronic ischemia with special reference to Moyamoya disease

The effects that occur in BBB during chronic ischemia have been investigated by many authors. It was demonstrated in experimental models the active role of metalloproteinases (MMPs) [11, 28] in determining the endothelial damage; as result, during hypoxic-ischemic stress, the vessels undergo noxious stimuli carrying to increased permeability and instability. The increased permeability involves different mechanisms in which cytokines, vascular endothelial growth factor (VEGF), and nitric oxide (NO) seem to play a crucial role. The tight junctions are the BBB component primarily involved; on the contrary, astrocytes appear to undertake a protective function [4]. Although the white matter, which represents the end of arterial circulation [8], is the brain area at higher risk to develop BBB breakdown during chronic hypoxic-ischemic insult, cortical collateral vessels present similar vulnerability. Such abnormalities in chronic ischemia have been also suggested after cerebrospinal fluid [34] and dynamic contrast-enhanced MR imaging studies [10].

MMD represents a rare pathological entity, characterized by clinical and genetic heterogeneity. It is a cerebrovascular stenoocclusive disorder of unknown etiology [35] with high incidence of strokes, both ischemic and hemorrhagic, predominantly due to the instability that characterizes the fragile vascularization of these patients. The combination between chronic hypoxic-ischemic stress and intrinsic characteristics of the disease makes the vessels particularly fragile. One of the milestones of the pathology is the presence of tiny vessels (so called moyamoya) that serve as collateral pathways, due to progressive narrowing of terminal portions of supraclinoid internal carotid, middle, and anterior cerebral arteries, with possible extension into the posterior circulation. It has been hypothesized that the fragility of moyamoya vessels is the principal pathological basis for hemorrhagic MMD. The collateral network, according to the stage of disease, is diffusely spread over the brain and can be divided into leptomeningeal, durocortical, subependymal, and inner thalamic-striatal [5]. The cortical microvascularization is characterized by significantly increased

Table 2 Summary of results

	Control	ACVD	MMD	*p* value
No. of patients	5	11	11	
Age (mean ± SD)	49.6 ± 12.7	66.3 ± 5.4	39.7 ± 19.1	0.0008
Male sex (%)	1 (20)	9 (81.8)	4 (36.4)	0.0295
Procedure	Clipping	STA-MCA bypass	STA-MCA bypass + EDS ± EMS	
Total incidence of extravasation (%)	0/5 (0)	8/11 (72)	10/11 (91)	0.2689
Grade				0.0015
0	5	3	1	
+	0	1	1	
++	0	4	0	
+++	0	3	9	
Median (IQR)	0 (0)	2 (0–3)	3 (3)	

ACVD, atherosclerosis cerebrovascular disease; *MMD*, moyamoya disease; *STA*, superficial temporal artery; *MCA*, middle cerebral artery; *EDS*, encephalo-duro-synangiosis; *EMS*, encephalo-myo-synangiosis

density and diameter, leading to increased surface [7], also observed during surgical procedures as reddish cortex.

The possible presence of BBB alterations in this pathology has been suggested by different authors, after the observation of high serum level of MMP-9 [11] leading to endothelial disintegration, but mainly after the demonstration of significant overexpression of the pro-angiogenic and barrier-destabilizing factor angiopoietin-2 in the M3 segment of the MCA obtained from patients during surgery [6]. This molecule is known to be overexpressed in highly vascularized brain tumors (such as gliomas and metastatic melanoma) and in inflammatory diseases (such as rheumatoid arthritis and psoriasis) and seems to lack of function in healthy vessels. Its overexpression in MMD, but not in ACVD, represents therefore the evidence of disease-specific mechanisms leading to development of MMD pathologic collaterals, regardless of ischemic stimuli. The result of activation of this pathway is that vessels are characterized by loss of tight junctions of endothelium and reduction in pericyte coverage, factors able to determine an increased vascular permeability and fragility.

Entity of BBB disruption

We took advantage of the peculiarity of NaFL to stain the brain parenchyma in the presence of BBB breakdown, to perform for the first time such a direct assessment of BBB permeability in living humans affected by MMD. This observation was easily carried out, slightly extending the analysis of videoangiographies, adding only a negligible time to the normal operation length. In our experience, NaFL is the only fluorophore able to cross the BBB and stain the cortical parenchyma in MMD and ACVD patients. In cases in which we performed ICG videoangiography (historical cases), dye extravasation was never observed, even in cases of prolonged analysis (i.e., intraoperative evidence of bypass failure with subsequent completion of a second anastomosis). The

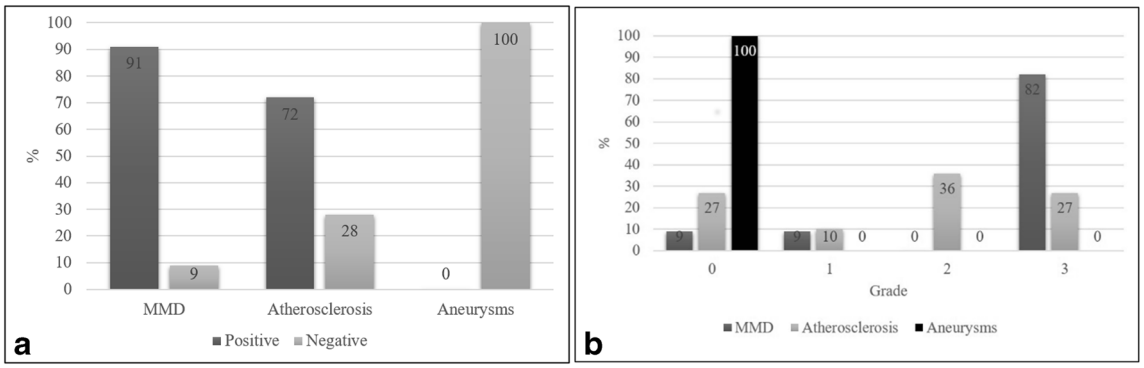

Fig. 4 Graphics showing statistical correlations between groups. **a** Incidence of NaFL extravasation among different groups. **b** Correlation among groups stratified for different grades

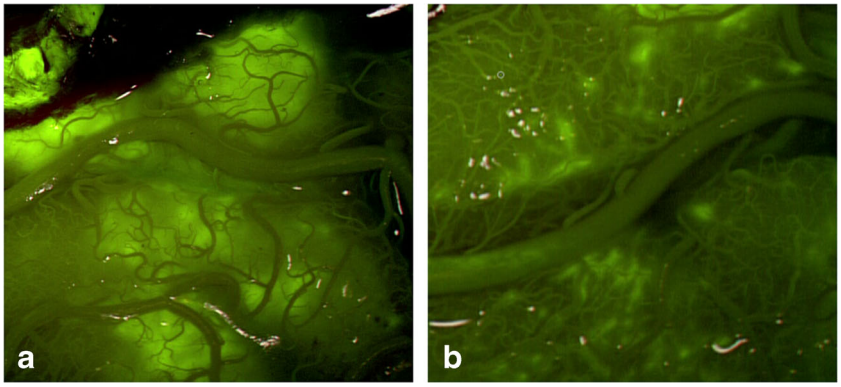

Fig. 5 Intraoperative photographs showing examples of cortical surface in MMD (**a**) and ACVD (**b**) patients after NaFL administration. Stronger, larger as well as more diffuse extravasation spots are evident in MMD

different behavior of these two fluorophores can potentially provide an idea about the degree of BBB permeability, being the molecular weight of the two substances within intravascular compartment clearly different. ICG is in fact a water-soluble low molecular weight dye (775 Da), characterized by high affinity with serum albumin (69.000 Da). After injection, it rapidly binds to plasma proteins and thereby it remains confined within intravascular space as high molecular weight complex [9]. Conversely, the low molecular weight of NaFL (360 Da) and absence of affinity to circulating macromolecules allows its free extravasation. The distinct extravasation patterns of ICG and NaFL indicate that the loss of BBB integrity in MMD is limited to small pore sizes based on intercellular ways of passage.

We can state therefore that the disruption occurring during chronic ischemia is never sufficient to allow the passage of serum proteins, normally bound to ICG. This finding is consistent with the pre-operative radiological image, in which in no cases there was evidence of areas of brain edema, occurring in case of serum protein extravasation.

Possible correlation with spontaneous hemorrhages

As stated above, our findings regarding the greater amount of spontaneous BBB breakdown in MMD prove a superior fragility of MMD vessels, probably leading to higher incidence of cerebrovascular hemorrhagic events compared to other chronic ischemic diseases; in fact, unlike pediatric patients, who usually present with transient ischemic attacks or cerebral infarction, about one half of adult MMD patients experience intracranial hemorrhages that seriously affect their prognosis [27]. This is mainly attributable to the pathological vascular network, but also to the higher tendency to aneurysm formation [17]. To support this, in the two pediatric cases of our series, we found only one small NaFL extravasation spot in one case (grade +), and no leakage points in the other, a completely opposite result compared to adult patients, in which we observed a grade +++ extravasation in all cases. Although the number of pediatric patients in our series is very small, this result can probably explain the extremely low incidence of hemorrhagic strokes in pediatric MMD, potentially due to protective factors able to reduce vascular fragility.

It must be said that in all adult MMD cases of our series, the onset of the disease was ischemic, thus not allowing us to make a direct correlation between hemorrhagic events and extravasation grade.

Moreover, although cerebral hemorrhage in patients with MMD is mainly located in the deep brain structures, the fragility affects all collaterals, so that the cortical vessels observed during our procedures can be considered representative for the global status of MMD vessels.

Possible correlation with post-operative hyperperfusion

Post-operative hyperperfusion represents a phenomenon more frequent in adult MMD population with a reported incidence up to 40% when including asymptomatic cases [12, 15], which can lead to transient neurological deficits in the early post-operative period. This can happen despite low flow revascularization obtained after standard STA-MCA bypass. Although the mechanism of such local cortical hyperperfusion remains unclear, the excessive arterial blood supply could cause oxidative stress that would generate free radicals, which could damage the BBB. Based on the assumption that adult patients with MMD have an intrinsic background that can facilitate angiogenesis and BBB disruption, predisposing to vasogenic edema and spontaneous hemorrhage, they could be therefore more vulnerable to post-operative hyperperfusion.

Reliable modalities are not available for intraoperative prediction of post-operative hyperperfusion. NaFL could represent, in our opinion, a useful tool to assess this risk during surgery for MMD, since it could portray the degree of altered vascular permeability of cerebral cortex subjected to STA-MCA bypass, leading to post-operative cortical vasogenic edema and/or hyperperfusion.

In none of our patients, we experienced post-operative symptomatic hyperperfusion (probably due to the small number of patients), and we do not routinely perform MR nor CBF studies in the immediate post-operative period, consequently further larger and focused studies are needed to establish a correlation between increased BBB permeability and this peculiar MMD phenomenon.

Study limitations

The main limitations of this study are represented by its retrospective nature and small cohort of patients.

Moreover, the mean age of each group is varied (MMD group, 40; ACVD group, 66), so that the aging process (a cause of BBB fragility) could represent a factor to consider in comparison of the BBB integrity among these groups.

We think also that our grading system is inevitably subjective, even if we tried to stratify the difference of dye extravasation with little space for interpretation.

Conclusions

For the first time, we demonstrated in vivo the presence of BBB impairment in patients affected by MMD, through the use of NaFL videoangiography during STA-MCA bypass procedures. In MMD patients, the BBB breakdown, even if similar to ACVD in terms of frequency, appeared to be of much greater intensity, probably because of additional pathophysiological mechanisms underlying this disease, more than chronic cerebral ischemia. Our findings could provide also an explanation to the higher association between adult MMD patients and hemorrhage, as well as post-operative hyperperfusion.

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Compliance with ethical standards

The study was approved by the local Ethics Committee (EA4/121/17). The paper is reported following the STROBE statement. All patients signed an informed consent form prior to the surgical procedure. A specific consent form was not required for study enrollment, because of its retrospective nature.

Conflict of interest The authors declare that they have no conflict of interest.

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