MOYAMOYA DISEASE AS A POSSIBLE CAUSE OF ISCHEMIC STROKE IN ADULT PATIENTS

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Moyamoya disease (MMD) is a rare progressive idiopathic arteriopathy that usually leads to ischemic stroke (IS) in young children, especially of East Asian origin. MMD can cause IS in the Caucasian race, too, but often remains unverified. The diagnosis of MMD relies on diagnostic radiology findings. Magnetic resonance imaging (MRI) is widely used in Japan to identify asymptomatic individuals with hereditary predisposition to MMD. There are no official statistics on MMD in Russia. A patient experiencing an acute cerebrovascular accident (CVA) is hospitalized to a stroke unit, where they undergo a multislice computed tomography (MSCT) scan of the brain. Below, we report the results of a complex radiological examination, which included MRI (T2, FLAIR, SWI, 3D-TOF), cerebral MSCT perfusion imaging, CT angiography of intracranial arteries, duplex ultrasonography of brachiocephalic arteries and was conducted in 4 adult Caucasian patients (3 men and 1 woman aged 38, 39, 51, and 57 years, respectively) with a past IS caused by MMD. We hope that the findings of different imaging techniques may be helpful in establishing the timely diagnosis of MMD and optimizing the treatment strategies.

Keywords: moyamoya disease, ischemic stroke, brain MRI, MR-angiography, CT-angiography, duplex ultrasonography, transcranial duplex ultrasonography

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БОЛЕЗНЬ МОЯМОЯ КАК ВОЗМОЖНАЯ ПРИЧИНА ИШЕМИЧЕСКОГО ИНСУЛЬТА У ВЗРОСЛЫХ

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Болезнь моямоя (БММ) — редкая прогрессирующая идиопатическая артериопатия, являющаяся, как правило, причиной ишемического инсульта (ИИ) у детей младшего возраста, особенно в странах Восточной Азии. В редких случаях БММ может вызвать ИИ у взрослых лиц европеоидной расы, однако зачастую остается неверифицированной. Для диагностики данной патологии применяют разные лучевые методы. В Японии отдается предпочтение магнитно-резонансной томографии (МРТ), где ввиду широкой распространенности БММ МРТ применяют для скрининга асимптомных лиц с наследственной предрасположенностью. Официальная статистика по БММ в России отсутствует. В случае развития острого нарушения мозгового кровообращения (ОНМК) пациенты поступают в стационар инсультной сети, где им проводят рентгеновскую мультиспиральную компьютерную томографию (МСКТ) головного мозга. Представлены клинические случаи применения комплексного лучевого исследования, а именно магнитно-резонансной томографии (МРТ) (T2, FLAIR, SWI, 3D-TOF), перфузионной компьютерной томографии (КТ) головного мозга, КТ-ангиографии интракраниальных артерий, ультразвукового дуплексного сканирования брахиоцефальных артерий (ДС БЦА) четырех взрослых пациентов (трех мужчин и женщины в возрасте 38, 39, 51 и 57 лет) европеоидной расы с БММ, ставшей причиной развития ИИ. Описание результатов применения разных лучевых методов может помочь в своевременной верификации данной патологии и оптимизации дальнейшей тактики лечения.

Ключевые слова: болезнь моямоя, ишемический инсульт, МРТ головного мозга, МР-ангиография, КТ-ангиография, ультразвуковое дуплексное сканирование, транскраниальное дуплексное сканирование.

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Moyamoya disease is a rare cerebrovascular disorder, a kind of idiopathic arteriopathy that manifests as progressive stenosis of terminal internal carotid arteries (ICAs) and/or proximal parts of arteries forming the circle of Willis, including the middle (MCA) and anterior (ACA) cerebral arteries, and is accompanied by the development of an abnormal vascular network at the base of the brain [1]. In Russia, no official statistics are available on MMD but the disease is recognized as a possible cause of stroke in young children [2, 3]. MMD was first described in 1957 by two Japanese doctors Takeuch and Shimizu; the name “moyamoya” proposed in 1967 means “a puff of smoke” in Japanese and refers to the angiographic appearance of the

abnormal blood vessels at the base of the brain [4, 5]. The highest prevalence of MMD is observed in East Asia (Japan and Korea), reaching ~3.16 cases per 100,000 population, which is 7–10 times higher than in other world regions [6, 7].

The underlying pathogenetic mechanisms of MMD are not fully clear. Common histopathologic findings in the affected vascular wall include fibrocellular intimal thickening, folded and contracted internal elastic lamina, proliferation of smooth muscle cells, and thinning of the media; no signs of inflammation or atherosclerosis are reported [8, 9]. The collateral vessels at the base of the brain traditionally referred to as moyamoya vessels are formed by dilated lenticulostriate, thalamic or choroidal anastomoses [9, 10]. Based on the severity of damage to the main cerebral arteries and the degree of involvement of the collateral vessels, 6 MMD stages are distinguished [11].

Genome-wide linkage analysis and whole-exome sequencing have identified the *RNF213* gene on chromosome 17q25 as the main susceptibility gene for MMD in East Asians [12]; later studies have demonstrated the remarkable variation of this gene across different ethnic groups [13]. According to Korean researchers, the 4950G>A polymorphism of the RNF213 gene is implicated in MMD in adults and therefore may be a potential biomarker for this disease [14].

MMD is characterized by bimodal age distribution with incidence peaks at 5–10 years and in the fourth decade of life [1, 7, 9]. Women are affected twice as often as men. The disease has ischemic and hemorrhagic presentations [7, 9, 15]. According to studies conducted in small cohorts of adult European patients with idiopathic MMD, cerebral ischemia is a typical manifestation in this subpopulation [16].

Patients with MMD are at high risk for recurrent vascular accidents: the Kaplan-Meier estimate for the risk of recurrent IS within 5 years after the first episode is 80.95% [17]. Therefore, the importance of timely MMD diagnosis cannot be overestimated. The primary treatment option for this condition is surgery (cerebral revascularization) which aims to reduce the risk of recurrent strokes [2, 6, 18].

This article highlights the role of MMD as a potential cause of IS in adults, requiring timely diagnosis.

Clinical cases

In 2020, 426 patients with a past history of CVA underwent a clinical examination at the Federal Center of Brain Research and Neurotechnologies (Moscow, Russia). Three patients with a history of IS were found to have MMD. One patient with MMD was examined at the outpatient facility. Only 1 patient had been diagnosed with MMD prior to this study; 3 patients had never been diagnosed with MMD before.

Patients

Patient B, 38 years old, suffered a lacunar stroke in 2016 manifesting as sudden dizziness that spontaneously resolved shortly afterwards. The patient was referred to Sklifosovsky Research Institute of Emergency Medicine, where he was diagnosed with stage 3 MMD. The patient had two extracranial-intracranial (EC-IC) bypass surgeries for his condition in 2017 and 2018.

Patient G, 39 years old, had IS in the right MCA territory in February 2020. Following treatment and rehabilitation, the patient was able to walk around his house using a cane and perform some self-care activities. On admission to the Center, the patient was in his late rehabilitation period; his stroke subtype was cryptogenic.

Patient Yu, 51 years old, developed clinical symptoms in September 2017, including sudden facial nerve paresis, difficulty

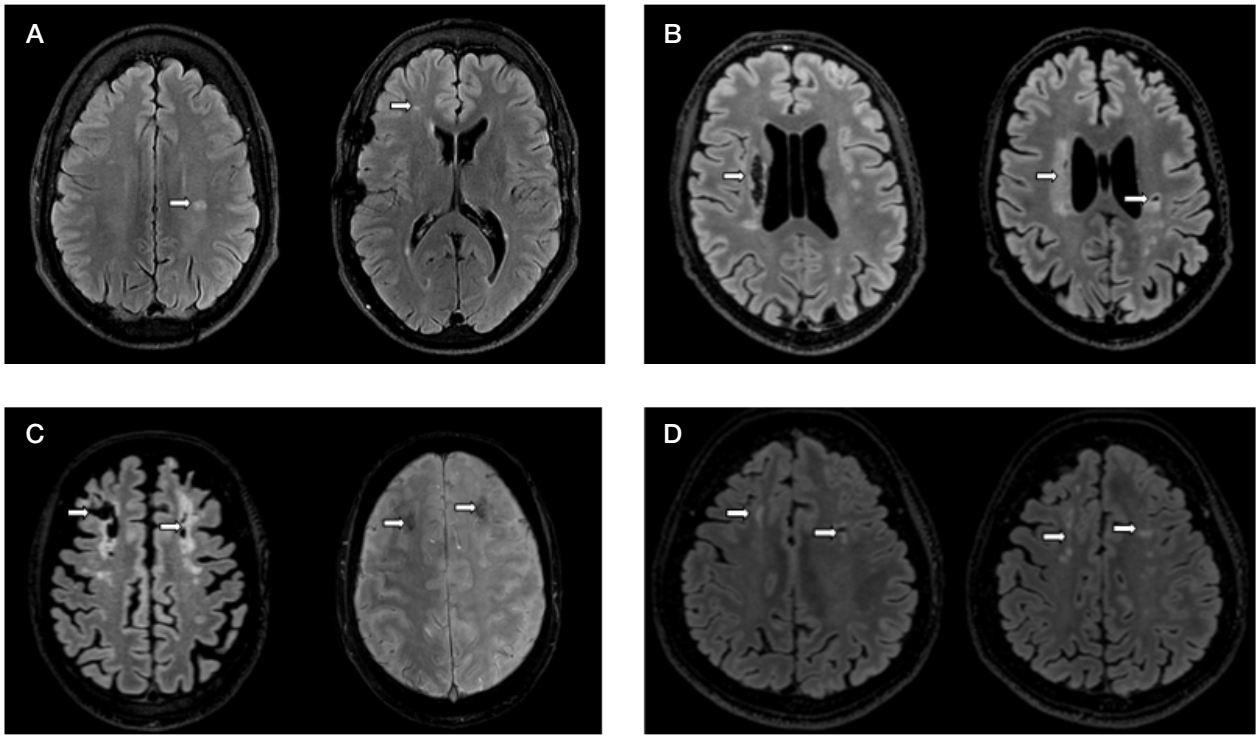

Fig. 1. MR images showing changes in the brain of adult patients with moyamoya disease after a cerebral infarction. **A**. Patient B (axial FLAIR): a small area of reactive changes in the left posterior frontal lobe white matter; small scanty areas of white matter gliosis in the right frontal lobe (the border zone between MCA and ACA) are indicated by *arrows*. **B**. Patient G (axial FLAIR): gliotic and cystic lesions in the putamen and the semioval center (the lateral lenticulostriate artery territory) in the right hemisphere; similar lesions in the left semioval center (the internal watershed area); the lesions are marked by *arrows* **C**. Patient Yu (left image: axial FLAIR; right image: axial SWI): hemorrhagic transformation (petechiae) after a past cerebral infarction (hemorrhage infarction type 1 according to ECASS II) in the frontal lobe white matter (the border zone between MCA and ACA) is indicated by *arrows*. **D**. Patient V (axial FLAIR): multiple areas of gliosis and a small lesion after a past lacunar stroke in the frontal lobe white matter (the border zone between MCA and ACA) are indicated by *arrows*.

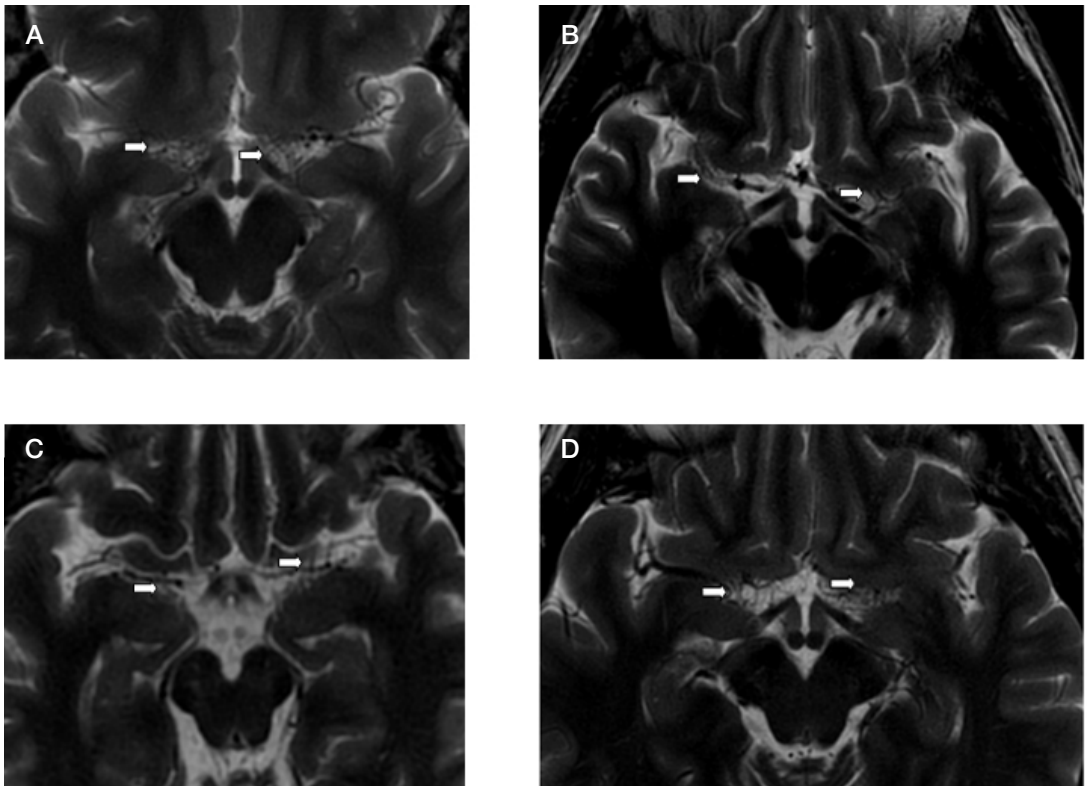

Fig. 2. MR images of the abnormal vascular network at the base of the brain of adult patients with moyamoya disease (axial T2 WI). Proximal parts of MCA segments are not visualized clearly; a network of small blood vessels indicated by *arrows* is visible in their projection. **A**. Patient B. **B**. Patient G. **C**. Patient Yu. **D**. Patient V

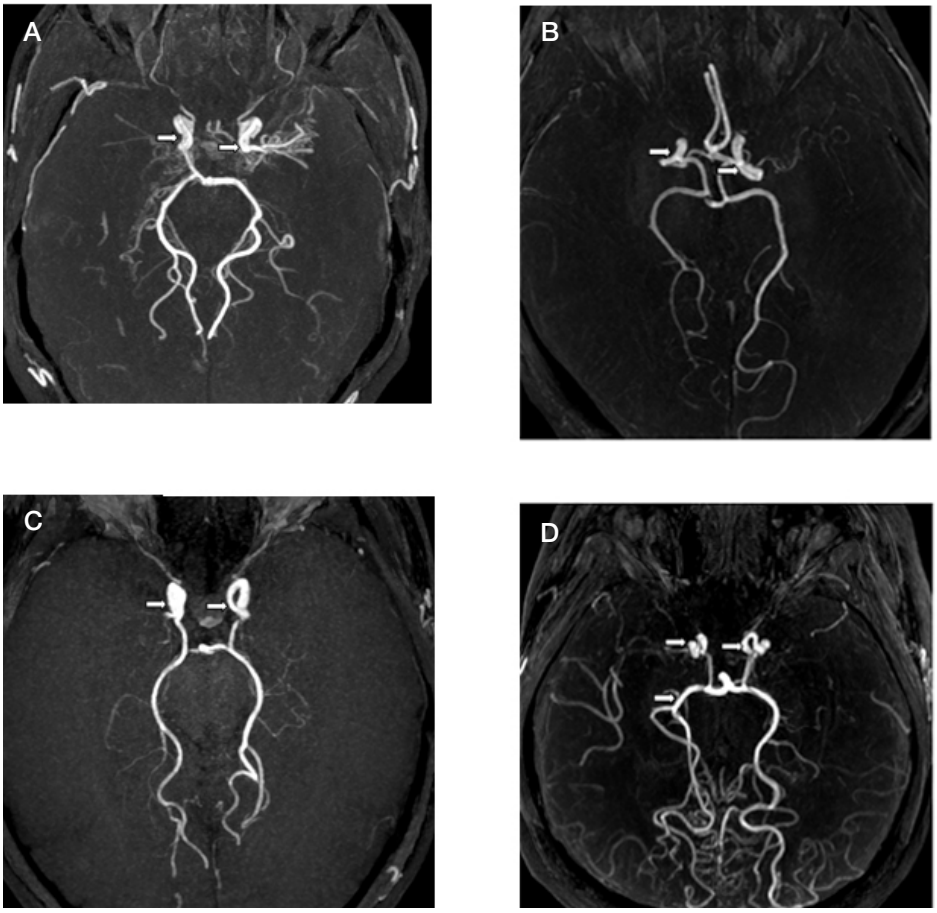

Fig. 3. 3D-TOF MR angiograms showing vascular changes in adult patients with moyamoya disease. **A**. Patient B: the absence of flow signal from distal ICA and MCA (*arrows*). Proximal parts of ACA are visible and stenotic. PCAs are intact. **B**. Patient G: significant luminal narrowing of distal ICA, the absence of flow signal from MCA (*arrows*). ACAs are intact. PCcoms and PCAs are slightly dilated. **C**. Patient Yu: the absence of flow signal from distal ICA and MCA and ACA (*arrows*). PCcoms and PCAs are intact. **D**. Patient V: the absence of flow signal from distal ICA and MCA and ACA. PCcoms and PCAs are dilated (*arrows*)

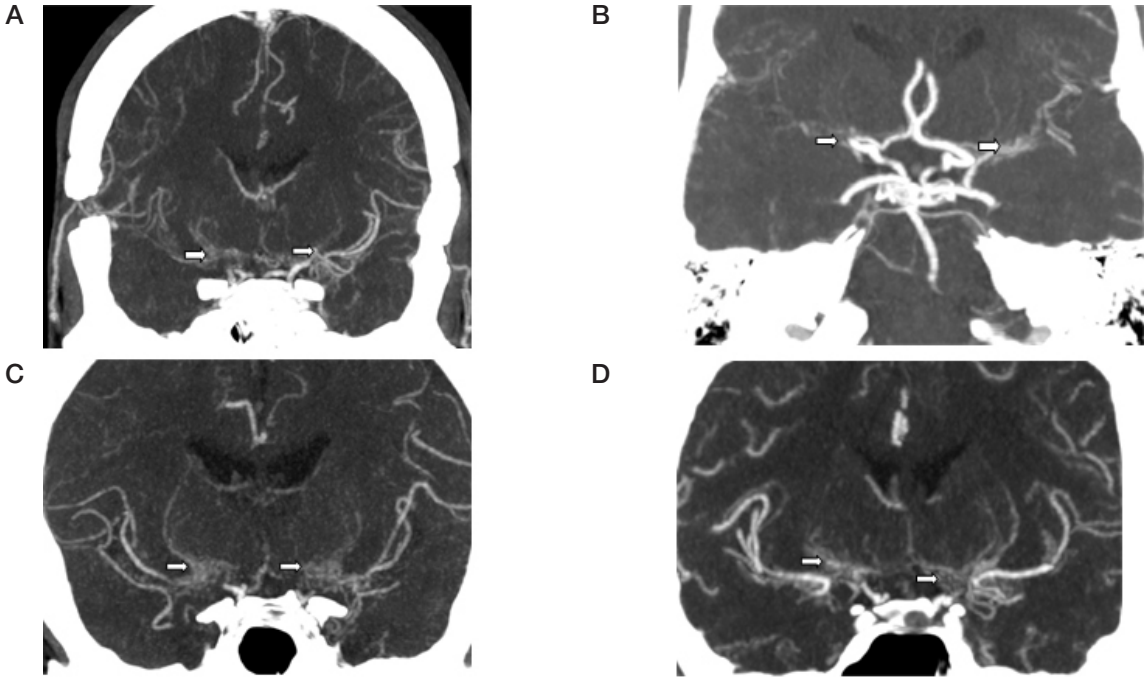

Fig. 4. Oblique coronal CT angiographic images of intracranial arteries showing vascular changes in the brain of adult patients with moyamoya disease. **A**. Patient B: distal segments of both ICAs and proximal parts of both MCAs are not visualized due to occlusion; a network of small anastomotic vessels is visible in their projection. The images show enhancement of lenticulostriate arteries in the basal ganglia area. Craniotomy marks are observed on temporal bones on both sides; circulation is visualized in extra- and intracranial anastomoses. **B**. Patient G: distal segments of both ICAs are stenotic, both MCA are occluded; a network of small anastomotic vessels is visualized in their projection. ACAs are visible along their course and have a normal diameter. **C**. Patient Yu: distal segments of both ICAs and proximal parts of both MCAs are occluded; a network of small anastomotic blood vessels is visualized in their projection. **D**. Patient V: distal segments of both ICAs and proximal parts of both MCAs are occluded, a network of small anastomotic blood vessels is visualized in their projection. Lenticulostriate arteries in the basal ganglia area are contrast-enhanced

swallowing and slurred speech. The patient was hospitalized to a local medical facility. MRI of the brain revealed multiple lesions in the white matter of both cerebral hemispheres. The lesions were interpreted as demyelinating, which determined the choice of further treatment until September 2019, when the patient underwent a few additional tests. The tests did not confirm multiple sclerosis. On admission to the Center, the official diagnosis was mixed encephalopathy, sequelae of cryptogenic stroke registered in September 2017 and March 2018.

Female patient V, 57 years old, had a lacunar IS in the left MCA when she was 36; at that time the patient developed mild

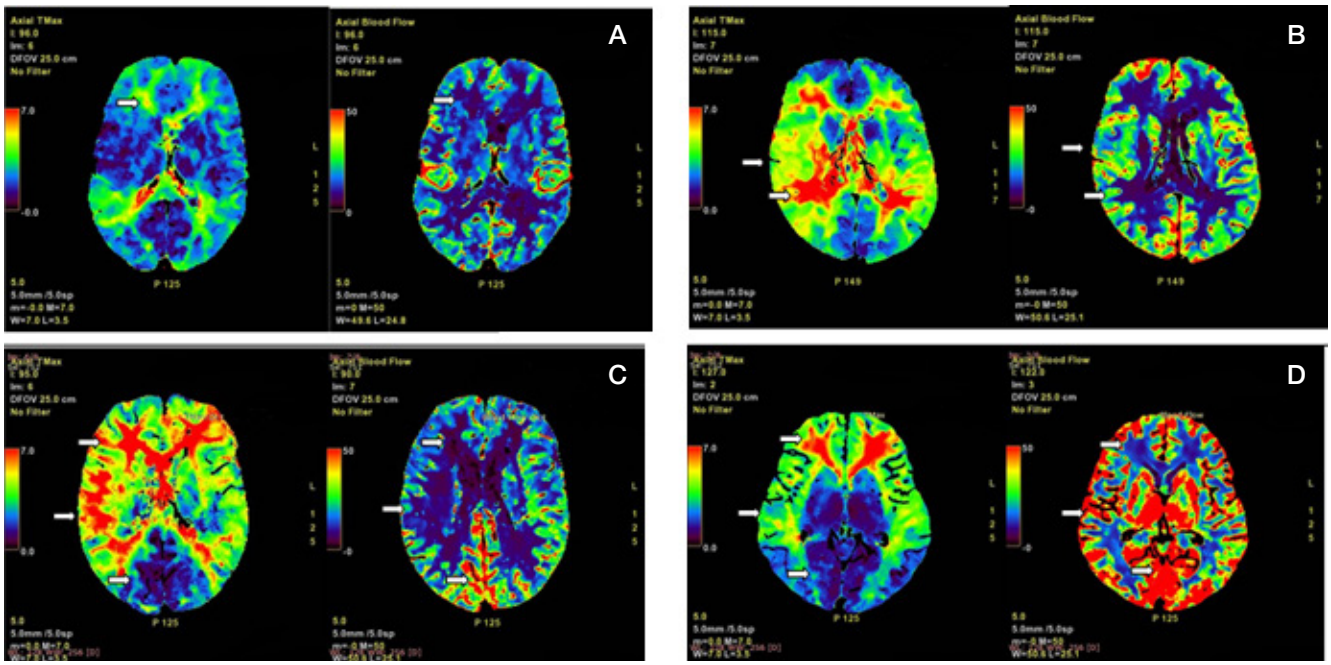

Fig. 5. CT perfusion imaging of the brain (axial planes). Perfusion maps for Tmax and CBF. **A**. Patient B: prolonged enhancement is observed in the border zones between MCA and ACA and between MCA and PCA (prolonged T_{max}: 4–5 s), perfusion is moderately reduced (*arrows*). **B**. Patient G: critical hypoperfusion in the border zones between MCA and ACA and between MCA and PCA (T_{max} > 6 s), moderate hypoperfusion in the MCA territory (T_{max} ~ 5 s) (*arrows*). **C**. Patient Yu: critical hypoperfusion in the border zones between MCA and ACA and between MCA and PCA (T_{max} > 6 s), hypoperfusion in the MCA and ACA territories (more pronounced on the right), hyperperfusion in the PCA territory (*arrows*). **D**. Patient V: critical hypoperfusion (T_{max} > 6 s) in the border zones between MCA and ACA, moderate hypoperfusion in the territories of cortical MCA and ACA branches, hyperperfusion in the PCA territory (*arrows*)

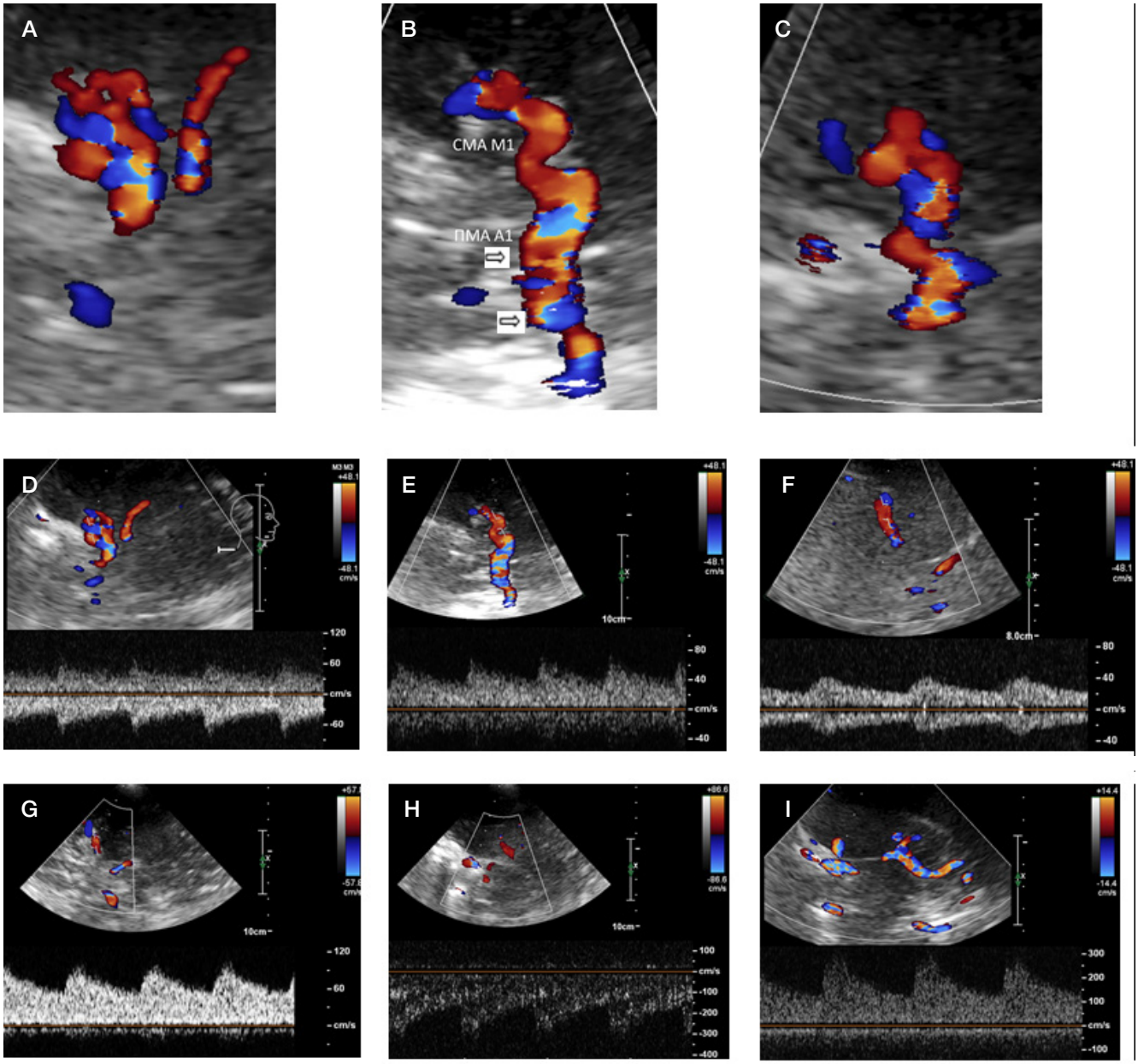

Fig. 6. Transcranial duplex ultrasonography of the anterior circulation, color Doppler (**A**–**C**), color Doppler combined with spectral Doppler (**D**–**G**). **A**, **D**. Patient B: differently directed color flows in the projection of the M1 segment of MCA. ACAs cannot be located. **B**, **E**. Patient G: single flows are located to the projection of the proximal M1 segment of MCA (up to the stenotic segment). Normally directed flows are seen in the A1-segments of ACAs (*arrows*). **C**, **F**. Patient V: differently directed intertwining flows can be located to the projection of the M1 segment of MCA; the image shows the Doppler spectrum for the M2 segment of MCA upstream of the stenotic region (collateral type). ACAs cannot be located. **G**. Patient Yu: M1 segments of MCA and A1 segments of ACA cannot be located. The image shows the Doppler spectrum for the M2 segment of MCA upstream of the stenotic region (collateral type) **H**. Patient Yu: the Doppler spectrum for the left terminal ICA, the linear velocity of the blood flow is increased at the sample site, suggesting arterial stenosis. The same flow pattern is observed in the right terminal ICA. **I**. Patient V: the Doppler spectrum for the left terminal ICA, increased linear velocity at the sample site, suggesting arterial stenosis. The same flow pattern is observed in the right terminal ICA

paresis in her right hand, which was interpreted as peripheral neuropathy; the hand restored its function within a week. The patient presented at the Center with complaints of transient loss of consciousness, frequent headaches and dizziness. The sharpened Romberg test revealed mild coordination impairment. The most recent neurological examination had been conducted 10 years prior. MRI findings of that time had been interpreted as variant anatomy of cerebral arteries.

At the Center, the examination protocol was the same for all patients and included MRI and MSCT of the brain and intracranial arteries, cerebral MSCT perfusion imaging, and color duplex ultrasonography of extra- and intracranial brachiocephalic arteries (BCA). MRI scans were performed on a 3T Discovery 370 MR scanner (GE; USA). The following sequences were obtained: T1-WI, T2-WI, isotropic 3D FLAIR pulse sequence (slice thickness: 1 mm), diffusion-weighted images (DWI), susceptibility weighted angiography sequence (SWAN), and time-of-flight angiography (3D-TOF) of intracranial arteries. Brain MSCT and MSCT perfusion imaging were performed using a 128-slice Optima scanner (GE; USA). Contrast enhancement was achieved with iopromide (370 mg iodine/ml). High-resolution duplex ultrasonography of BCA was performed using a Philips Epiq 7G scanner (Philips; USA).

Brain MRI findings

All patients had signs of a past cerebral infarction and gliotic foci in the hemispheric white matter, in the border zone between

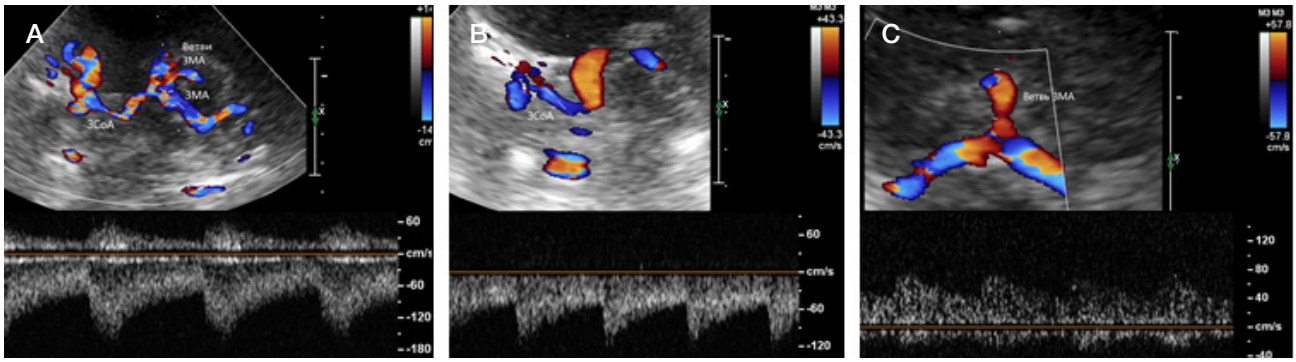

Fig. 7. Transcranial duplex ultrasonography of PCcom and PCA (color Doppler and spectral Doppler). **A**. Patient V: color Doppler for PCcom, PCA (segments P2-P3) and its branches. The pattern may suggest increased blood flow in these arteries. **B**. Patient G: high-velocity blood flow in PCcom. **C**. Patient Yu: high-velocity blood flow in the temporal branch of PCA

MCA and ACA. One patient (patient G) had signs of a past infarction in the deep perforating branches of the right MCA (Fig. 1). Patient Yu had areas of hemorrhagic transformation (petechiae). No intracranial hemorrhages were detected in either patient. The obtained T2-weighted images showed a network of small blood vessels in the proximal MCA territory on both sides both MCA trunks were not detectable at this level (Fig. 2).

Unenhanced MR angiography demonstrated significant narrowing/occlusion of terminal ICA and proximal MCA segments. ACAs were intact in patients B and G, but their diameter was small in one of these patients. Proximal ACAs were affected in patients Yu and V (Fig. 3). Posterior cerebral arteries (PCAs) and posterior communicating arteries (PCcoms) were dilated in all 4 patients.

Findings of multislice computed tomography of the brain

The CT-angiography of intracranial arteries revealed an abnormal vascular network (Fig. 4; *arrows*) in place of M1 MCA trunks and the enhancement of lenticulostriate arteries in the basal ganglia area, corresponding to different stages of MMD. The abnormal vascular network was well defined on the images of patients B and V, which was interpreted as stage 3 of the disease, and not so well developed in patients Yu and G, who had more pronounced neurological deficit and larger (both in number and size) post-infarction lesions, which was interpreted as later MMD stages characterized by the regression of moyamoya vessels at the base of the brain. Distal MCA and ACA were visible, their diameter being normal in some patients.

Signs of cerebral hypoperfusion in the MCA and ACA territories and increased posterior cerebral perfusion were observed in 3 of 4 patients (Fig. 5). The fourth patient (Patient B) had previously received an EC-IC bypass on both sides, so a reduction in cerebral perfusion in the border zones between MCA and ACA and between MCA and PCA was not so pronounced in this patient.

Findings of duplex ultrasonography of brachiocephalic arteries

Duplex ultrasonography did not detect any significant changes in extracranial BCAs; their diameters and velocity characteristics fell within the reference range (in most patients, these parameters approximated the lower limit). Diameters of vertebral arteries (VAs) varied significantly, blood flow in VAs was either normal or slightly increased.

Transcranial scans revealed stenosis of both terminal ICAs in patients Yu and V, inferred from the local hemodynamic changes (Fig. 6H, I). Single and multiple differently directed intertwining flows were detected in the M1 segments of MCA in the color Doppler mode. Spectral Doppler demonstrated that their velocities were low and peripheral resistance was either moderate or significantly reduced, which is typical for collateral blood flow (Fig. 6A–G). Besides, all patients had high-velocity blood flow in PCcoms directed toward the vertebrobasilar system (VBS) and increased blood flow in PCAs and their branches. Three to four PCA segments were visualized (Fig. 7). Blood flow was compensatorily increased in the distal VA (V4) and the basilar artery (BA) in patients B and V; such compensation was not observed in patients G and Yu.

Discussion

Vascular changes typical for MMD can be detected by different imaging techniques. The T2-weighted images of all 4 patients showed abnormal vascular networks at the base of the brain in place of large M1-segments of MCA. MR-angiography conducted without a contrast agent revealed occlusion of distal (supraclinoid) ICA and proximal parts of MCA; in 2 patients, ACA was also affected. However, the abnormal vascular network had a puff of smoke appearance on MR angiograms in only one case. MSCT angiography allowed us to visualize lenticulostriate arteries in the basal ganglia and abnormal blood vessels at the brain base in greater detail, confirming MMD in all 4 patients.

Duplex ultrasonography of extracranial BCA detected no pronounced specific changes in ICA or VA. A reduced ICA diameter, which is a diagnostic criterion [1], was not detected in any of 4 patients. This might have been due to the degree of occlusion, which is not typical for other types of ICA damage. In MMD, the supraclinoid segments of ICA are occluded upstream of the PCcom divergence site; they are represented by communicating segments of ICA and their bifurcations. This is key in the redistribution of the cerebral blood flow from ICA via PCcom in VBS and then via PCA and its branches through cortical and leptomeningeal anastomoses back to MCA and ACA. Thus, signs of distal ICA occlusion in patients with MMD [1] can be seen on ultrasound scans in the absence of PCcom.

On intracranial scans, the abnormal vascular network at the base of the brain was visible if it was well developed. Otherwise, no signal was captured from the proximal MCA. Yet the M2-segment of MCA could be located, showing a relatively normal blood flow and thus raising a possibility of wrong interpretation. Velocity characteristics of blood flow in MCA branches and the distal segments of their trunks varied significantly but peripheral vascular resistance was reduced in all 4 patients, indicating collateralization.

Bilateral ICA occlusions co-occurred with small areas of past infarctions and gliotic lesions in the border zone between MCA and ACA. The inconsistency between the large arteries occlusions and the size of infarctions suggested an old history of a pathological process leading to the formation of these occlusions and sufficient collateral compensation. Cerebral infarctions occurring in the setting of MMD can be categorized as hemodynamic, associated with a reduction in blood flow due to low arterial blood pressure. Another possible cause of cerebral infractions in MMD is regression of collateral vessels, leading to circulatory decompensation. In our patients, perfusion deficit (CBF) with prolonged Tmax was inferred from CT perfusion imaging data in the border zones between MCA and ACA (deep and subcortical white matter of frontal lobes). Hyperperfusion was observed in 3 patients except for the patient with an EC-IC bypass. In patient V, the collateral vascular network was very well developed.

Conclusion

Our findings suggest that MMD can be diagnosed based on the known diagnostic criteria and using different imaging techniques: MRI, MSCT and duplex ultrasonography of brachiocephalic arteries. Diagnostic errors may be due to the unavailability of angiography for neuroimaging or the lack of awareness about MMD as a possible cause of IS in adults.

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