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Diagnostic value of color-coded duplex sonography in patients with ischemic stroke and congenital changes in the circle of Willis

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SOUHRN

Willisův okruh (circle of Willis, CoW) tvoří hlavní oběhový systém v lidském mozku. Byla popsána dlouhá řada variací CoW i jejich souvislost s ischemickou cévní mozkovou příhodou (iCMP).
Popisujeme tři případy mladých pacientů s kombinací iCMP a anomáliemi CoW, u nichž srovnáme hodnotu barevně kódované duplexní sonografie (color-coded duplex sonography, CCDS) s dalšími diagnostickými zobrazovacími metodami, jako jsou magnetická rezonanční angiografie (MRA) a digitální subtrakční angiografie (DSA).
U uvedených pacientů byla zjištěna řada rizikových faktorů jako stenóza nebo trombóza nitrolebních mozkových cév, mechanická komprese cév, genetická mutace spojená s významným rizikem trombózy a užívání perorálních kontraceptiv. U pacientů byla nejdříve sepsána jejich anamnéza, následně byli vyšetřeni neurologem, byla provedena laboratorní vyšetření (celkový krevní obraz, lipidový profil, vyšetření na HIV1/2, syfilis RPR), následoval screening zaměřený na markery spojené se zvýšeným rizikem trombózy, rentgen srdce a plic, vyšetření likvoru, CCDS, DSA, MRA. Výsledky CCDS a ostatních zobrazovacích metod byly naprosto shodné.
V článku autoři pojednávají o patogenní úloze vrozených anomálií CoW, incidenci ischemických cévních mozkových příhod a vysoké diagnostické hodnotě CCDS při vyhledávání uvedených anomálií.

Keywords:
Color-coded duplex sonography
Congenital abnormalities of the circle of Willis
Ischemic stroke
Magnetic resonance angiography

ABSTRACT

The circle of Willis (CoW) forms the main circulatory system in the human brain. A large number of variations of the CoW is known, and also their association with ischemic stroke.
Three cases of young patients with combination of ischemic stroke and anomalies in the CoW are presented, and the value of the color-coded duplex sonography (CCDS) is compared to other imaging diagnostics such as magnetic resonance angiography (MRA) and digital subtraction angiography (DSA).
In these patients we found multiple risk factors such as: stenosis or thrombosis of intracranial brain vessels, mechanical compression of vessels, a genetic mutation associated with an increased risk of thrombosis, intake of oral contraceptives. For clinical evaluation several methods were used: detailed medical history, neurological status, laboratory examinations (complete blood count, biochemistry, lipid profile, HIV1/2, Syphilis RPR test), screening for markers associated with an increased risk of thrombosis, chest X-ray, spinal fluid study, CCDS, DSA, MRA. A full conformity in the data from CCDS and other imaging methods was found.
The authors discuss the pathogenetic role of congenital anomalies of CoW, incidence of ischemic stroke and the high diagnostic value of CCDS for finding such anomalies.

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Introduction

The circle of Willis (CoW) is the anastomosed arterial ring in the brain, which integrates the internal carotid and vertebral-basilar systems. Sir Thomas Willis described the anatomy of the basal intracranial vessels for the first time in 1664.

There is considerable variability in the anatomy of the CoW, often with asymmetry, and such extend that configuration can only be found in a small number of cases. A full CoW with a balanced pair of arteries was found only in 18–20% of the general population [1]. The cerebral arteries may be absent or can be found with some anomalies – hypoplastic, doubled or even tripled. Anatomical studies indicate a lack of anterior communicating artery (ACoA) in 1% of patients, the absence or hypoplasia of the proximal part of the anterior cerebral artery (ACA) in 10%, the absence or hypoplasia of posterior communicating artery (PCoA) in 30%, anterior trifurcation in 3–22% [2]. According to different authors, frequency of a hypoplastic vertebral artery (VA) varies between 1.9 and 6%; hypoplasia of both vertebral arteries is rarely found [3,4]. Fetal type cerebral blood flow can be found in about 10% of the cases (36) [5].

Cerebral blood flow is maintained relatively stable thanks to the autoregulation of the cerebral arteries. It is defined by several factors: vascular resistance of the cerebral arteries, perfusion pressure and autoregulatory mechanisms. The cerebral perfusion pressure depends on the difference between mean arterial pressure and intracranial pressure. The autonomous control is capable of maintaining the blood flow in a wide range of variations of the mean arterial pressure. In healthy subjects, brain blood flow is relatively constant during fluctuations in mean arterial pressure of about 50–150 mmHg [6,7]. The protective role of collateral circulation is dependent upon several factors, including anatomic variations, systemic arterial pressure, patient age and stage of development of occlusive disease [8,9]. The CoW is the main "physiological anastomosis" in the brain circulation which is able to sustain brain perfusion in cases of acute occlusion of large arteries [10–12]. Following an occlusion of a major blood vessel, the fall in perfusion pressure distally generates a gradient between adjacent arterial beds. This results in to changes of blood flows' direction and speed [9,10]. It occurs almost immediately (within 1–4 s) indicating that metabolic factors are less likely related to this change [13–15]. The CoW forms the main collateral circulatory system.

Other collateral vessels are considered to be of secondary significance, such as the leptomeningeal and dural arterioles, cortical vessels, extracranial and intracranial collaterals, as well as some rarely occurring collateral vessels such as the thecal plexus, middle meningeal artery, maxillary and ethmoid artery. Anastomoses between the distal segments of the main brain arteries also contribute to collateral blood flow. The number and size of these vascular anastomoses is high in ACA and middle cerebral artery (MCA), low between MCA and PCA and with the lowest frequency between ACA and posterior cerebral artery (PCA). Various collateral connections, between vertebral and basilar segments of the posterior circulation, are provided by distal branches of major arteries in the brain.

The collateral vessels are formed during the prenatal period. Some pathophysiological conditions may lead to secondary emergence. For example, focal cerebral ischemia can lead to a release of angiogenic peptides with a known potential for collateral vessel formation. Even though these vessels may have been "designed" to atenuate necrotic areas, rather than increase cerebral blood flow [12]. However, angiogenesis can promote collateral growth in the periphery of the ischemic zone. The state of collateral circulation must be taken into account during the color-coded duplex sonography in the evaluation of cerebrovascular "hemodynamically significant steno-

Table 1 – Cerebral collateral circulation.

Intracranial	**Arteries connected**	**Connecting artery**
Circle of Willis	Internal carotid artery and basilar/posterior cerebral arteries	Posterior communicating artery
	Anterior cerebral arteries	Anterior communicating ARTERY
Vertebrobasilar and circle of Willis	Internal carotid artery and vertebral/basilar arteries	Trigeminal, otic and hypoglossal arteries
Tectal plexus	Posterior cerebral artery and superior cerebellar artery	Tectal rami, connecting supra and infratentorial arteries
Cerebral artery branches	Branches of the middle, anterior and posterior cerebral arteries	Anastomoses of terminal branches within and between arterial territories
Leptomeningeal		
Pial plexus	Neighboring branches of major cerebral arteries	Arterioles from branches of same or adjacent arteries
Meningeal	Cerebral and meningeal arteries	
Extracranial	**Arteries connected**	**Connecting artery**
Orbital plexus	Ophthalmic and middle meningeal, maxillary, ethmoidal arteries	Terminal branches
Rete mirabile caroticum	Internal and external carotid	

sis" [15]. The collateral potential of the vessels is determined by the caliber of their lumen. Collateral circulation to the brain is summarized in Table 1. During carotid endarterectomy a solid example for the rapid compensatory ability of the CoW can be observed. After clamping the ipsilateral internal carotid artery, transcranial monitoring shows an increase in blood flow in the contralateral anterior cerebral artery within only two to three heartbeats.

Importance of collateral blood flow is high. It is known that acute cerebral infarction, due to occlusion of the carotid artery, has worse outcome in cases of underdeveloped collateral network. The annual stroke incidences in patients with occlusion of the carotid artery ranges from 0–5% in asymptomatic patients, up to 27% in symptomatic patients [6,16]. There is a surprisingly lower rate of stroke (4% in 10 years) in the ipsilateral side of the occluded artery, in patients with bilateral occlusive disease of the carotid artery that have been treated with carotid endarterectomy. The most probable reason for these findings is the improvement of collateral flow in both sides – operated and occluded. The presence and effectiveness of collateral circulation is one of the main factors that explain this clinical presentation variability [8]. Cerebral collateral circulation has a function to maintain sufficient regional perfusion of ischemic brain tissue. Varying anatomical features of the cerebral circulation can determine patterns of stroke in occlusive carotid artery disease (i.e. border against territorial zone). Infarction in border vascular areas is often associated with incomplete CoW. In patients with complete CoW, carotid occlusion leads to minimal or no neurological deficit. Intraarterial and intravenous thrombolysis in patients with a developed collateral blood flow results in: smaller infarct zone progression, distinctly smaller infarction volume, better prognosis, and even more – it increases the treatment window – "first symptoms to start of treatment".

Clinical cases

Diagnostic methods

Detailed medical history, neurological status, paraclinic examinations (complete blood count, biochemistry, lipid profile, HIV1/2, Syphilis RPR test), screening for markers associated with an increased risk of thrombosis, chest X-ray, spinal fluid study, color-coded duplex sonography (CCDS), digital subtraction angiography (DSA), magnetic resonance angiography (MRA). A full accordance in the data from CCDS and other imaging methods was observed.

Clinical case 1

A 24 y.o. female patient (family history – her mother died of PE at age of 30), presented with acute weakness in the right limbs. She had a history of a transient ischemic attack with speech impairment, few days before hospitalization. The patient did not show any pathological changes in laboratory results – lipid profile, markers associated with an increased risk of thrombosis, spinal fluid examination and serology (HIV1/2, Syphilis RPR test). Standard stroke treatment of antiagregants, statin, watersaline solutions, oxygen was performed. The imaging results showed: MRA (patient 1 – Figs.1 and 2), and DSA (patient 1, Figs. 3 and 4). CCDS (patient 1 – Figs. 5–7) demonstrated an incomplete CoW – right anterior trifurcation of internal carotid artery (ICA), marked with yellow arrow on figure and a hypoplastic left VA which is not a part of the basilar artery formation. Therefore the arterial territory of the left MCA is not bound with the arterial territory of the right MCA, and by PCoA is not bound with the left VA. In this case the congenital vascular anomaly in combination with family history is the main risk factor for acute stroke (hemodynamically driven) in the MCA arterial basin.

Clinical case 2

A 26 y.o. female patient presented with episode of sudden headache, numbness and weakness in the left extremities, with a history of taking oral contraceptives for 2 years for menstrual cycle regulation. Laboratory tests determined a heterozygote mutation in mutant allele PAI-1 4G/5G and mutation MTHFR (A 1298C + C677T), with no other significant pathological laboratory findings. The patient was treated with antiagregants, statin, watersaline solutions and oxygen. Magnetic resonance imaging (MRI) of the brain with MRA, and CCDS (patient 2 – Figs. 8–12) were performed. An evidence of congenital changes in the CoW were found – hypoplastic right ICA and MCA and stenosis of the M1 segment of the MCA on the same side (patient 2 – Fig. 13). The left PCoA was missing. In this case the combination of a genetic predisposition for an increased risk of thrombosis (a heterozygote mutation in allele PAI-1 4G/5G and MTHFR mutations), intake of oral contraceptives, and also anomalies in CoW were causes for acute ischemic stroke in the right MCA basin with severe left-sided central hemiparesis.

Clinical case 3

A 33 y.o. female patient born in VIII lunar month without any prior relevant disorders, received complaints of double vision, dizziness, unsteady gait, numbness in the right limbs, "blurred" speech, during a head deflexion. The patient had a history of "fainting" in the morning, after getting up and also recent complaints of "loss of parts of the visual field". A history of oral contraceptives use for 2 years prior to hospitalization was noted. During clinical observation during hospitalization in the neurology department, deterioration in the patient's condition was noted. Symptoms of oculi-motor malfunction (horizontal gaze paresis, with expressed horizontal and vertical nystagmus, with rotary components) severe bulbar and pseudobulbar syndrome, glosoparesis, and spastic quadriparesis marked more in the lower limbs with bilateral positive Babinski's sign, while maintaining a clear level of consciousness – an incomplete locked-in syndrome.

CCDS examination found no evidence of hemodynamically significant changes in the carotid arteries. A bilateral hypoplasia of vertebral arteries was noted (with diameter 0.21 cm for the left VA and 0.17 cm for the right). Both VA were presented with a decreased blood flow and increased vascular resistance, more apparent on the left. Normal blood flow was found for MCA and ACA bilaterally. There was evidence of an anterior trifurcation of right ICA. Retrograde blood flow was found through both PCA with increased vascular resistance forming a steal pheno-

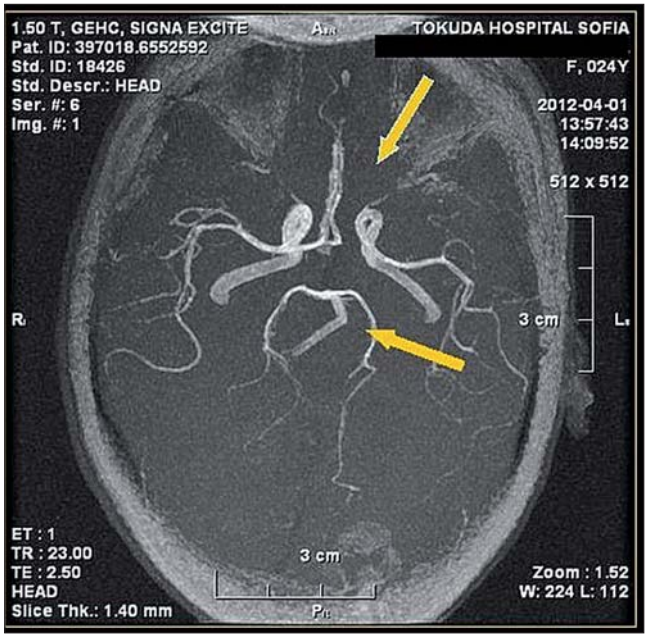

Fig. 1 – MRA front trifurcation on the right ICA (arrow up), missing left VA (arrow down).

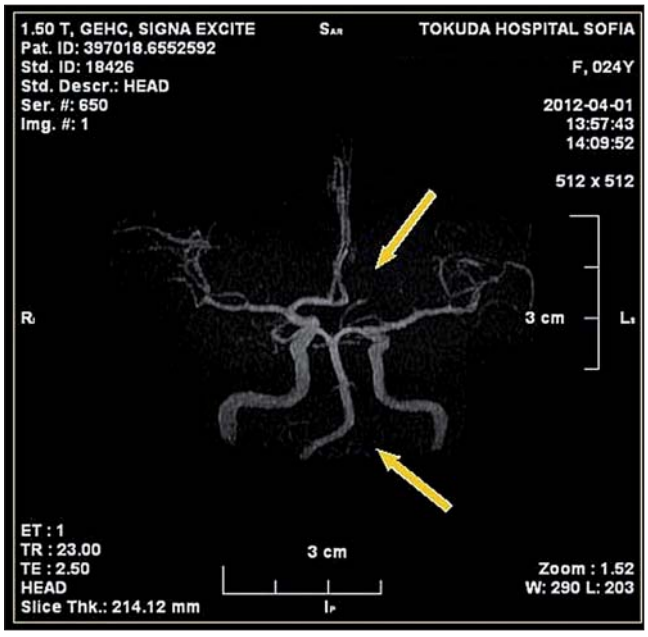

Fig. 2 – MRA front trifurcation on the right ICA (arrow up), missing left VA (arrow down).

menon bilaterally. There was evidence of increased vascular resistance with a severely diminished blood flow for the basilar artery (initial thrombosis). MRA at admission revealed a front trifurcation of the right ICA – both ACA and the right MCA came out of the right ICA. Bilateral abnormal anatomy of the PCA – both originate from the internal carotid arteries. Practically quadrifurcation on the carotid arteries at the siphon was demonstrated – an anomaly in the development of CoW. Right PcoA presented itself with a normal wide lumen, while the left was relatively smaller in caliber but well visualized. Bilateral evidence of hypoplastic vertebral arteries was also found.

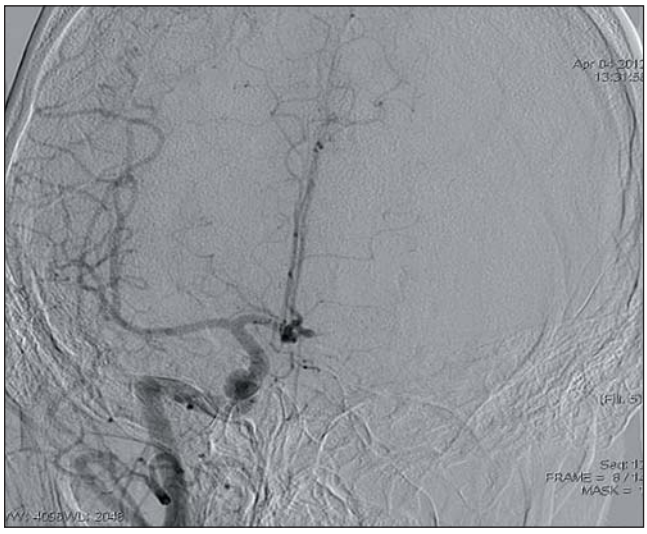

Fig. 3 – Front trifurcation of right ICA.

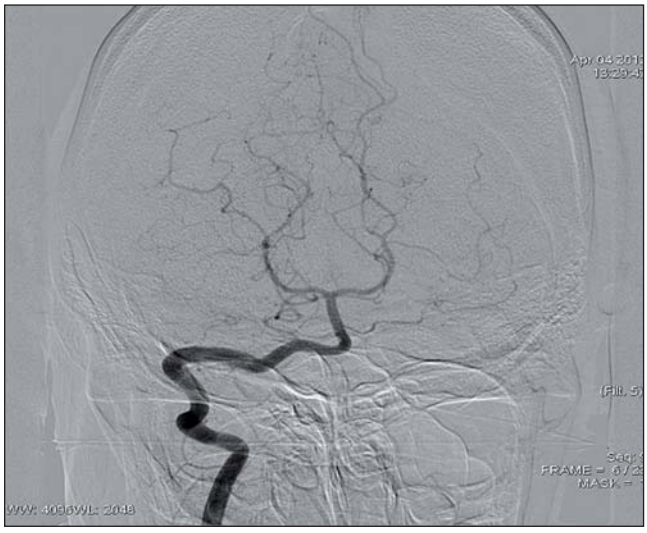

Fig. 4 – DSA – Right VA – dominant, high caliber, makes BA on its own. No anomalies or stenosis.

Immediately after the formation of the BA there were findings of a missing basilar section of about 15 mm.

This is a case of the young patient with congenital changes in the CoW (proven by MRA – Figs. 14 and 15, TSDS – Figs. 16–20) – front right trifurcation, interrupted CoW, lack of PcoA left, hypoplasia of both VA, probable hypoplasia of the basilar artery and two-year use of contraceptives developed an acute ischemic stroke in the vertebral-basilar circulatory system with basilar artery thrombosis after a strong head deflexion. Because of no possibility for i.v. thrombolysis (out of time window), worsening of patients condition, and taking into mind risk/benefit we started heparin treatment according to ESO Guidelines. After four days, a significant improvement of neurological symptoms was observed, and CCDS findings of blood flow to the basilar artery with increased resistance and lowered systolic velocity, marking an initial recanalization. Subsequently, the patient was continuously anticoagulated and rehabilitated, to achieve a relatively steady state and favorable outcome.

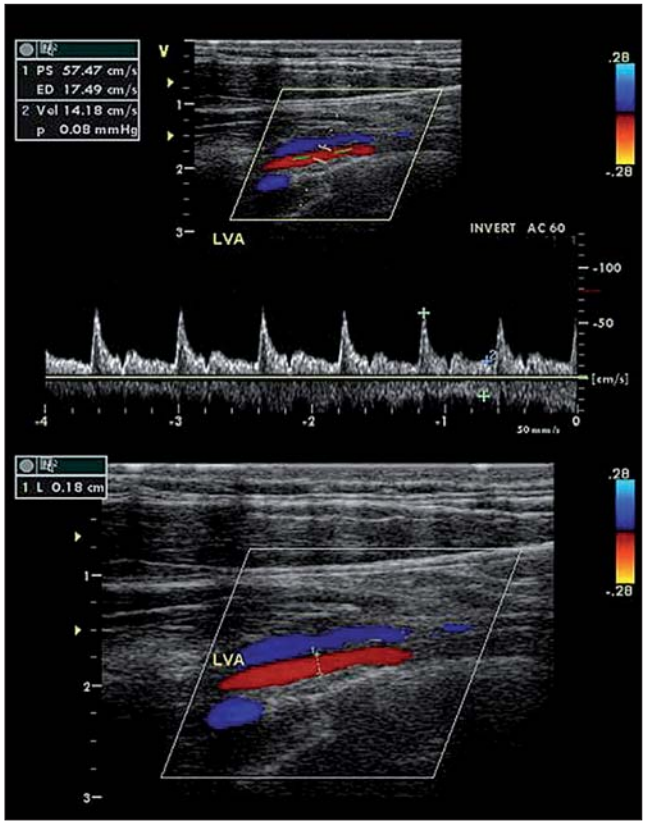

Fig. 5 – CCDS – hypoplasia of left VA.

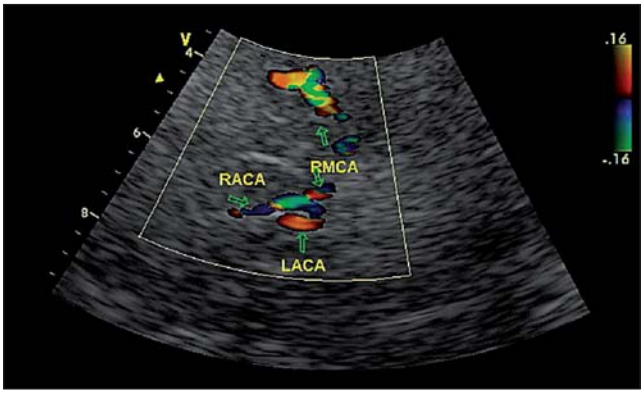

Fig. 6 – TCCDS – front trifurcation on the right.

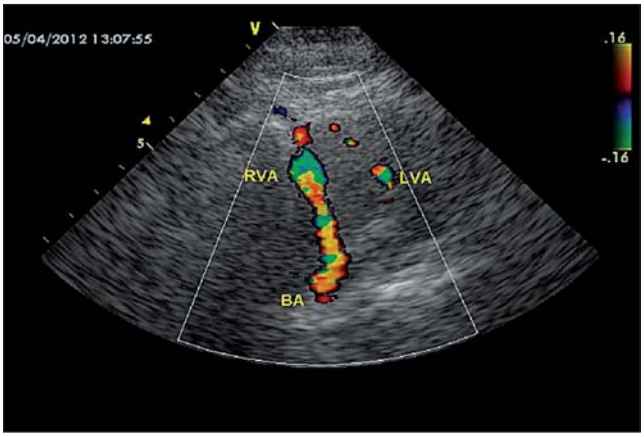

Fig. 7 – TCCDS – V4 segment of right VA, left VA and BA.

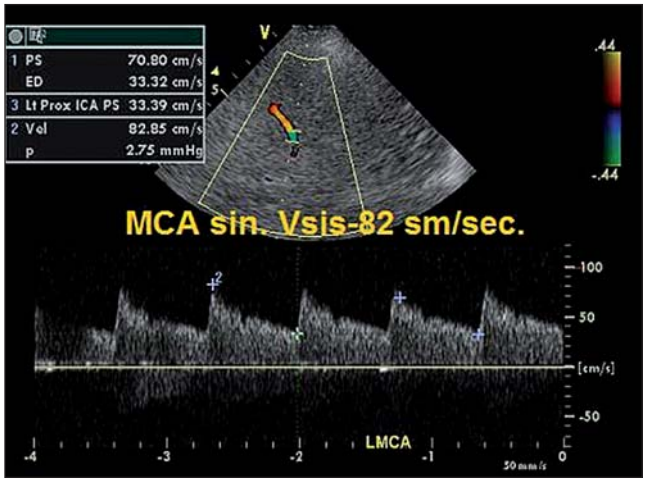

Fig. 8 – TCCDS – left M1 segment.

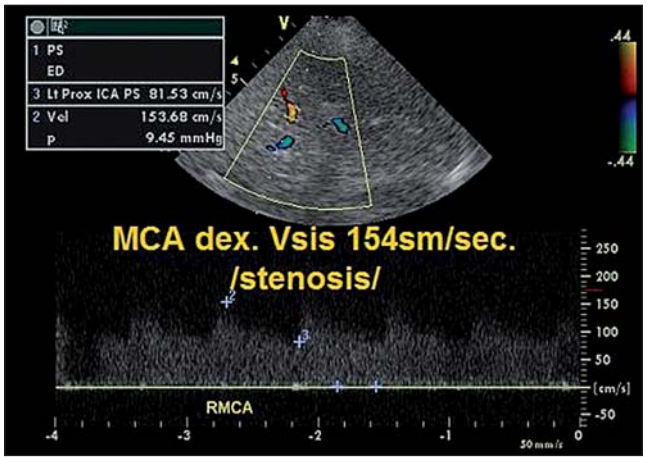

Fig. 9 – Stenosis of the right M1 segment.

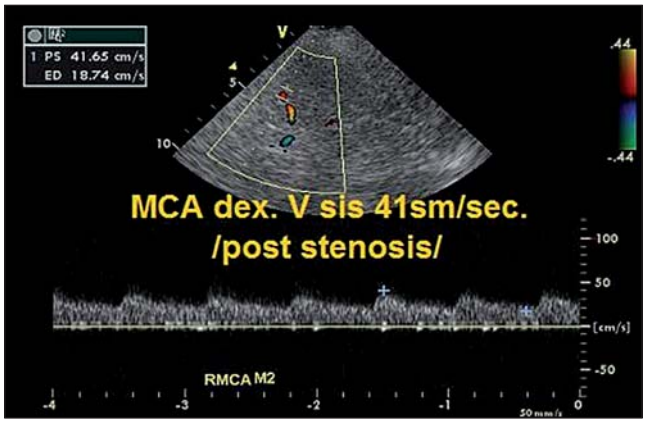

Fig. 10 – Post stenosis blood flow in the M1 segment of right MCA.

Discussion

Cerebrovascular diseases are a major problem of modern world. They are related with high mortality and high level of disability. Ischemic stroke in young patients (18–39 years) has a frequency of 0.5–0.7% among the general population. The etiology of many of them remains unclear. The anomalies in CoW have an important role

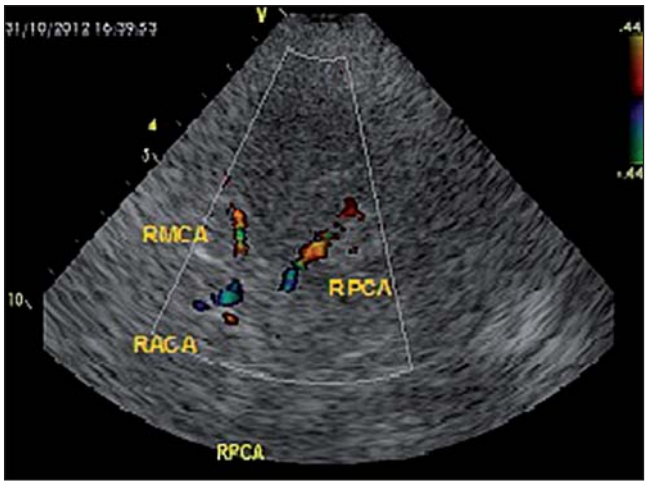

Fig. 11 – Hypoplasia of right ICA.

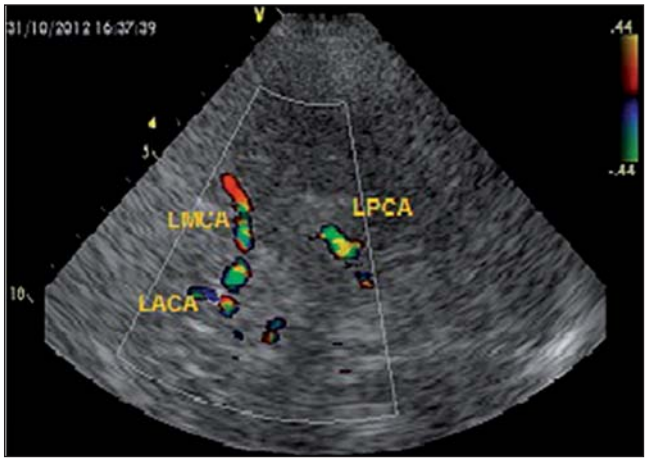

Fig. 12 – Hypoplasia of right ICA.

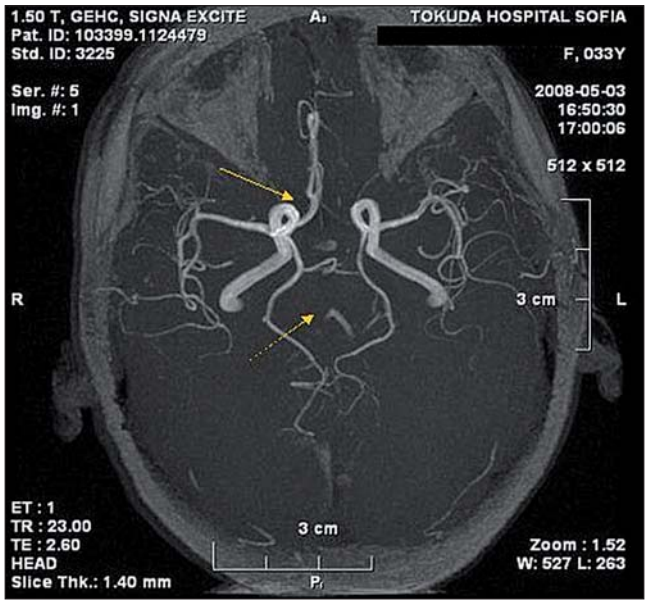

Fig. 14 – MRA – front trifurcation on the right, bilateral hypoplasia of the VA. Occlusion of the BA in its proximal segment.

in the pathophysiology of many of these ischemic strokes, there is a close correlation between congenital CoW changes and the increased risk of stroke.

According to different authors, the frequency of hypoplastic vertebral artery (VA) varies between 1.9 and 6%, (more common for the right VA), but rare hypoplasia of both vertebral arteries is also found [3,17]. In such cases, bilateral hypoplasia may be combined with other congenital changes to CoW. This significantly increases the risk of ischemic stroke.

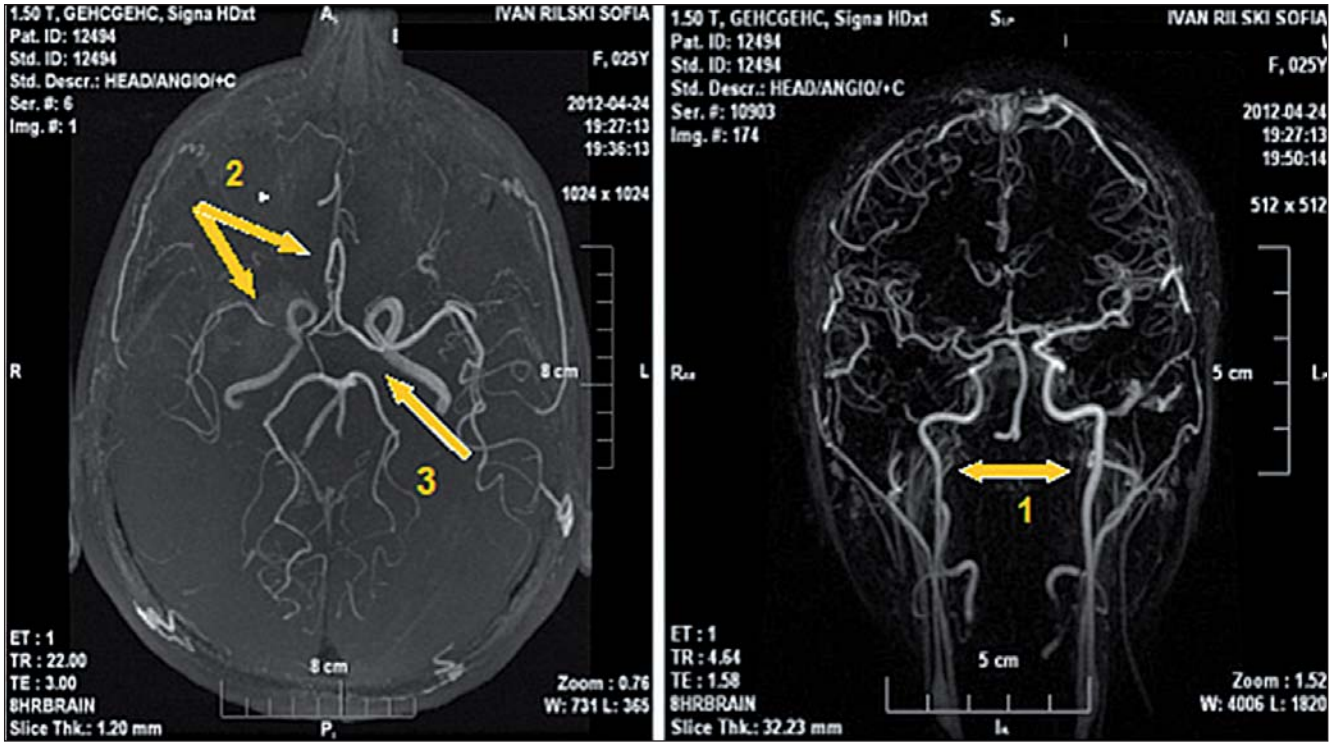

Fig. 13 – Hypoplasia of right ICA (1), hypoplasia/stenosis of M1 and A1 for MCA and ACA (2), missing right PcoA (3).

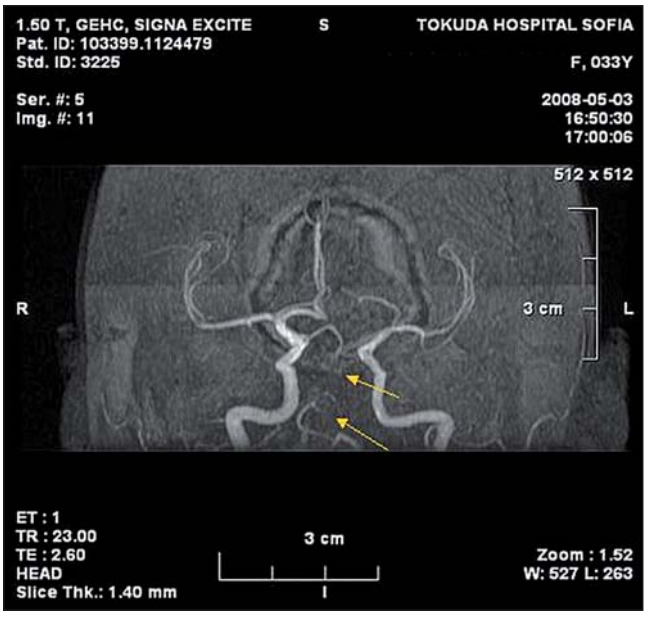

Fig. 15 – MRA – front trifurcation on the right, bilateral hypoplasia of the VA. Occlusion of the BA in its proximal segment.

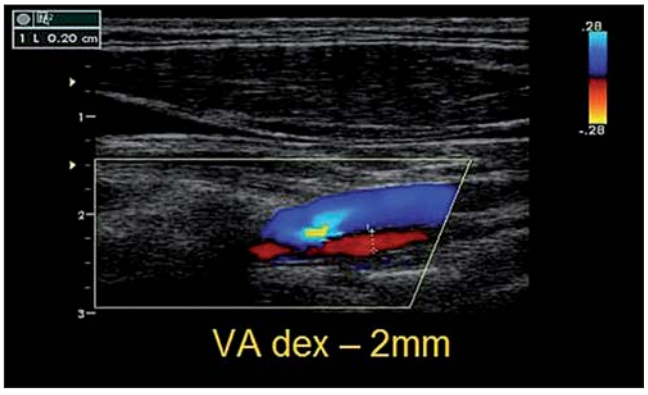

Fig. 16 – Hypoplasia of the right VA – 0.2 cm.

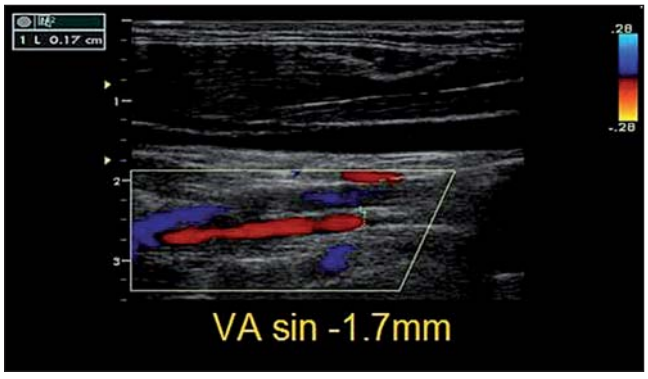

Fig. 17 – Hypoplasia of the left VA – 0.17 cm.

There are three basic configurations of PcoA described – fetal, adult and transitional [5]. In fetal configuration the diameter of the ipsilateral P1 segment of PCA is smaller than the diameter of PcoA so that the main blood flows to the occipital units is mainly by ICA. In transitional configuration PcoA is equal in size to P1 segment of PCA, while older configuration P1 has a diameter larger than PcoA so that blood flows to the occipital shares entirely

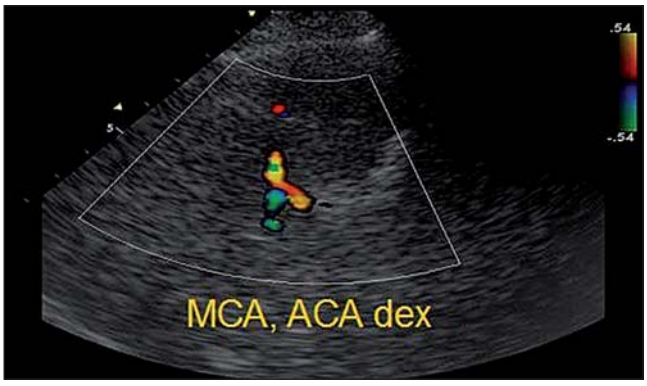

Fig. 18 – TCCDS – front trifurcation of right ICA.

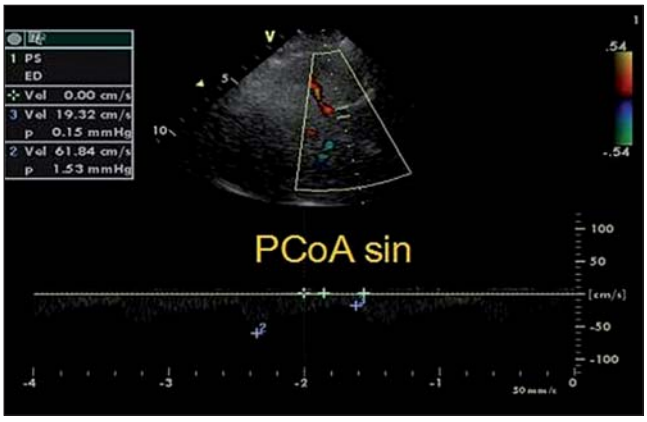

Fig. 19 – TCCDS – retrograde blood flow for PcoA.

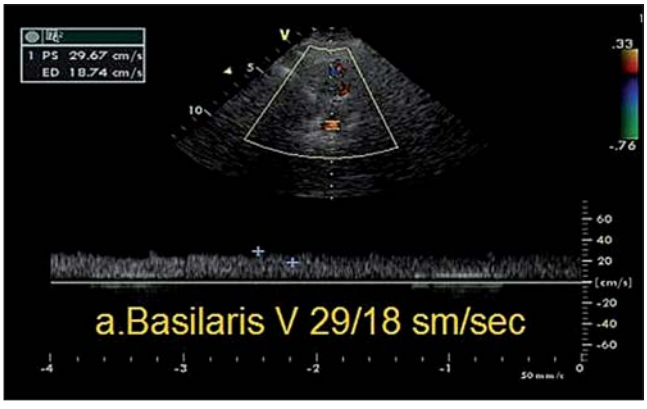

Fig. 20 – TCCDS – thrombosis of BA.

from the vertebral-basilar system. Fetal type of cerebral blood flow occurs in about 10% of people, in which case the PCA comes directly from ICA and forms the so-called "rear trifurcation" as is clinical case 3. Very rarely a bilateral posterior trifurcation is found. A combination of congenital abnormalities of CoW such as front trifurcation combined with fetal-type circulation and hypoplastic vertebral arteries can lead to a higher risk of transient ischemic attacks and ischemic strokes in the brain stem [18]. We have the same findings in clinical case 3.

In the aforementioned three clinical cases, the patients had vascular anomalies and developed ischemic stroke at a young age. We found also high diagnostic role of noninvasive CCDS and MRA, as well as their full concordance.

CCDS is a highly reliable method of assessment of cerebral hemodynamics, vasomotor reactivity and determination of patients with potential risk for ischemic stroke or transient ischemic attack. It also can show the pattern of collateral circulation in patients with carotid occlusion, can find microembolic signals, and also can take account of the vasomotor activity toward CO_2 levels (a marker of cerebral vascular reserve and autoregulation) [19]. Reduced vasoreactive response suggests abnormal brain perfusion and poor collateral blood flow. Studies have shown an association between impaired vasomotor regulation and increased risk of stroke in patients with carotid stenosis [20]. Transcranial color-coded Doppler sonography (TCCDS) combined with compression tests of ICA can quickly assess the collateral ability of CoW [21]. This makes TCCDS a reliable method for the assessment of cerebral hemodynamics. Comparative studies between transcranial ultrasound and angiography techniques have shown that TCCDS has a high level of sensitivity and specificity in the evaluation of blood flow in AcoA and PcoA [22,23]. Furthermore TCCDS can not only diagnose blood flow of collateral arteries, but it can also be used in the detection of alternating or reverse blood flow to the rear circulation (steal phenomenon), in the detection of microembolic signals. It can provide a reliable monitoring for arterial recanalization during systemic thrombolysis, and enhance the level of arterial recanalization [24,25]. TCCDS is the only diagnostic method providing information on cerebral hemodynamics in real time. In comparison to other imaging methods TCCDS demonstrated 79% sensitivity and 94% specificity for the detection of intracranial stenosis.

Conclusion

In conclusion, the three cases exhibit congenital changes of the CoW and their role for the occurrence of acute ischemic stroke. Many studies have shown large number of anatomical variations of incomplete or interrupted CoW and their association with a higher incidence of stroke. We believe that the combination of CoW variations with other risk factors increases the possibility of ischemic stroke, despite good opportunities for compensatory brain blood circulation. In the patients we present, there is a different combination of risk factors such as congenital changes of extra- or intracranial brain vessels, genetic mutations associated with increased risk of thrombosis, administration of oral contraceptives.

A full accordance of the data from CCDS and other diagnostic imaging was observed. This proves that CCDS in experienced hands is highly reliable method for fast and accurate orientation in patients with acute stroke in various vascular abnormalities. The main advantages of CCDS are that it can be done at the bedside of the patient, can be repeated if necessary or can be applied for a prolonged surveillance. Last but not least, CCDS has low cost compared to other diagnostic methods and the lack of necessity for application of contrast agent.

Conflict of interest
No conflict of interest.

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None.

Ethical statement
I declare, on behalf of all authors that the research was conducted according to Declaration of Helsinki.

Informed consent
I declare, on behalf of all authors that informed consent was obtained from all patients participating in this study.

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