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Hypoplasia of the ipsilateral internal jugular vein is associated with worse outcome in acute anterior circulataion stroke

Hipoplazija ipsilateralne unutrašnje jugularne vene je udružena sa lošijim ishodom akutnog moždanog udara u prednjoj cirkulaciji

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Abstract

Background/Aim. Disruption of cerebral venous blood drainage leads to cerebral venous congestion, an increase in intracranial pressure and decrease of the cerebral perfusion pressure. The exact role of the cerebral venous circulation in acute stroke is not yet known. The main blood drainage from the brain and the superficial parts of the face and neck is drained by a paired internal jugular vein (IJV). Congenital anomalies of IJV may disrupt the blood collection from the brain, which leads to congestion of the cerebral venous circulation. The aim of our study was to determine the association between the hypoplastic ipsilateral IJV and clinical outcome of patients with acute ischemic anterior circulation stroke. **Methods.** This prospective case series study involved the patients with the anterior circulation stroke and ultrasonographic criteria for unilateral hypoplasia of the ipsilateral IJV. Data from the 74 consecutive patients with acute anterior circulation stroke admitted to the Special Hospital for Cerebrovascular Diseases "Sveti Sava", Belgrade, from September 2015 to January 2016 were included. Ultrasonography of IJV diameter and the collection of the hemodynamic data were performed in all patients. Neurological deficits on admission were evaluated using the National Institutes of Health Stroke Scale (NIHSS) score. The clinical outcome was assessed using the modified Rankin Scale (mRS) score (from 0 to 6) at 30 days or at discharge, whichever occurred sooner. Good and poor outcomes were defined as an mRS score of 0–2 and 3–6, respectively. **Results.** Ipsilateral hypoplastic IJV was diagnosed in 13 (17.6%) patients with anterior circulation stroke. In this group, 9 stroke patients (69.2%) had mRS ≥ 3. Of the remaining 4 patients with mRS ≤ 2, three had bilateral hypoplasia of IJV and one patient had smaller diameter of the IJV, but did not fulfill the ultrasonographic criteria for hypoplastic venous anomaly. **Conclusions.** In our case, a series of the patients with anterior circulation stroke with ultrasonographic criteria for unilateral hypoplasia of the ipsilateral IJV (on stroke side) have worse clinical outcome compared with the patients with bilateral hypoplasia.

Key words:
brain infarction; jugular veins; echocardiography, doppler; treatment outcome.

Apstrakt

Uvod/Cilj. Poremećaj odvođenja venske krvi iz mozga dovodi do cerebralne venske kongestije, povećanja intrakranijalnog pritiska i pada cerebralnog perfuzionog pritiska. Tačna uloga cerebralnog venskog sistema u akutnom moždanom udaru još uvek nije dovoljo poznata. Glavni izvodni put krvi iz mozga, gornjeg dela lica i vrata su unutrašnje jugularne vene (VJI). Urođene anomalije VJI remete odvođenje venske krvi iz mozga, što dovodi do kongestije u venskom sistemu mozga. Cilj ove studije je bio da utvrdi povezanost između hipolazije istostrane VJI i kliničkog ishoda akutnog ishemijskog moždanog udara (AIMU) u prednjoj cirkulaciji. **Metode**. Ova prospektivna studija slučaja obuhvatila je bolesnike sa AIMU u prednjoj cirkulaciji i jednostranom hipoplazijom istostrane VJI prema ultrasonografskim kriterijumima. U studiju su slučajnim izborom bila uključena 74 bolesnika sa AIMU u prednjoj cirkulaciji koji su hospitalizovani u Specijalnoj bolnici za cerebrovaskularne bolesti „Sveti Sava" u Beogradu, od septembra 2015 do kraja januara 2016. Kod svih bolesnika je ultrazvučnim pregledom određivan dijametar VJI. Težina neurološkog deficita na prijemu procenjivana je pomoću *National Institutes of Health Stroke Scale* (NIHSS). Klinički ishod bolesti procenjivan je preko modifikovanog Rankin Skora (mRS) od 0 do 6, na dan otpusta. Dobar i loš ishod su definisani preko mRS skora. Skor 0–2 je smatran dobrim, dok je 3–6 smatran lošim. **Rezultati**. Istostrana hipoplastična VJI

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dijagnostikovana je kod 13 (17,6%) bolesnika sa AIMU u prednjoj cirkulaciji. U ovoj grupi devet (69,2%) bolesnika imalo je mRS ≥ 3. Od preostala četiri bolesnika sa mRS ≤ 2, tri su imala obostranu hipoplaziju VJI, dok je četvrti bolesnik imao užu VJI koja nije ispunjavala ultrazvučne kriterijume za hipoplaziju VJI. **Zaključak**. Bolesnici sa akutnim infarktom mozga u prednjoj cirkulaciji sa jednostranom hipoplazijom istostrane VJI (na strani infarkta mozga) imaju lošiji ishod u odnosu na bolesnike sa obostranom hipoplazijom VJI.

Ključne reči:
mozak, infarkt; vv. jugulares; ehokardiografija, dopler; lečenje, ishod.

Introduction

Acute ischemic stroke (AIS) can occur as a result of cerebral artery or vein occlusion. There are a lot of data about the significance of artery circulation, but, on the other hand not so many about the influence of the venous circulation. Acute ischemic stroke occurs when the cerebral blood flow (CBF) decreases under 10–12 mL/100 g tissue/min. [1]. CBF depends on the level of cerebral perfusion pressure (CPP). CPP represents the difference between mean artery pressure and vein pressure, which explains the influence of the vein pressure on CPP [2].

In supine position, the largest part of the blood drains by the internal jugular vein (IJV). This is the biggest vein in the neck, it follows the carotid artery and it unites with the subclavian vein distally to form the brachiocephalic vein (innominate vein). Further, it runs into the vena cava superior and then into the right atrium [3].

Anomalies of the IJV are not so rare and can be the cause of the venous circulation insufficiency. There are different kinds of anomalies – anomalies on the venous valve, vein hypoplasia or atresia [4]. Hypoplasia of IJV is the cause of venous insufficiency and the increase in the intracranial blood pressure due to the reduced blood flow [5]. Intracranial blood pressure increase leads to the CPP decrease and consequently enlargement of a brain infarction along with worse clinical outcome [6]. Stable CPP allows adequate exchange of the nutrients and oxygen in the brain tissue, which is of crucial importance in an acute stroke, and it has an impact on the survival of the tissue.

The aim of our study was to determine the importance of the presence of hypoplastic ipsilateral IJV on the outcome of acute territorial stroke of the anterior circulation by ultrasonography.

Methods

This was a case series of patients with the acute ischemic anterior circulation stroke admitted to the Special Hospital for Cerebrovascular Diseases "Sveti Sava" in Belgrade, from September 2015 to January 2016. Seventy-four consecutive patients, older than 30 years of age, with the acute anterior ischemic stroke, were enrolled in the study. The patients with thrombosis of IJV, the acute venous stroke, history of malignancy or severe infection, were excluded. The patients in our study were assessed regarding demographic data, comorbidities and vascular risk factors. A stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS), at admission and discharge, by board of certified neurologist [7]. The eligible candidates were those with the NIHSS between 4 and 25 points. The clinical outcome was assessed using the modified Rankin Scale (mRS) score (from 0 to 6) on a discharge day. Good and poor outcomes were defined as an mRS score of 0–2 and 3–6, respectively. All patients underwent the native multiphasic computed tomography [CT-General Electric (GE), Bright speed] or the magnetic resonance imaging (MRI) (MR Signa, HD×, 1.5T, GE, Milwaukee) of the brain performed on the 1.5-Tesla system at first 72 hours after the onset of a stroke. The radiological assessment was provided by an experienced neuroradiologist. For clinical classification of ischemic strokes we used The Oxfordshire Community Stroke Project criteria to assess the brain infarct size and location. All patients in our study had total anterior circulation infarct (TACI) or partial anterior circulation infarct (PACI) [8].

The ultrasound examinations of IJVs were performed using the MyLab 70 XVision ultrasound machine (Esaote, Genoa, Italy) by a neurologist who was blinded for the patient's neurological conditions. We used 5–7 MHz the ultrasound (US) linear probe and US settings for the examination of venous vessels [9]. The IJV was scanning with a minimal probe pressure, with thick US gel. The US probe was placed on the level of cricoid cartilage on either side, or 1–2 cm above IJV valves. The patients laid on their back with their head positioned at 30º. This position was the same as one when patients were lying on a hospital bed. M-mode was used for the assessment of IJV, in transversal plane (Figure 1). The patient was breathing spontaneously and after five respirator cycles we recorded a maximum vein diameter [7]. M-mod was used because of the variations in the diameter of veins during the respiratory cycle. The diametar of hypoplastic IJV was Dmax ≤ 5 mm [4]. The functional stroke outcome on a discharge day was estimated using mRS [10].

The Ethical Committee of the Special Hospital for Cerebrovascular Diseases "Sveti Sava" approved the study. Informed consent was obtained by all patients.

Statistical analysis

Statistical analysis was performed using Statistical software package (SPSS). We used the methods of descriptive statistics and absolute and relative numbers, measures of central tendency and measures of dispersion. Differences in frequency distribution between the studied groups were estimated by chi-square (χ^2) test and confirmed by Fisher's exact test. To evaluate predictors of good and worst outcome for patients with AIS in our study we preformed logistic regression analysis. χ^2 test was used to

evaluate presence of statistical significance regarding type of ischemic area and presence of IJV hypoplasia in both TACI and PACI regarding treatment outcome.

The studied variables were considered statistically significant if the probability of risk for accidental difference between empirical and theoretical values was less than 0.05 ($p < 0.05$), and highly statistically significant if the probability was less than 0.01 ($p < 0.01$).

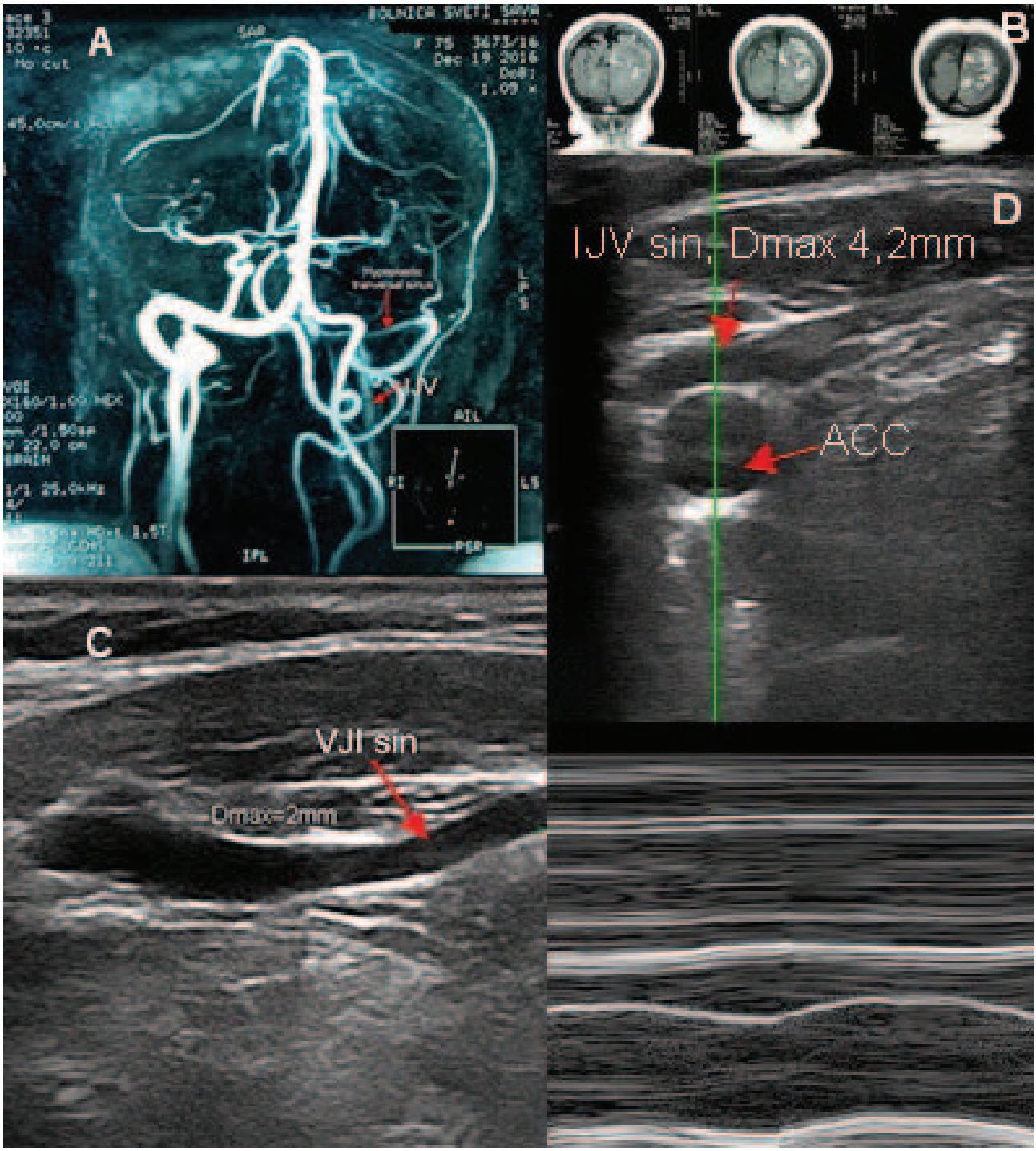

Fig. 1 – 65-year-old woman with an acute onset of right limb weakness with neglect. A) Magnetic resonance (MR) cerebral venogram showing left transversal sinus and internal jugular vein (IJV) hypoplasia (arrows); B) Brain MR tomogram showing partial anerior circulation infarct (PACI); C) IJV on B-mode showing a maximal diameter 2mm, D. Duplex imaging IJV on M-mode at transversal plane showing small-caliber lumen of the left IJV, with a maximal diameter 4.2 mm (ACC – common carotid artery).

Results

This study included 74 patients, 39 (52.7%) female and 35 (47.3%) male patients. The mean age of the female study patients was 73.2 years (from 65 to 84 years of age) and of the male study patients 70.3 years (from 54 to 80 years of age). The most prevalent risk factor was hypertension (Table 1). According to the Oxford classification, of the patients with AIS, 27 (36.5%) of them had TACI and 47 (63.5%) had PACI. There was no significant difference in relation to gender – 52.1% of women had TACI and 53.5% had PACI. Right IJV was dominant in 47 (63.5%) and left IJV in 27 (36.5%) patients.

Table 1

Risk factors in the patients with anterior circulation stroke (n = 74)

Risk factor	Patients n (%)
Hypertension	62 (83.8)
Diabetes mellitus	17 (22.9)
Hyperlipidemia	11 (14.8)
Atrial fibrillation	26 (35.1)
Ischemic heart disease	22 (29.7)
Smoking	12 (16.2)
TACI	27 (36.5)

TACI – total anterior circulation infarct.

Sixty-one (82.4%) patients had no hypoplasia of IJV while 13 (17.6%) of them had ipsilateral hypoplasia of IJV. The group with hypoplastic IJV and the stroke on the same side, had TACI in 38.5% and PACI in 61.5% cases.

Right IJV was hypoplastic in 6 patients (41.7%), with the mean diameter of 4.4 mm. Left IJV was hypoplastic in 7 patients (58.3%) with the mean diameter of 4.2 mm. The mean diameter of hypoplastic IJV was 4.4 ± 0.5 mm [mean ± standard deviation (SD)], the median was 4.4 mm, the minimal diameter was 3.4 mm and the maximal was 5.0 mm. On the contralateral side, the diameter was 7.6 ± 2.2 mm (median 8.3 mm; minimum 3.5 – maximum 11.5 mm).

Comparing the clinical outcome in the group of patients with territorial infarction in anterior circulation and ipsilateral hypoplasia, we did not find a statistically significant difference. Similar percentage of patients in both group (without and with ipsilateral hypoplasia) had good or worse outcome. Four (20%) had mRS < 2 and 9 (16%) had mRS ≥ 3 (χ^2 test; $p = 0.73$).

We found a statistically significant difference comparing the clinical outcome in the group of patients with territorial infarction in anterior circulation and unilateral ipsilateral hypoplasia IJV only on a stroke side. Nine (69.2%) patients with unilateral hypoplasia on a stroke side had poor outcome while only one (7.7%), in the group with good outcome had unilateral hypoplasia. (Fisher's exact test; $p = 0.014$).

In the group of 13 patients with ipsilateral IJV hypoplasia, 4 (30.8%) patients had good outcome. Based on the NIHSS values for a stroke severity, 3 patients had mild and one patient had moderate stroke. Three patients with good clinical outcome had bilateral hypoplasia of IJV, whereas only one patient had unilateral hypoplasia with a small diametar of contralateral IJV (6.3 mm) (Table 2).

In the multivariate regressional analysis as the outcome predictor in our study for the patients with AIS, we stressed out the infarction size (Table 3), and thus we separately evaluated the presence of IJV hypoplasia and the infarction size on the treatment outcome in the patients with TACI and PACI (Table 4). In the group of patients with TACI, there was a statistically significant difference in frequencies of the participants without hypoplasia, with unilateral and with bilateral TACI in relation for treatment outcome (Table 4), while in the group of patients with PACI, there were no statistically significant differences in the frequencies of participants regarding presence and side of PACI in relation for treatment outcome (Table 4).

Table 2

Demographic and clinical features of patients with internal jugular vein (IJV) hypoplasia

Patient No	Age (years)	Gender	Infarct side	Oxford scale	Etiology TOAST	NIHSS (admission)	AP Dmax ipsilateral IJV (mm)	AP Dmax contralateral IJV (mm)	mRs (discharge)
1	74	F	L	TACI	2	22	4.8	8.8	6
2	84	F	L	TACI	1	15	3.7	9.4	5
3	75	F	R	TACI	1	14	4.4	11.5	4
4	78	F	R	PACI	2	7	4.2	8.6	4
5	65	F	L	PACI	2	8	4.1	8.3	4
6	74	M	L	PACI	4	11	4.9	8.3	4
7	80	M	L	TACI	1	7	3.4	8.3	3
8	70	F	L	PACI	2	8	4.8	8.3	3
9	54	M	R	PACI	5	11	4.9	8.4	3
10	82	F	R	TACI	2	15	5	5	2
11	66	F	R	PACI*	2	3	4.1	6.3	1
12	73	M	L	PACI	1	6	4.6	4.3	1
13	74	F	R	PACI	5	4	4	3.5	1

M – male; F – female; R – right; L – left; TACI – total anterior circulation infarct; PACI – partial anterior circulation infarct; * – billaterall frontal stroke; TOAST – Trial of ORG 10172 in Acute Stroke Treatment: 1 – large-artery atherosclerosis; 2 – cardioembolism; 3 – small-artery occlusion-lacune; 4 – stroke of other determined etiology; 5 – stroke of undetermined etiology; NIHSS – National Institute of Health Stroke Scale; AP Dmax – anterior posterior maximal diametar IJV; mRs – modified Rankin Scale.

Table 3

Multivariate logistic regression analysis of the evaluated parameters and treatment outcome in the patients with the acute ischemic stroke

Parameters	With/Without other conditions	
	ExpB (95% CI ExpB)	*p*
Alcohol	0.178 (0.021–1.492)	0.112
Ischemic area (TACI/PACI)	0.106 (0.012–0.945)	0.044*
NIHSS on admission	1.137 (0.971–1.330)	0.110

***p* < 0.05; CI – confidence interval. For other abbreviations see under Table 2.**

Table 4

Distribution of treatment outcome frequencies regarding the type of ischemic area and presence of internal jugular vein (IJV) hypoplasia

Ischemic area (IJV hypoplasia)	Outcome, n (%)		*p*
	good	poor	
TACI			
none	0 (0)	22 (100)	0.000
unilateral	0 (0)	4 (100)	
bilateral	1 (100)	0 (0)	
PACI			
none	16 (41.0)	23 (59.0)	0.113
unilateral	1 (16.7)	5 (83.3)	
bilateral	2 (100)	0 (0)	

***p* < 0.05.**
For abbreviations see under Table 2.

Discussion

In this study, we attempted to determine the influence of cerebral vascular congestion (CVC) on the outcome of an acute territorial ischemic stroke in anterior circulation, in terms of present hypoplastic jugular vein on the infarction side. We hypothesized that the cerebral venous congestion might influence the stroke outcome through impact on CPP or through disbalance of cerebrospinal fluid (CSF) resorption. It is known that CPP depends on the mean arterial and intracranial pressure, while the intracranial pressure resembles the cortical veins pressure [2]. Further, the cortical veins pressure depends on the pressure in IJV. In a supine position, IJV drain the largest portion of the blood from the brain. The ultrasound studies that evaluated anatomical characteristics of IJV showed that congenital small IJV or hypoplastic IJV were present in 10%–23% of the population [4, 5]. Our findings are in correlation with the previous reports where we pointed out that 16.7% of the patients were diagnosed with hypoplastic IJV.

IJV that are of a small diameter decreased the blood volume flow with the consequent congestion in the intracranial venous system, since, the blood flow rate was shown to be directly proportional to the average velocity and the vein diameter [11]. Some studies showed that the right IJV diameter was wider, stressing out that right IJV was dominant particularly in 2/3 of the patients [12, 13]. Our study correlates with previous reports since we found that in 63.5% of the evaluated patients the right IJV was of a wider diameter.

A great proportion of studies in last decade dealing with CVC was done on the patients with multiple sclerosis (MS), indicating as possible causes: neck veins with multifocal lumen narrowing, jugular reflux and jugular veins hypoplasia [11, 14]. Further, it was stressed out that CVC was thought to be among the causes of leukoaraiosis and normotensive hydrocephalus [15, 16]. Previous reports pointed out that in these neurological conditions, there was a chronic decreased reuptake of CSF in dural sinuses due to the elevated venous pressure, which lead to the presence of stasis in capillaries. These processes altogether directly influence CPP [17]. It was also noticed that the small IJV presence lead to chronic cerebral venous insufficiency and congestion [11].

Some studies demonstrated that in an acute territorial infarction, on MRI, on the side of infarction, the deep medullar veins could be seen and that they were the predictors of a severe deficit according to the NIHSS and poor outcome [18]. Our findings stressed out that the patients with unilateral hypoplasia on the infarction side had poorer outcome then others. It should be pointed out as well, that the patients with bilateral hypoplasia had a satisfactory outcome in both groups (PACI and TACI). Our study demonstrated that the TACI patients with unilateral hypoplasia had poorer outcome, while one patient with bilateral hypoplasia had better outcome. This observation might be explained by the fact that in such a case there could be some kind of the venous blood flow reorganization from jugular to non-jugular (most likely to vertebral plexus) and thus preventing blood drainage from the brain misbalance, further preventing as well the cerebral venous congestion [19]. CVC in the acute cerebral infarction leads to an increased pressure in veins and capillaries, impairing the blood-brain barrier, that is already damaged by the acute ischemic stroke, leading to the vasogenic edema [20]. In addition, the cerebral venous congestion leads to a decrease in the perfusion pressure along with a reduction in the cerebral blood flow, causing further damaging of the brain tissue. The

deep medullar veins are dilated due to the venous insufficiency and congestion in the patients with leukoaraiosis [21].

There are no studies with the ultrasonographic follow-up measurements of IJV in acute stroke. However, one angiographic study reported that the IJV and venous sinus hypoplasia may be the cause of the fatal edema in malignant media syndrome [6].

This is in line with our results, where we stressed out that the presence of IJV hypoplasia on infarction side was associated with poorer prognosis, and bilateral hypoplasia with the better outcome.

Despite the obtained results from our study, we should stress out the study limitations. The main limitation refers to a sample size of the stroke patients with IJV hypoplasia. Therefore, further studies are needed to be conducted on a larger number of participants for more sensitive interpretation of treatment outcome in the patients with the acute myocardial infarct regarding the presence of unilateral or bilateral IJV hypoplasia.

Conclusion

Ipsilateral, hypoplastic IJV is the cause of poor clinical outcome in the patients with the acute anterior circulation stroke due to reduced drainage of blood from the affected cerebral hemisphere. It is possible that in the acute phase, the venous circulation cannot adapt to the new situation fast enough, which further leads to an increase in the intracranial pressure, edema and a poor clinical outcome. In our study, the patients with bilateral hypoplasia of IJV had good clinical outcome. The main reason for this is probably a good adaptation of venous circulation to narrow IJV and enhanced drainage of the blood from the brain to non-jugular pathway most likely through the vertebral veins. The routine ultrasound examination of veins might be of a great importance in selection of the patients with territorial infarction who are expected to develop edema and thus progression of the neurological condition influencing poorer treatment outcome.

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