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Brachiocephalic Vessels Ultrasound Index of Arterio-venous Ratio (IAVR) and Headache as a Diagnostic Tool for Intracranial Venous Stasis in Arterial/Venous Ischemic Stroke's Differentiation

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Abstract

Summary: Identification of signs of intracranial venous stasis using ultrasound methods in combination with determination of headache intensity according to the visual-analogue scale allows us to suspect the venous genesis of ischemic stroke before using neuroimaging methods, which can contribute to the selection of adequate therapy and to improve the prognosis and long-term outcomes of the disease.

Objective: To study the prognostic value of a complex of clinical demographic and instrumental indicators for developing a model for early differential diagnosis of ischemic stroke of arterial and venous origin.

Material and Methods: Examined 124 patients with ischemic stroke: 22 with venous stroke due cerebral venous sinus thrombosis (VIS), 53.5±16.7y and 102 with atherothrombotic stroke (AIS), 68.3±12.1y which were verified by native CT; CT-angiography, PCT (perfusion CT: CBF, CBV, MTT), brachiocephalic vessels ultrasound index of arteriovenous ratio (IAVR) and transcranial duplex scanning for all. IAVR was obtained due duplex scanning of carotid common arteries (CCA) and internal jugular veins (IJV) according to the formula:

V max IJV optimal =2S CCA × Vps CCA/ 3S IJV…… (1)

IAVR = max IJV actual / V max IJV optimal × 100%, where…… (2)

IAVR – index of arteriovenous ratio, (%)

Vps CCA – peak systolic velocity of the CCA, cm/s

Vmax IJV – maximum blood flow velocity, cm/s.

S – vessel cross-sectional area, cm^2, as well as.

To assess the neurological status of patients, rating scales were used, including a visually analog headache intensity scale.

Results: The greatest prognostic significance was possessed by such parameters as the indicator of arteriovenous blood flow ratio and the value of headache intensity on a visual-analogue scale. A model for the differential diagnosis of AIS and VIS, which has high specificity and sensitivity, has been developed. Velocity indicators in the veins of Rosenthal and the vein of Galen are additional signs of intracranial venous stasis.

Keywords

Arterial ischemic stroke (AIS), Venous ischemic stroke (VIS), Cerebral

venous sinus thrombosis, Ultrasound index of arteriovenous ratio (IAVR), Visual analog headache intensity scale

List of Abbreviations

AIS: Arterial Ischemic Stroke; **VIS:** Venous Ischemic Stroke; **IJV:** Internal Jugular Veins; **MSCT:** Multispiral Computed Tomography; **MSCTA:** Multispiral Computed Tomographic Angiography; **CCA:** Common Carotid Artery; **IAVR:** Ultrasound Indicator of Arteriovenous Ratio of Brachiocephalic Vessels; **PCT:** Perfusion Computed Tomography; **NIHSS:** National Institutes of Health Stroke Scale; **VPS:** Velocity Peak Systolic

Introduction

The study of ischemic stroke remains one of the priority areas of neurology because of its prevalence and severity of consequences. Despite the fact that at present, arterial stroke is quite well studied, approaches to the diagnosis and treatment of 22-30% of cases in its classification are developed and systematized for cryptogenic stroke [1]. Indeed, the etiology of a stroke cannot always be determined, and the cause of its occurrence remains unknown [2-4]. Generally, the term "stroke" refers to cerebral artery disease. At the same time, with the pathology of cerebral venous structures, the formation of a focus of ischemia is also possible, but this happens relatively less often and has been studied to a much lesser extent.

It is known that venous stroke (VIS) accounts for 0.5–1% of all ischemic strokes [5]. Strokes associated with cerebral venous sinus thrombosis are prone to secondary hemorrhages in 40% of cases, which is significantly more likely than arterial [6, 7] and due to the severity of vasogenic edema in VIS [8, 9]. It is important that the main approach to the treatment of VIS, which is more prone to secondary hemorrhage [10], is anticoagulant therapy, the safety of which in this group of patients has not been completely determined [11, 12]. It is known that even with a favorable outcome within 6 months, approximately 30% of patients experience the development of chronic headache in the presence of hemorrhagic transformation. According to the results of a three-year follow-up, the number of patients with chronic headache increases to 60% [13, 14]. The complexity of the urgent diagnosis of VIS lies in often absence of specific clinical manifestations [15-17]. However, the most common occurrence of severe headache. This symptom occurs among patients' complaints in approximately 75-90% of cases [18-21]. In 25% of cases, headache is the only complaint of the patient; often, there is no connection between the localization of the headache and the site of sinus thrombosis [7]. Moreover, it can imitate migraine [22-24]. Early diagnosis of the relationship of headache with cerebral venous sinus thrombosis, even in the absence of neurological signs, is crucial for the timely detection of the disease [25, 26]. At the same time, headache is an extremely common symptom, and the vast majority of patients with isolated headache do not have cerebral venous sinus thrombosis [27], which is why the economic feasibility of routine imaging remains very uncertain [28]. All this explains the need to search for new non-invasive and non-radiation accessible methods of emergency differential diagnosis of ischemic stroke of arterial and venous origin.

Materials and Methods

The study included 124 patients admitted to the clinic with non-hemorrhagic stroke from 2010 to 2013 and was in accordance with the ethical standards of the Helsinki Declaration and was approved by the Institute's Local Ethics Committee. The exclusion criteria were: aphasia, impaired consciousness, an anamnesis of stroke, hemorrhagic stroke, thrombolytic therapy, brain tumor, arterial aneurysms or other vascular malformations, the presence of stenoses of the brachiocephalic arteries more than 50%, hemodynamically significant tortuosity of the carotid arteries, increased blood pressure above 130/90 mm, jugular vein thrombosis, any cancer.

The study protocol included an assessment of the neurological status of the patient with used scales: National Institutes of Health Stroke Scale, Barthel, Rankin. A visual analogue scale was used to assess headache intensity. The patient himself evaluated his pain in the range from 0 (no pain) to 10 (the maximum possible pain). Patients underwent general clinical and laboratory examination. All patients underwent native multispiral computed tomography (MSCT) and multispiral perfusion computed tomography (PCT) for 40 minutes after admission to the hospital. Native MSCT was also performed on days 5-7 to detect secondary hemorrhage. Color duplex scanning of brachiocephalic vessels and transcranial duplex scanning were performed upon admission to the hospital, and the following were assessed: maximum blood flow velocity in the Galen vein and Rosenthal veins (a larger value of the blood flow velocity in one of the Rosenthal veins was taken into account, regardless of the side of the lesion).

The definition brachiocephalic vessels ultrasound index of arteriovenous ratio (IAVR) is based on the fact that the normal cross-sectional area of the internal jugular vein exceeds the cross-sectional area of the common carotid artery by 75-100%. It is also known that the maximum blood flow velocity in the IJV is 1/3–1/2 of the peak systolic blood flow velocity (VPS cm/s) by CCA. Knowing the cross-sectional areas of the IJV and CCA, as well as the peak systolic velocity of the CCA in each case, it is possible to determine the "optimal" speed from the IJV and compare it with the actual one using formulas (1) and (2) [29]:

V_{max} IJV optimal = 2S CCA × VPS CCA/ 3S IJV…… (1)

IAVR = max IJV actual / V max IJV optimal × 100%, where…… (2)

IAVR – index of arteriovenous ratio, (%)

VPS CCA – peak systolic velocity of the CCA, cm/s

V_{max} IJV – maximum blood flow velocity, cm/s.

S – vessel cross-sectional area, cm^2.

During the hospital period, the outcome of the disease was evaluated. A favorable outcome was the presence of positive dynamics in clinical status or the absence of negative dynamics (based on a dynamic assessment by a neurologist and the use of rating scales).

Statistical processing of the material was carried out using the STATISTICA 9.0 software package (StatSoft, Inc. www.statsoft.com). Comparison of quantitative traits in groups was performed using the Mann – Whitney and Kruskal-Wallis test. When assessing qualitative characteristics, the Pearson $\chi 2$ criterion with Yates correction was used. Differences were accepted as statistically significant at $p < 0.05$.

To develop a prognostic model for the differential diagnosis of VIS and AIS, a regression analysis in the form of binary logistic regression was used. The quality of the model was assessed by constructing a classification matrix. (Statistical Package for the Social Sciences program). Validation of this model was carried out on a sample of newly recruited patients (44 people), of whom nine had VIS and 35 had AIS. During validation, the model correctly classified VIS in 77.8% of cases, AIS in 94.29% of cases.

Results

The examined patients are divided into two groups based on the genesis of the stroke (venous and arterial). Comparative characteristics of the studied groups of patients are presented in table 1.

Table 1: Comparative characteristics of the studied groups of patients according to the main clinical and demographic, laboratory, as well as ultrasound indicators.

Indicators	Stroke		P
	Venous (n = 22)	Arterial (n = 102)	
Age (years), Me (Q25; Q75)	57 (43; 63)	71 (59; 77)	0.2
Gender, male / female, n (%)	11 (59) / 11 (50)	52 (51) / 50 (49)	0.9
Arterial hypertension, n (%)	16 (72.7)	89 (87.3)	0.2
Anamnesis of transient ischemic attack, n (%)	1 (4.5)	2 (2)	0.9
Diabetes, n (%)	1 (4.5)	11 (10.8)	0.6
Visual analogue scale of headache intensity (points), Me (Q25; Q75)	8 (6; 8)	3 (2; 4)	0.001
NIHSS (points), Me (Q25; Q75)	9 (2; 21)	9 (6; 14)	1
Barthel Index, Me (Q25; Q75)	35 (0; 60)	45 (15; 65)	0.2
Rankin Scale (points), Me (Q25; Q75)	4 (3; 4)	4 (3; 5)	0.7
Hypercoagulation, n (%)	10 (45.5)	25 (24.5)	0.11
Hypocoagulation, n (%)	1 (4.5)	4 (3.9)	0.7
Favorable outcome, n (%)	20 (90.9)	86 (84.3)	0.6
The maximum blood flow velocity in the vein of Rosenthal(cm/s), Me (Q25; Q75)	25 (24; 33)	15(10 ; 18)	0.001
The maximum blood flow velocity in the vein of Galen (cm/s), Me (Q25; Q75)	33 (30; 35)	18 (13; 25)	0.0002
IAVR (%), Me (Q25; Q75)	45 (23; 52)	70 (68; 73)	0.00001

Analyzing the data obtained, we can conclude that, despite the absence of statistically significant differences in the main clinical and demographic indicators, patients with VIS were younger in comparison with patients with AIS, less likely to suffer from arterial hypertension and diabetes mellitus, they were more likely to have a favorable outcome.

In case of VIS, a characteristic symptom was a headache, as well as signs of cerebral venous stasis according to ultrasound methods, which are clearly demonstrated by such indicators as enlarged of maximum blood flow velocity in the Rosenthal veins and Galen vein as well as IAVR decreasing.

To select indicators that have the greatest prognostic ability in the differential diagnosis of VIS and AIS, we used a regression analysis in the form of binary logistic regression. The variable Y was used as a dependent variable, characterizing the genesis of a stroke and assuming the value Y=1 in the case of AIS and Y=0 in the presence of AIS. The following factors were selected as a group of factors presumably predictive in diagnosing the genesis of stroke: the patient's age, manifestation of the disease, the values of headache intensity on admission, IAVR of brachiocephalic vessels, maximum blood flow velocity in Rosenthal veins and Galen vein.

Regression analysis left the headache intensity and ultrasonic IAVR of blood flow as the factors influencing the probability of the patient having VIS. Both factors had a significant impact on the assessment of the predictive probability of the presence of VIS. The higher the headache intensity and the lower the IAVR value of blood flow, the more likely the patient will be diagnosed with VIS associated with cerebral venous sinus thrombosis. Using regression coefficients, for each patient, according to the measured values of indicators, the predicted probability of having VIS in accordance with the formula (3) can be calculated

$$P(Y=1/X1,X2)=\frac{1}{1+e^{-(4,626+0,856\cdot X1-0,192\cdot X2)}} \quad \ldots\ldots\ldots\ldots (3)$$

where P - is the forecast probability;

e – the base of the natural logarithm (mathematical constant);

X1 – headache intensity value on a visual analogue scale at admission;

X2 – IAVR, %.

The probability value varies from zero to 1. If the predited probability is greater than 0.5, then the patient will be diagnosed with VIS. If the probability value is less than 0.5, then the patient will be diagnosed with AIS. Using the classification matrix, it was determined that the constructed model 98% correctly classifies patients with AIS and 95.2% correctly identifies VIS patients. The values of these indicators are high, and this means that the constructed model has a high prognostic ability (Table 2).

The volumes of the training and independent samples

Table 2: Classification matrix for patients with venous and arterial strokes.

Supposed Stroke Diagnosis	Established stroke diagnosis		Percentage correct classifications
	Arterial	Venous	
Arterial	99	2	98
Venous	1	20	95.2

arwhich is due to the small number of cases of venous strokes due to the rarity of the disease. The quality of the developed model will be refined as data on patients with VIS are accumulated.

Discussion

Using the standard approach for the urgent diagnosis of stroke does not allow to detect ischemic stroke of venous origin. MSCT allows to detect cerebral venous thrombosis, PCT can provide additional information for the differential diagnosis of the genesis of stroke, however, these methods cannot be used in emergency diagnosis in all cases of acute ischemic stroke. Obviously, to improve the quality of the diagnosis of stroke, additional clinical and instrumental methods are required, the use of which, on the one hand, would not lead to a loss of time required to implement the standard protocol for examining urgent patients with acute cerebrovascular accident, and on the other, it would not additional significant financial costs. According to the data obtained, a decrease in the IAVR of the blood flow of the brachiocephalic vessels 50% and lower in combination with an increase in the intensity of the headache according to visual score data of more than 4 points is in favor of the VIS, thus, the prognostic model for the differential diagnosis of stroke allows one to suspect its venous genesis even before the use of neuroimaging methods, being the rationale for the appointment of MSCT with the mandatory conduct of the venous or equilibrium phase of the scan, as well as PCT. Indirect signs of intracranial venous stasis are elevated maximum blood flow velocity in one or both Rosenthal veins of more than 25 cm/s and Galen's vein above 30 cm/s, obtained by transcranial duplex scanning.

Conclusion

Current standards for the differential diagnosis of stroke do not allow early detection of patients with VIS with sufficient effectiveness. The study made it possible to identify additional signs of intracranial venous stasis, the detection of which is not associated with radiation exposure and does not require the introduction of an iodine-containing contrast medium. It is noteworthy that the use of non-invasive (including ultrasound) techniques in the AHA/ASA 2018 recommendations is considered preferable in cases where the subsequent implementation of mechanical thromboextraction is not implied, while the use of multimodal (using MSCT and MRI) approach to the diagnosis of stroke is not recommended due to a possible delay in the decision to perform thrombolytic therapy (Class III, level of evidence B, randomized trials is no exist) [30]. Assessment of velocity parameters in the Galen vein and Rosenthal veins during transcranial scanning is an additional indirect sign of intracranial venous stasis, but the use of the method is limited by the absence of an acoustic window according to various data in 10-20% of cases [31-33]. The use of ultrasonic IAVR (within the protocol of color duplex scanning of brachiocephalic vessels), as well as the assessment of headache intensity according to the visual analogue scale in the developed model, improve the quality of early diagnosis of acute ischemic stroke and get the predicted likelihood of a patient having a venous stroke without the need for the cumbersome formula presented above. It should be noted that when using the visual analogue scale of headache intensity, there are a number of limitations: the subjectivity of its assessment, the presence of aphasia, as well as impaired consciousness in a patient with a stroke, while IAVR is an easy-to-use accessible parameter that can make a significant contribution to diagnosis of VIS.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any financial, commercial or other relationships that may be perceived by the academic community as representing a potential conflict of interest.

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