Comprehensive Ultrasound Assessment of the Craniocervical Circulation in Transient Global Amnesia

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Objectives—Structural changes and metabolic stress have been reported on diffusion-weighted magnetic resonance imaging in the cornu ammonis 1 area of the hippocampus in patients with transient global amnesia (TGA), but a consensus on pathogenesis is still lacking. The aim of our study was to perform a comprehensive ultrasound analysis of the cerebrovascular circulation in our population of patients with TGA.

Methods—One hundred patients with TGA and 50 age- and sex-matched control participants underwent ultrasound examinations of the cervicocranial circulation.

Results—The most significant risk factor for TGA was arterial hypertension ($P < .01$). There were no significant atherosclerotic lesions on the large arteries of the neck (mean internal carotid artery stenosis ± SD, 28.7% ± 11.7%) or on the large intracerebral arteries (good structural and hemodynamic status; $P > .05$). Rarely detected microembolic signals or a right-left cardiopulmonary shunt excluded an emboligenic mechanism of TGA ($P > .05$). The internal jugular vein valves were incompetent in 54% of patients with TGA, and this condition was associated with an increased risk of TGA (odds ratio, 4.16; 95% confidence interval, 1.91–9.04). The mean values of the breath holding index and pulsatility index, as parameters of small-vessel function, were within normal ranges and without differences between the TGA and control groups ($P > .05$).

Conclusions—Our ultrasound examination did not detect significant structural atherosclerotic changes of cervicocranial arteries, and an emboligenic mechanism was excluded. Only a significant rise of blood pressure in TGA and significant valvular insufficiency of the internal jugular vein were established. New research should clarify whether these simultaneous functional circulatory changes have relevance for metabolic stress in the cornu ammonis of the hippocampus.

Key Words—head and neck; neurosonology (adult); transient global amnesia; ultrasound examination; vascular (access)

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Abbreviations

CA1, cornu ammonis 1; CT, computed tomography; IJV, internal jugular vein; MRI, magnetic resonance imaging; OR, odds ratio; PI, pulsatility index; TEE, transesophageal echocardiography; TGA, transient global amnesia; TIA, transient ischemic attack

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The decades-old enigma of the pathogenesis of transient global amnesia (TGA) is still not fully resolved, although modern diagnostic procedures, particularly brain diffusion-weighted magnetic resonance imaging (MRI) and MR spectroscopy improved the understanding of this entity.[1] Advanced MRI studies in patients with TGA showed structural changes in the hippocampal cornu ammonis 1 (CA1) field, a brain area that plays an important role in memory processes.[2] These changes were evident 48 to 72 hours after the onset of clinical symptoms but were not registered 1 month after

the episode.[2] However, there is no consensus on the nature of these alterations, and the various mechanisms in the pathogenesis of TGA are still under consideration, such as migraine and spreading cortical depression, focal ischemia, embolization, venous flow disturbances, epileptic phenomena, and, most recently, acute metabolic stress in the vulnerable CA1 sector of the hippocampal cornu ammonis.[1–3] The aim of this research was to perform an ultrasound analysis of the cerebrovascular circulation in patients with TGA to assess the importance of the vascular mechanism in the pathogenesis of TGA in our population.

Materials and Methods

In a prospective study, we included 100 adult patients (≥18 years) with TGA, who were treated at the Neurology Clinic, Clinical Center of Serbia, from January 1, 2008, to January 1, 2015. The inclusion criterion was a diagnosis of TGA based on the diagnostic criteria of Hodges and Warlow.[4] The exclusion criteria were diagnosis of a transient ischemic attack (TIA), acute stroke, nonconvulsive epileptic status and epileptic amnesia, hypoglycemia, head trauma, and psychiatric illness according to *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, classification.[5] The control group comprised 50 age- and sex-matched inpatients at the Neurology Clinic who were treated in the same period for diseases of the peripheral nervous system and were selected according to the same exclusion criteria. The study was approved by the Review Board of the Neurology Clinic, Clinical Center of Serbia, and Ethics Committee of the Clinical Center of Serbia. All participants gave informed consent for participation in the study. The study was conducted in accordance with the World Medical Association Declaration of Helsinki.

Data on the clinical presentation, emotional stress or physical exertion with the Valsalva maneuver before episode onset, duration of amnesia, blood pressure during the TGA episode, previous cerebrovascular disorders, previous TGA, and vascular risk factors were obtained by interviews with the patients and their companions. All patients underwent the same diagnostic protocol, including a neurologic examination and laboratory analysis (full blood count, C-reactive protein, biochemical analysis, lipid levels, coagulation screening status, thyroid status, and immunologic analysis if it was indicated to exclude vasculitis). Brain computed tomography (CT) on a 64-slice multidetector row CT scanner was done on the first assessment in all patients with TGA and followed by a control CT scans in 35% within the first week. Magnetic resonance imaging examinations on a 1.5-T scanner (Avanto; Siemens AG, Erlangen, Germany) with T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences was done in 85% of patients with TGA within a month. Computed tomography of the brain was performed in the control group primarily (60%) and MRI optionally (40%) within a month. Standard electroencephalography, an ocular fundi examination, and a cardiac examination with electrocardiography and transthoracic echocardiography were done in all participants. The TGA group also underwent electroencephalography after sleep deprivation. Participants with a suspected right-to-left cardiac shunt based on positive bubble test results on transcranial ultrasound imaging underwent transesophageal echocardiography (TEE). All ultrasound examinations were performed within 7 days of TGA onset.

All participants underwent the following ultrasound scans, performed by blinded trained sonologists:

1. Color triplex examination of cervical segments of the carotid and vertebral arteries[6] with Mannheim criteria for intima-media thickness and atheromatous plaques.[7] The competence of the internal jugular vein (IJV) valve was investigated by assessment of venous flow at rest (regular breathing) and at deep inspiration with the Valsalva maneuver; the occurrence of venous reflux was treated as a positive test result[8] (α-10; Hitachi Aloka Co, Ltd, Tokyo, Japan; 7.5–14-MHz transducer).
2. Transcranial color Doppler examination of the intracranial circulation[9] performed in a standard manner, with measurements of the mean velocity (centimeters per second) and pulsatility index (PI) in the cerebral arteries. An assessment of cerebral vasomotor reactivity by a breath-holding test with apnea of 30 seconds was performed in all participants, and the lowest normal breath-holding index value was considered 0.69 (Digi Lite; Rimed, Raanana, Israel, 2-MHz transducer).[9]
3. Transcranial color Doppler detection of microembolic signals during 30 minutes of bilateral middle cerebral artery recording[10] (Rimed Digi Lite; monitoring frame with two 2-MHz transducers).
4. Transcranial color Doppler detection of a right-to-left cardiopulmonary shunt and bubble study[11,12]

(Rimed Digi Lite; monitoring frame with two 2-MHz transducers).

5. Transthoracic echocardiography in all participants (Hitachi Aloka α-10; tissue harmonics technology, 2-MHz transducer) as well as TEE in patients with positive bubble test results[13] (Acuson Sequoia C256; Siemens Medical Solutions, Mountain View, CA; multifrequency 2.5–4-MHz 3V2C transducer with secondary tissue harmonics technology).
6. Patients with paradoxical embolisms were underwent an ultrasound examination of the veins in the extremities, pelvis, and abdomen[14] (Hitachi Aloka α-10; 7.5–14-MHz transducer).

Results were tabulated. Statistical analyses included a descriptive analysis and a logistic regression analysis. $P < .05$ was considered statistically significant.

Results

The study groups were comparable in terms of age, with mean ages of 62 years in the TGA group and 61 years in the control group ($P = .569$; Table 1). Female participants were more common in both groups (67% in the TGA group and 60% in the control group; $P = .549$). Among patients with TGA, 41% had a university degree education; 48% graduated from high school; and 11% had an elementary school level of education.

The clinical presentation of TGA comprised a typical clinical picture in all participants. The amnesia duration ranged from 2 to 15 hours (mean ± SD, 5.9 ± 3.4 hours). The neurologic examination revealed normal findings in all patients. In most of the patients with TGA (97%), increased blood pressure was registered at the beginning of the TGA episode, ranging from 150/90 to 220/120 mm Hg, with a mean value of 165/95 mm Hg. Multiple old lacunar infarcts were detected on MRI scans in 6 of 100 patients with TGA (and 2 of 50 controls), which were localized: frontoparietotemporal bilaterally in 3 patients with TGA, in the region of the basal ganglia in 2, and paraventricular bilaterally in 1.

Table 1 shows demographic characteristics, risk factors, and precipitating factors in both study groups. Most patients with TGA (89%) were previously treated for arterial hypertension, but in 8% of these patients, the high pressure was measured the first time (altogether 97%). The patients with arterial hypertension had an 8 times higher risk of TGA compared to those without arterial hypertension (odds ratio [OR], 8.09; $P < .001$). The Duration of the hypertension diagnosis ranged from 2 to 29 years (mean, 7.7 ± 6.1 years). A longer duration of hypertension was more frequently registered in the TGA group than the control group ($P < 0.01$). Hypertensive changes on the ocular fundi were diagnosed in 76 of 100 patients with TGA compared to the control group (19 of 50), and they were significantly associated with an increased risk of TGA (OR, 2.31;

Table 1. Demographic Characteristics, Risk Factors, and Precipitating Factors in the TGA and Control Groups

Variable	TGA (n = 100)	Control (n = 50)	*P*	OR (95% CI)
Age	61.6 ± 9.4	60.6 ± 10.8	.569	0.99 (0.96–1.02)
Male/female	33/67	20/30	.549	0.81 (0.40–1.62)
Arterial hypertension	89 (89)	25 (50)	.000	8.09 (3.51–18.68)
Duration of arterial hypertension, y	7.7 ± 6.1	4.4 ± 5.8	.003	0.89 (0.83–0.96)
Hypertensive changes on fundi	76 (76)	19 (38)	.019	2.31 (1.15–4.63)
Heart rhythm disorders	15 (15)	6 (12)	.515	1.40 (0.51–3.82)
Ischemic heart diseases	20 (20)	11 (22)	.776	0.89 (0.39–2.03)
Diabetes mellitus	16 (16)	8 (16)	>.999	1.00 (0.40–2.52)
Hyperlipidemia	71 (71)	31 (62)	.267	1.50 (0.73–3.07)
Previous TIA or stroke	17 (17) 11 TIA, 6 stroke	4 (8) 2 TIA, 2 stroke	.040	8.65 (1.11–67.47)
Previous TGA	10 (10)	0 (0)	.044	6.18 (0.79–13.75)
History of migraine	9 (9)	5 (10)	.842	0.89 (0.25–3.27)
Peripheral vein thrombosis	6 (6)	2 (4)	.465	1.53 (0.26–11.45)
Cigarette smoking	26 (26)	15 (30)	.700	0.86 (0.41–1.82)
Alcoholism	4 (4)	3 (6)	.587	0.65 (0.14–3.04)
Emotional stress	35 (35)	11 (22)	.099	1.94 (0.88–4.25)
Valsalva maneuver	39 (39)	5 (10)	.001	5.85 (2.13–16.03)

Data are presented as mean ± SD and number (percent) where applicable. CI indicates confidence interval.

$P < .05$). A documented history of previous TIA or stroke (lacunar type in all cases) was more common in the TGA group than the control group (OR, 8.65; $P = .040$). No statistical difference was detected between study groups with regard to the frequency of arrhythmia or history of ischemic heart disease, diabetes, hyperlipidemia, previous TGA, migraine, peripheral vein thrombosis, cigarette smoking, or alcoholism (Table 1).

With regard to precipitating factors, a previous Valsalva maneuver was strongly associated with a TGA episode (OR, 5.85; $P = .001$); it was the consequence of lifting heavy objects (19 of 39), strain at defecation (17 of 39), and cough with prolonged expectoration (3 of 39). Emotional stress was associated with a TGA episode at the level of a statistical trend ($P = .099$; Table 1). The emotional stress comprised a reaction to receiving unpleasant news (15 of 35), tumultuous interpersonal discussion (9 of 35), fear of imminent medical intervention (7 of 35), and sexual intercourse (4 of 35).

Table 2. Laboratory Parameters in the TGA and Control Groups

Parameter	TGA (n = 100)	Control (n = 50)
Total cholesterol, mmol/L	5.55 ± 1.09	5.80 ± 0.94
High-density lipoprotein, mmol/L	1.25 ± 0.30	1.22 ± 0.24
Low-density lipoprotein, mmol/L	3.83 ± 0.98	3.61 ± 1.05
Triglycerides, mmol/L	1.85 ± 0.72	2.11 ± 1.02
Glucose, mmol/L	5.55 ± 0.99	5.70 ± 0.99
Fibrinogen, g/L	3.60 ± 0.78	3.70 ± 0.93

Data are presented as mean ± SD.

The laboratory analysis performed at admission to the hospital did not reveal any parameter associated with an increased risk of TGA ($P > .050$ for all; Table 2).

There were no significant differences between TGA and control groups in common carotid artery intima-media thickness values, frequency of carotid plaques, or severity of stenosis on the carotid artery examination (Table 3). The plaques in the carotid arteries were fibrocalcified and stable, except that the plaques were lipid and unstable in 3 of 100 patients with TGA and 1 of 50 controls. The mean stenosis rates in the carotid arteries were 28.7% ± 11.7% in the TGA group and 29.3% ± 10.9% in the control group, including 8 patients with diabetic polyneuropathy. The mean systolic velocity in both internal carotid arteries was 73 ± 26 cm/s in the TGA group; it was 37 ± 14 cm/s in both vertebral arteries; and they were within normal age-defined ranges. The logistic regression analysis showed that the presence of an incompetent IJV valve (54% in the TGA group) was significantly associated with an increased risk of TGA (OR, 4.16; $P < .001$; Table 3). No patients with TGA had a diagnosis of peripheral venous thrombosis during a TGA episode, based on clinical and ultrasound examinations.

The mean middle cerebral velocity was 45 ± 10 cm/s, and the basilar artery velocity was 29 ± 8 cm/s in the TGA group (in the range of physiologic values). No intracranial stenosis in blood vessels of the circle of Willis circle was identified in the TGA and control groups. The mean PI values were within the normal range in both the middle cerebral and basilar arteries,

Table 3. Ultrasound Parameters in the TGA and Control Groups

Parameter	TGA (n = 100)	Control (n = 50)	*P*	OR (95% CI)
Right CCA IMT, mm	0.997 ± 0.247	0.986 ± 0.197	.300	0.41 (0.08–2.21)
Left CCA IMT, mm	1.029 ± 0.241	0.990 ± 0.182	.141	0.26 (0.04–1.57)
Plaques on CCA	51 (51)	30 (60)	.384	0.73 (0.36–1.48)
ICA stenosis, %	28.7 ± 11.7	29.3 ± 10.9	.772	1.07 (0.96–1.05)
IJV incompetence	54 (54; 29 B, 25 U)	11 (22; 4 B, 7 U)	<.001	4.16 (1.91–9.04)
Right MCA PI	0.85 ± 0.28	0.83 ± 0.16	.232	2.03 (0.64–6.47)
Left MCA PI	0.85 ± 0.28	0.83 ± 0.17	.595	1.34 (0.45–4.01)
BA PI	0.95 ± 0.27	0.91 ± 0.21	.075	2.57 (0.91–7.26)
Right MCA BHI	1.28 ± 0.43	1.31 ± 0.37	.290	1.45 (0.73–2.89)
Left MCA BHI	1.26 ± 0.38	1.35 ± 0.36	.162	1.63 (0.82–3.24)
Microembolic symbol+	13 (13; 7 B, 6 U)	5 (10; 2 B, 3 U)	.201	2.34 (0.63–8.63)
Bubble test+	16 (16; 7 C, 9 P)	9 (18; 2 C, 7 P)	.965	0.98 (0.40–2.39)
TEE	2 PFO, 4 ASA, 2 MVP	1 PFO, 1 ASA, 1 MVP	.469	1.36 (0.31–6.83)

Data are presented as mean ± SD and number (percent) where applicable. ASA indicates atrial septal aneurysm; B, bilateral; BA, basilar artery; BHI, breath-holding index; C, cardial; CCA, common carotid artery; CI, confidence interval; ICA, internal carotid artery; IMT, intima-media thickness; MCA, middle cerebral artery; MVP, mitral valve prolapse; P, pulmonal; PFO, patent foramen ovale; and U, unilateral.

and no significant differences were detected between study groups (Table 3). The mean breath-holding index values were within the normal range in both groups, and no difference was detected between the groups (Table 3).

A small number of patients in both groups had microembolic signals, with no statistically significant difference between the groups (Table 3). Also, no differences were registered with regard to the number of patients with positive bubble test results or pathologic TEE results between groups (Table 3).

Discussion

We report a group of patients with TGA who underwent detailed a neurosonologic examination comprising extracranial and cranial vessel assessments. In our study, patients with TGA were older, as reported in the literature: typically between 50 and 70 years.[2,15] Women had TGA more frequently, which was reported by other authors as well.[16,17] It was observed that our patients with had higher education mostly, which corresponds to a high level of previous well-informed treatment of vascular risk factors. There were rare references in the literature about the professions of patients with TGA, but there are data on an obsessive-meticulous personality structure, emotional hypersensitivity, and the importance of psychophysical stress for the occurrence of TGA.[15,17,18] We found that emotional stress as a precipitating factor increased the risk of TGA, although at the level of a statistical trend only. It is likely that emotional stress is associated with an acute rise of blood pressure, precipitating a TGA episode. We found a significant proportion of patients with TGA in whom procedures with the Valsalva maneuver immediately preceded the onset of TGA. The recurrence of TGA was rare, and the literature cited data between 6% and 10%, which is in accordance with the data in our study (10%).[2]

During the episode of TGA, 97% of patients had acutely increased blood pressure. The presence of other risk factors was significantly less frequent or controlled well by medications. In some studies, analogous results were encountered in relation to vascular risk factors.[18,19] In the same context, there were studies that compared the vascular risk factors in TGA and TIA; the most common risk factors were arterial hypertension and hyperlipidemia, but they were found considerably less often in TGA in comparison with TIA.[20] On the other hand, some authors listed very rare occurrences of vascular risk factors in patients with TGA, arguing even that the mechanism of ischemic TGA should be rejected.[17,21] There is also evidence that compared with patients with migraine or TIA, those with TGA do not seem to face a heightened risk of stroke.[22]

The signs of atherosclerosis were not particularly prominent in the large arteries of the neck and brain in our patients with TGA. Approximately half of the patients with TGA did not have atheromatous plaques in the carotid arteries, whereas the other half had only mild to moderate carotid atherosclerosis. No significant difference was detected with regard to the common carotid artery intima-media thickness between patients with TGA and control participants, which was consistent with previously reported results.[23–25] Also, in accordance with other reports, no significant difference between study groups was registered with regard to the velocities of the main neck and cerebral arteries of the circle of Willis, which were within the physiologic range.[24,25]

The rare occurrence of microembolic signals in the patients with TGA in our study indicated that embolism had no essential role in the development of TGA. Although the detection of microembolic signals in patients with TGA has rarely been the subject of research by other authors, one recent study showed no significant occurrence of microembolic signals in patients with TGA as well.[24] In our study, the same was related to transcranial color Doppler detection of a right-to-left cardiac or pulmonary shunt, thus excluding the importance of paradoxical embolism in the pathogenesis of TGA, which could be precipitated by a frequently reported Valsalva maneuver. Some previous investigations have shown a significantly higher incidence of a patent foramen ovale in patients with TGA, such as 55% in TGA compared to 27% in controls in a study by Klötzsch et al,[27] supporting the role of paradoxical embolism of terminal branches of the basilar artery in the development of TGA.[28,29] Recent investigations indicated no significant difference in the incidence of a patent foramen ovale in patients with TGA in relation to controls, as in our study; a patent foramen ovale was actually significantly less frequent in patients with TGA than those with TIA.[20,30]

In this examination, normal breath-holding index values in most of the patients with TGA excluded impairment of vasomotor reactivity of cerebral vessels and confirmed patency of large and small brain arteries.

Maybe the results would have been different if the breath-holding index had been determined at the beginning of TGA episodes, while blood pressure was elevated. In the literature, cerebral small blood vessel disease has been associated with TGA, although with no clear estimate of its importance.[15,31] However, there was evidence that the small lesions in the hippocampus of patients with TGA were probably microvascular lesions, since the nature of changes on diffusion-weighted MRI, single-photon emission CT, and positron emission tomography has shown the evolution that corresponded to vascular lesions.[15,32–34]

Numerous studies of venous ultrasound and MRI examinations have shown the significant frequency of IJV valve failure in patients with TGA: from 50% to 85%, both bilaterally or unilaterally.[8,16,35,36] Our previously published pilot study also indicated that 55% of patients with TGA had IJV valve incompetence.[37] The results of this study, with double the number of patients with TGA, confirmed that more than half (54%) had IJV valve incompetence, which was significantly more than the control group ($P < .01$). Retrograde venous flow through the IJV causes congestion of the venous sinuses, Rosenthal basilar vein, and veins in the mesial part of the temporal lobe and hippocampus, structures that are relevant for memory processes.[15,35,36] Venous congestion might have led to the occurrence of small venous thrombosis in the mesial part of the temporal lobe, particularly the hippocampus, resulting in TGA.[16,38] The problem with this interpretation is that the chronic venous incompetence of the IJV valve should lead to more frequent recurrences of TGA, but it was known that the TGA relapsed rarely.[39] Recent research also did not find evidence of intracranial IJV reflux on time-of-flight MR angiography.[26,40]

In recent years, the use of diffusion-weighted MRI and MR spectroscopy revealed metabolic disturbances in vulnerable neurons of the hippocampus, particularly in the CA1 region of the cornu amonis.[2] These disorders were shown as small round hyperintensities (1–3 mm) on diffusion-weighted MRI, the largest occurring between 48 and 72 hours from the onset of TGA and then gradually withdrawing; after 30 days, these changes were no longer detectable.[2,41] Diffusion-weighted MRI showed restricted diffusion in these changes, whereas MRI spectroscopy revealed an increased amount of sodium aspartate as a sign of anaerobic glycolysis. These findings indicated acute and short-term metabolic stress in the CA1 region.[2,3,42] We did not find typical MRI lesions in the temporal lobe, just old lacunar lesions of different distributions. In this study, we did not have the purpose or the ability to follow the evolution of MRI changes. Our patients had MRI from 2 to 4 weeks after the start of TGA episodes.

Can the results of our study be linked with modern knowledge about TGA? Based on the results of our comprehensive clinical and ultrasound research, the strongest connection with TGA in our data set of patients was the presence of incompetent IJV valves (as a possible basis for venous stasis in the veins and venules of the brain) and the sudden increase of blood pressure during a TGA attack (as a cause of acute vasospasm of the cerebral arteries and arterioles).

In conclusion, our ultrasound examination did not detect significant structural changes in the main arteries of the neck, the large arteries of the brain, or the small arteries of the brain. An embolic mechanism was excluded. The patients with TGA did not have the typical risk factors for cerebrovascular disease, or they were controlled well by medication. The only exception was that the patients had a jump in blood pressure during TGA attacks in the setting of IJV valve incompetency. New research should clarify whether these simultaneous functional circulatory changes have relevance for metabolic stress in the cornu ammonis of the hippocampus, especially during the early hours of a TGA attack.

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