Vascular Risk Factors and Internal Jugular Venous Flow in Transient Global Amnesia: A Study of 165 Japanese Patients

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Background: The etiology of transient global amnesia (TGA) remains unclear. We studied the pathophysiology of TGA in 165 Japanese patients. *Subjects and Methods:* TGA was diagnosed in hospitalized patients from 2004 to 2015. We analyzed clinical characteristics, magnetic resonance imaging findings, and maximum intima-media thickness of the common carotid artery, and the reflux of internal jugular venous (IJV) flow by ultrasonography, and statistically compared patients with TGA with age-matched and sex-matched patients who have had a transient ischemic attack (TIA), small-vessel occlusion (SVO), and normal controls (each group, N = 165). *Results:* Patients with TGA showed lower prevalence of vascular risk factors than patients with TIA and SVO did. Eleven patients (6.7%) had 2 episodes of TAG, but specific clinical variables could not be recognized in these patients. The maximum intima-media thickness was significantly thinner in TGA (1.1 ± .7 mm) than in SVO (1.6 ± .9 mm; $P = .001$). The percentages of cases whose IJV flow reflux was increased by Valsalva maneuver showed no difference ($P = .573$) between TGA (26.0 %) and SVO (29.4%). MR diffusion-weighted imaging yielded small hyperintense signals in the hippocampus in 64 of 90 (71.1%) patients between 24 and 72 hours. Potential precipitating specific factors or events before the attacks could be recognized in 40 cases (24.2%) of 165 patients. *Conclusion:* Arterial ischemia and IJV flow reflux might not contribute to TGA pathophysiology. The vulnerability of the hippocampus to physical or emotional stress might be suspected as an underlying mechanism in some patients with TGA. **Key Words:** Transient global amnesia—vascular risk factor—internal jugular venous flow—MRI—precipitating specific events.

Introduction

Transient global amnesia (TGA) is a clinical syndrome of anterograde amnesia that is reversible within 24 hours, accompanied by repetitive questioning. There should be no focal neurologic symptoms during the attack and no significant neurologic deficits after the attack. The prognosis is generally benign. There has been no consensus yet regarding the underlying cause of TGA.[1-4] Hypotheses include an arterial or venous vascular etiology, including hypotension, vasospasm, and paradoxical embolism, a migrainous phenomenon, epilepsy, and a psychogenic disorder. None of these hypotheses consistently explains

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Received April 5, 2017; revision received May 3, 2017; accepted May 7, 2017.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.05.010

the clinical features of TGA. Atherosclerotic risk factors are not believed to be associated with TGA. Most case-control studies find no difference in the prevalence of these risk factors between patients with TGA and age-matched and sex-matched controls.[2-9] In contrast, 1 large case-control study reported, in 2014, patients with TGA were more likely than age-matched and sex-matched controls to have hyperlipidemia, previous ischemic stroke, and ischemic heart disease. Compared with a cohort of patients with transient ischemic attack (TIA) admitted during the same time period, patients with TGA were less likely to have hypertension, diabetes mellitus (DM), a history of ischemic stroke, and atrial fibrillation.[10]

Punctate areas of signal abnormality on diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) in the hippocampus are often identified in patients with TGA.[11] These lesions are associated with small reductions in the apparent diffusion coefficient values and may be located in the unilateral or bilateral hippocampi. These lesions are less common in the hyperacute phase and become more prevalent after 12 hours, with a peak incidence between 12 and 72 hours.[12-14] These unique findings are valuable to the diagnosis of TGA. Recently, venous congestion was proposed as an alternative pathogenesis for TGA. Specific events appeared as frequent triggers for TGA, including Valsalva maneuver, vigorous activity of the arms, sympathetic activation from acute emotional events, and cold-water immersion.[15] Increases in intrathoracic pressure or venous return could lead to central venous congestion affecting the deep venous system that drains the hippocampus.[15] Venous congestion better explains the appearance of the DWI-MRI lesions, particularly the time course and reversibility of the lesions. Several studies with Doppler ultrasound reported venous reflux in internal jugular vein (IJV) valve incompetence at high prevalence in patients with TGA compared with controls.[13,15-19] However, other Doppler ultrasound and MR angiography (MRA) studies have not found evidence of intracranial venous reflux in patients with TGA compared with controls, despite the high prevalence of IJV valve incompetence in these patients.[19-21] The aims of this study are to evaluate the vascular risk factors, MRI findings, and Doppler ultrasound findings for venous reflux in the IJV in 165 Japanese patients with TGA.

Subjects and Methods

Subjects

We retrospectively studied the clinical characteristics, laboratory and radiological image findings, causative disorders, and risk factors of 165 hospitalized patients with TGA from April 2004 to December 2015. The diagnosis of TGA was based on the diagnostic criteria[22,23]: anterograde amnesia witnessed by an observer with resolution of symptoms within 24 hours, cognitive impairment limited to amnesia with no clouding of consciousness or loss of personal identity, and no focal neurological or epileptic signs, or recent history of head trauma, or seizures. TIA was diagnosed as having a focal neurologic syndrome that was attributable to vascular etiology lasting less than 24 hours,[24] and small-vessel occlusion (SVO) was diagnosed on the basis of the Trial of Org 10172 in Acute Stroke Treatment criteria.[25] The control group was composed of the healthy individuals who visited the hospital as outpatients for a checkup.

Clinical Characteristics

Baseline clinical characteristics included age, sex, classical vascular risk factors including hypertension, DM, dyslipidemia, and smoking habit, and history of ischemic heart disease and ischemic stroke. Laboratory findings included total cholesterol, low-density lipoprotein-cholesterol (LDL-cholesterol), high-density lipoprotein-cholesterol (HDL-cholesterol), triglycerides, and hemoglobin A1c (HbA1c). At the onset of TGA, moreover, the precipitating specific factors for TGA, including physical exertion, emotional stress, contact with cold water, and other Valsalva-like activities (e.g., gastroscopy, dental procedure, vomiting, defecation, singing, and others), were evaluated.

MRI and MRA

The intracerebral lesions were analyzed by conventional imaging, including DWI and fluid-attenuated inversion recovery imaging on a 1.5T MRI. All patients with TGA had undergone MRI and MRA, which were taken on admission and at 24-48 hours after the onset of symptoms. MRI combined with MR venography was performed in some cases.

Ultrasonography

Maximum intima-media thickness (max-IMT) of the common carotid artery was measured by ultrasonography using the LOGIQE9, GE Yokogawa Medical (Hino, Japan). Fifty patients with TGA were compared with 100 age-matched and sex-matched patients with SVO.

IJV flow was assessed by Doppler sonography (5 MHz). IJV ultrasonography was performed in 50 patients with TGA and 34 patients with SVO. IJV was monitored during a pressure-controlled Valsalva maneuver, and visualized on Doppler sonography as a circumscribed retrograde flow jet. Valve closure was induced with a controlled Valsalva maneuver, which was performed by blowing into a disposable syringe attached to a manometer. The measurements were obtained twice on both jugular veins during rest, a moderate Valsalva maneuver (70 mm Hg) for 10 seconds, and a maximum Valsalva maneuver for 4 seconds.[26] The retrograde flow component area was analyzed with a computerized image analysis system, and