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Right-to-left shunts may be not uncommon cause of TIA in Japan

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ABSTRACT

Background and purpose: Although 30% to 60% of transient ischemic attacks (TIAs) have embolic sources, the etiology of the remaining TIAs is unknown. Right-to-left shunt (RLS) is one of the most important etiologies of cryptogenic stroke. The aim of this study was to determine whether RLS is related to transient ischemic attack (TIA) of unknown etiology.
Methods: We performed transesophageal echocardiography (TEE) and/or transcranial Doppler (TCD) studies for consecutive TIA patients in order to detect RLS from April 2004 to December 2006. TIA patients were divided into three groups, as follows: 1) Cardioembolic TIA, with a patent cardioembolic source, 2) thrombotic TIA, with an atherothrombotic and/or lacunar mechanism, and 3) undetermined TIA, without identified cause of TIA. We compared the characteristics and presence of RLS among these three groups.
Results: We enrolled 124 TIA patients (age: 67±13 years old, 80 men). There were 13 patients with Cardioembolic TIA, 25 with Thrombotic TIA, and 86 with Undetermined TIA. TEE and/or TCD were able to detect RLS in 61 of the 124 (49%) patients. RLS was frequent in patients with Undetermined TIA compared with those in the other TIA groups (60% in the Undetermined TIA group, 28% in the Thrombotic TIA group, and 15% in the Cardioembolic TIA group; $p<0.001$). Smoking and previous history of TIA were frequent in the Thrombotic TIA group ($p=0.030$ and $p=0.016$, respectively).
Conclusion: RLS may play an important role in the etiology of TIA of undetermined cause.

1. Introduction

Transient ischemic attack (TIA) is associated with the risk of early stroke, death, and disability [1]. Indeed, the appropriate strategy of treatment of patients with TIA is needed to prevent subsequent cerebral infarction [2,3]. Although 30–64% of cases of TIA have apparent embolic sources, such as carotid arterial disease or cardiac disease,[4,5] there are many patients with TIA of unknown etiology [6].

Paradoxical embolism is associated with cryptogenic stroke and may be a cause of stroke in a large number of patients [7]. We suspect that patients with TIA of unknown or undetermined causes frequently have right-to-left shunt (RLS). The aim of this study was to determine the frequency of RLS in consecutive TIA patients, and to investigate whether TIA of undetermined cause is related to RLS.

2. Methods

From April 2004 to December 2006, we enrolled consecutive patients with TIA who were admitted to our hospital within 14 days of onset. TIA was defined as a sudden onset of a focal neurological deficit or amaurosis fugax, suspected to be of cerebrovascular origin, lasting less than 24 h. We excluded patients who did not consent to transesophageal echocardiography (TEE) or transcranial Doppler sonography (TCD).

On admission, information on the symptoms and duration of TIA were obtained from patients or their families. We also obtained the following information about patient history and medication: 1) gender and age; 2) vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking); 3) potential cardiac sources of emboli; 4) arterial lesions (occlusive lesions of the carotid or vertebrobasilar artery able to cause neurological symptoms); and 5) previous illnesses (TIA, cerebral infarction, and ischemic heart disease). Vascular risk factors were identified as follows: 1) hypertension, use of antihypertensive agents, or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; 2) diabetes mellitus, use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin ≥6.4%; 3) hyperlipidemia, use of antihyperlipidemic agents, or serum cholesterol level >220 mg/dL; and 4) smoking or any lifetime experience with cigarette use.

All patients were examined by 12-lead ECG, 24-hour ECG Holter monitoring, and transthoracic echocardiography to detect potential cardiac sources of emboli, which included atrial fibrillation, dilated cardiomyopathy, acute myocardial infarction, intraventricular thrombus, mitral valve disease, prosthetic cardiac valves, and atrial septal

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defect. We performed carotid duplex sonography for all patients to evaluate significant arterial lesions in the ipsilateral carotid system.

Brain magnetic resonance (MR) studies including diffusion-weighted imaging (DWI) and MR angiography were performed for all patients to investigate cerebral and cerebral arterial lesions. TCD and TEE were performed to test for the presence of RLS. Evaluation of extra- and intracranial vascular lesions was performed by carotid duplex sonography, MR angiography, CT angiography, and/or digital subtraction angiography. Diagnosis of deep venous thrombosis (DVT) and pulmonary embolism was performed using duplex sonography, scintigraphy, and/or contrast CT. Laboratory studies, including complete blood cell count, blood biochemistry, and coagulation system tests, were performed. In this study, the interpretations of all studies were blinded to the patient's clinical status. Patients and their families gave written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki.

2.1. MR imaging

MR imaging studies were performed using a commercially available echo planar instrument on a 1.5-T MR unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI). The neuroimaging protocol for acute stroke in our hospital included a fluid-attenuation inversion recovery (FLAIR) sequence (repetition time [TR]/echo time [TE], 8002 ms/109 ms; TI, 2000 ms; field-of-view, 24 cm; acquisition matrix, 256×224; and section thickness, 6.0 mm with a 1.0 mm intersection gap), diffusion-weighted trace sequence (TR/TE, 8000 ms/78 ms; *b* values, 0 and 1000 s/mm^2; field-of-view, 24 cm; acquisition matrix, 128×192 matrix; and 6.0 mm with a 1.0 mm intersection gap), and time-of flight MR angiography covering the circle of Willis (TR/TE, 28 ms/6.9 ms; 20° flip angle). The acquisition time for all DWI examinations was <1 min. MRI findings were reviewed by experienced radiologist blinded to clinical status.

2.2. TCD study

Bilateral middle cerebral arteries were insonated from the temporal window at a depth of 50–55 mm using a 2 MHz handheld transducer (MultiDop T; DWL, Lindau, Germany/Pioneer TC 8080; Nicolet Vascular, Madison, WI) when both middle cerebral arteries were detectable. When we could not detect middle cerebral artery flow from the temporal window, we detected it in the siphon of the internal carotid artery through transorbital access. A contrast study was performed to detect RLS. Contrast material was prepared by agitating 9 mL saline and 1 mL air with two syringes over a 3-way stopcock. The agitated saline was rapidly injected into a right antecubital vein during provocative maneuvers (Valsalva maneuver and coughing). Bolus injection was repeated 3 times. Doppler audio signals on TCD examination were recorded onto digital audiotape and/or hard disc. Microembolic signals were identified by typical visual appearance on the spectral display and characteristic sounds, according to standard consensus criteria [8]. We validated suspected microembolic signals by "off-line" assessment without patient's clinical information.

2.3. TEE study

We performed TEE using an ultrasound unit (HDI-5000; Philips Medical System, Bothell, WA) with a 4 to 7 MHz wideband multiplane transducer for transesophageal imaging. TEE was performed in awake patients using lidocaine gel for local pharyngeal anesthesia. TEE studies included imaging of all valves and cardiac chambers. Gain settings were adjusted to distinguish background noise and spontaneous echocardiographic contrast. We circumferentially assessed the left atrial cavity and left atrial appendage to locate fixed or mobile echo-dense masses that could be clearly differentiated from the cardiac wall. A contrast study was performed to detect patent foramen ovale (PFO). PFO was diagnosed when at least 3 microbubbles were identified in the left atrium within 3 cardiac cycles from the right atrium [9]. Atrial septal aneurysm was diagnosed when the atrial septum protruded into the left or right atrium or both for at least 15 mm. We observed all segments of the thoracic aorta, including the descending aorta, aortic arch, and ascending aorta, to detect aortic plaque. Complicated aortic lesions were defined as those having increased intimal thickness for at least 4 mm in the ascending aorta or the arch of the aorta. The examinations were recorded on super VHS

Table 1
Clinical backgrounds of TIA patients

Variables	Cardioembolic TIA group *n*=13		Thrombotic TIA group *n*=25		Undetermined TIA group *n*=86		*P*
Age, y, mean (SD)	69	(13)	63	(13)	68	(12)	0.071
Male, *n* (%)	9	(69)	20	(80)	51	(59)	0.155
Duration of symptom, min, mean (SD)	508	(617)	152	(323)	204	(373)	0.063
Vascular risk factors, *n* (%)							
Hypertension	8	(62)	19	(76)	51	(59)	0.316
Diabetes Mellitus	2	(15)	10	(40)	19	(22)	0.136
Hyperlipidemia	4	(31)	16	(64)	39	(45)	0.116
Smoking	6	(46)	18	(72)	36	(42)	0.030
Past history, *n* (%)							
TIA	0	(0)	7	(28)	8	(9)	0.016
Stroke	1	(8)	2	(8)	12	(14)	0.813
Ischemic heart disease	1	(8)	4	(16)	7	(8)	0.491
Atrial fibrillation, *n* (%)	10	(77)	0	(0)	2	(2)	<0.001
Arterial lesion[a], *n* (%)	0	(0)	16	(64)	5	(6)	<0.001
Right-to-left shunt, *n* (%)	2	(15)	7	(28)	52	(60)	<0.001
Atrial septal aneurysm[b], *n* (%)	1/12	(8)	1/19	(5)	11/72	(15)	0.454
Aortic complicated lesion[b], *n* (%)	3/12	(25)	8/19	(42)	24/72	(33)	0.608
Ischemic lesion on DWI, *n* (%)	3	(23)	15	(60)	14	(16)	<0.001
Deep venous thrombosis[c], *n* (%)	1/7	(14)	0/10	(0)	5/58	(9)	0.533
D-dimer, μg/dl, mean (SD)	1.2	(1.1)	1.0	(1.3)	1.5	(5.2)	0.736

SD, standard deviation; TIA, transient ischemic attack; DWI, diffusion-weighted image.

[a] "Arterial lesion" is the occlusive lesion of carotid or vertebrobasilar artery which is able to cause the neurological symptom.

[b] TEEs were performed in 12 patients of Cardioembolic TIA, 19 of Thrombotic TIA and 72 of Undetermined TIA.

[c] In order to detect the deep venous thrombosis, duplex sonography, scintigraphy, and/or contrast CT were studied in 7 patients of Cardioembolic TIA, 10 of Thrombotic TIA and 58 of Undetermined TIA.