in the emergency department. If they have been performed and the findings are negative, up to 7 days might be appropriate. Patients with a TIA within the past 2 weeks but who were not hospitalized, should undergo prompt (within 24–48 h) assessments by means of carotid Doppler ultrasonography for TIA consistent with carotid territory, blood work and cardiac evaluation using ECG, rhythm strip, and echocardiography to determine the mechanism of ischemia and subsequent preventive therapy.

Hospital Admission

Ideally, all patients with suspected TIA should be immediately hospitalized to ensure rapid diagnostic evaluation and acute stroke therapies. However, admitting all patients with suspected TIA would probably be problematic, as hospital resources (staff and beds) would become insufficient and costs would soar. Neither 100% hospitalization nor 100% outpatient evaluation of patients with TIA is ideal. For acute hospitalization after suspected TIA, risk stratification in the emergency room might help triage patients (high risk) for hospitalization and outpatient (low risk) management [30]. The $ABCD^2$ score can function in this role. In addition, the presence of ischemic lesions on DWI and an apparent TIA etiology, such as large artery atherosclerosis and AF, could improve stroke risk predictions after TIA.

The NSA evidence-based guidelines for TIA management [10] state that hospitalization should be considered for patients with a first TIA within the past 24–48 h to facilitate the possible early deployment of lytic therapy and other medical management strategies if symptoms recur and to expedite the institution of definitive secondary prevention. Additionally, timely hospital referral for a recent TIA (within one week) is always advisable, and hospital admission is generally recommended in the case of crescendo TIAs or duration of symptoms for more than 1 h, symptomatic internal carotid artery stenosis >50% in diameter, a known cardiac source of embolus such as AF, a known hypercoagulable state, or an appropriate combination of the California or ABCD scores.

The scientific statement of AHA/ASA [1] recommends admitting patients with TIA to hospital if they present within 72 h of the event and if any of the following criteria are present: $ABCD^2$ score of ≥3, $ABCD^2$ score 0–2 and uncertainty that diagnostic workup can be completed within 2 days as an outpatient, or $ABCD^2$ score 0–2 and other evidence indicating that focal ischemia caused the event.

The Clinical Guidelines for Acute Stroke Management published by the National Stroke Foundation [16] describe that all patients with suspected TIA presenting to a general practitioner or emergency department should be rapidly assessed. Those identified as high risk ($ABCD^2$ score ≥4 and/or those with any of AF, carotid territory symptoms or crescendo TIA) should be admitted to a stroke unit (or where available, referred to a specialist TIA clinic if they can be assessed within 24 h) to facilitate rapid specialist assessment and management. Those identified as low risk ($ABCD^2$ score <4

and without AF or carotid territory symptoms or crescendo TIA) should start initial therapy (e.g. aspirin) and then be managed in the community setting by a general practitioner or private specialist or, where possible, be referred to a specialist TIA clinic and seen within 7 days (fig. 1c).

Treatment

All patients with TIA are at risk of subsequent stroke and cardiovascular events including myocardial infarction and death. Several interventions that have proven effective in preventing these events are covered by international guidelines and include anticoagulation for cardioembolic TIA, antiplatelet therapy for non-cardioembolic TIA, CEA for >50% symptomatic carotid stenosis, blood pressure (BP)-lowering drugs, statins, improved glycemic control, dietary modification, exercise and smoking cessation [12]. Patients with suspected TIA should be evaluated to determine etiology and be treated to prevent subsequent stroke as soon as possible after TIA onset.

Antiplatelet Therapy

The NICE [14] and Stroke Foundation of New Zealand [12] guidelines recommended starting antiplatelet therapy immediately for all individuals with suspected TIA until brain imaging results are available. Primary intracerebral hemorrhage (ICH) is a rare cause of TIA, and 99% of strokes after TIA are due to cerebral infarction, and no clear evidence indicates that the inadvertent administration of aspirin to patients with ICH before imaging is harmful [12]. Japanese guidelines recommend administering 160–300 mg/day of aspirin for patients with acute TIA (within 48 h) [13]. Daily long-term antiplatelet therapy should be prescribed immediately for the secondary prevention of stroke and other vascular events in patients with non-cardioembolic TIA. Aspirin monotherapy (50–325 mg/day), aspirin (25 mg) combined with extended-release dipyridamole (200 mg) twice daily, and monotherapy with clopidogrel (75 mg) are all acceptable options for initial therapy [10, 20–22]. In addition, cilostazol (200 mg/day) is recommended by the American College of Chest Physicians Evidence-based Clinical Practice Guidelines [22]. Antiplatelet agents that can be applied in Japan comprise aspirin (75–150 mg/day), clopidogrel (75 mg), cilostazol (200 mg/day) and ticlopidine (200 mg/day) [13]. Combining aspirin with clopidogrel increases risk of hemorrhage and is not recommended for long-term secondary prevention after TIA [16, 20, 21].

Anticoagulation Therapy

Long-term oral anticoagulation with a target international normalized ratio (INR) of 2.5 (range, 2.0–3.0) is recommended for patients with TIA and emboligenic cardiac diseases such as persistent or paroxysmal valvular or nonvalvular AF [10, 12, 16, 20–23]. The Japanese guidelines recommend a target INR range of 2.0–3.0 for patients

aged <70 years of age and 1.6–2.6 in those aged ≥70 years [13]. The American College of Chest Physicians Evidence-based Clinical Practice Guidelines [22] recommend oral anticoagulation therapy with dabigatran (150 mg b.i.d.) over adjusted-dose vitamin K antagonist therapy for patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF. The AHA/ASA Science Advisory for oral antithrombotic agents for the prevention of stroke in nonvalvular AF recommends warfarin, dabigatran, apixaban, and rivaroxaban to prevent a first and recurrent stroke in patients with nonvalvular AF [23]. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions and other clinical characteristics, including time in the INR therapeutic range if the patient has been treated with warfarin [23]. An update of the 2010 ESC guidelines for the management of AF recommends that novel oral anticoagulant drugs, including dabigatran, apixaban, and rivaroxaban, should be considered instead of adjusted-dose vitamin K antagonist [24].

Carotid Revascularization

CEA is recommended for patients with recent TIA and ipsilateral severe carotid artery stenosis (70–99%). For patients with recent TIA and ipsilateral moderate carotid stenosis (50–69%), CEA is recommended depending on patient-specific factors such as age, sex, and comorbidities. When the degree of stenosis is <50%, there is no indication for CEA. Carotid artery stenting is indicated in patients at a high risk of CEA, such as those with coronary artery disease [10, 12, 13, 16, 20, 21]. In patients with symptomatic internal carotid artery stenosis for whom CEA is a reasonable option, surgery should be performed as soon as the patient is fit for the procedure, preferably within 2 weeks of TIA (cerebral or retinal) [10, 14, 16, 20].

Treatment to Reduce the Cardiovascular Risk

All individuals with a history of TIA should be considered for treatment to reduce cardiovascular risk, and risk factors for recurrent cerebrovascular ischemic events should be appropriately treated. This includes lowering BP and blood cholesterol (with lifestyle modifications and/or drug therapy) for all patients with atherothrombotic TIA, regardless of baseline BP and cholesterol values [10]. The New Zealand guidelines recommend assessing every individual with TIA and informing them of their risk factors for stroke and adverse cardiovascular events, and of possible strategies to modify identified risk factors [12].

Blood Pressure Lowering

Reducing BP is recommended to prevent both recurrent stroke and other vascular events from arising in persons who have had an ischemic stroke or TIA and are beyond the first 24 h [20]. The absolute target BP is uncertain but a benefit has been associated with an average reduction of about 10/5 mm Hg, and normal BP levels have been defined as <120/80 mm Hg [20, 21]. After TIA that is not due to dissection or

cardiogenic embolism, BP should be reduced to <140/90 or <130/80 mm Hg for diabetics, regardless of the initial level, unless the patient has symptomatic hypotension. An angiotensin-converting enzyme inhibitor alone or in combination with a diuretic, or with an angiotensin receptor blocker is useful [10, 20].

Cholesterol Lowering

Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level of >100 mg/dl, and who are without known coronary heart disease [20].

Diabetes Management

Fasting blood glucose levels of <126 mg/dl (7 mmol/l) are recommended. Diet, exercise at least three times a week and oral hypoglycemic agents or insulin should be prescribed as needed to control diabetes for the long-term secondary prevention of stroke [9]. Diabetes should be managed with lifestyle modification and individualized pharmacological therapy [21].

Behavioral Changes

Cessation of smoking, maintaining an appropriate body weight, and enforced exercise are recommended to reduce the risk of recurrent TIA or stroke [10, 12–16, 20].

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Features of Patients with Transient Monocular Blindness: A Multicenter Retrospective Study in Japan

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Background: Transient monocular blindness (TMB) is associated with a transient ischemic attack (TIA). The purpose of this study was to investigate the features of TMB in the Japanese population using data from a multicenter retrospective study of TIA. *Methods:* The subjects were consecutive TIA patients admitted to 13 stroke centers within 7 days after symptom onset. We compared clinical characteristics of patients with TMB and those without TMB who had other symptoms of cerebral TIA. *Results:* A total of 464 patients were registered between January 2008 and December 2009, and 444 patients (283 men, mean age: 68.5 years) were included in the analysis. Thirteen patients (2.9%) presented with TMB. Patients with TMB were less likely to arrive at the specialized stroke center quickly than those without TMB ($P = .013$). Stenotic lesions in the extracranial internal carotid artery were more common in patients with TMB (33.3% versus 9.1%, $P = .022$). *Conclusions:* TMB was not common in our TIA inpatients. This study suggests that patients with TMB should immediately undergo a diagnostic workup, including brain and vessel imaging, and cardiac evaluation, as is performed in patients with other cerebral TIA symptoms. A larger, prospective cohort is needed to confirm the risks and outcomes of patients with TMB in the Japanese population. **Key Words:** Transient ischemic attack—amaurosis fugax—transient monocular blindness—atrial fibrillation—carotid artery disease—diffusion-weighted imaging.

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Introduction

Amaurosis fugax, also known as transient monocular blindness (TMB),[1,2] is a short-term visual loss in one eye, attributed to retinal ischemia or vascular insufficiency. TMB is commonly caused by ipsilateral carotid artery stenosis and is a well-known risk factor for early ischemic stroke or retinal ischemia in a transient ischemic attack (TIA). Although TMB is thought to be less frequent in the Japanese population than in Western populations,[3,4] limited data exist regarding its frequency and clinical features. Therefore, in the present study, we aimed to clarify the frequency and clinical features of TMB using data from a multicenter retrospective study of TIA in Japan.

Materials and Methods

This study was a retrospective, observational, multicenter study, and the methods were described in detail elsewhere.[5] In brief, we enrolled all consecutive patients with TIA admitted to 13 stroke centers in Japan within 7 days after symptom onset between January 2008 and December 2009. In accordance with the Classification of Cerebrovascular Diseases III from the National Institute of Neurological Disorders and Stroke,[6] a diagnosis of TIA was made if focal neurologic symptoms with a vascular etiology lasted less than 24 hours, irrespective of the presence of ischemic insults observed on imaging. A diagnosis of TMB was made if patients had transient "visual loss in one eye" as the first symptom. An independent attending physician made the decisions regarding hospitalization and patient management. Each local ethics committee approved the retrospective collection and submission of patient's clinical data to the study office in the National Cerebral and Cardiovascular Center.

The patients' baseline characteristics, including sex, age, history of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation (AF), and premorbid antiplatelet and anticoagulation therapies, were collected from medical records. Data on ambulance use, clinical symptoms of TIA, and time from onset to hospital arrival were also obtained. Arrival time from onset was classified into 5 categories: less than 3 hours, 3-6 hours, 6-12 hours, 12-24 hours, or 24 hours or more. We examined clinical outcome, duration of hospitalization, and development of cerebral infarction or recurrence of TIA during hospitalization. For outcomes, we investigated TIA or TMB and cerebral infarction together as ischemic stroke.

Acute ischemic lesions were evaluated at admission by diffusion-weighted imaging (DWI) on a 1.5-T magnetic resonance imaging scanner. Hyperintense DWI lesions were defined as the presence of at least 1 lesion consistent with acute cerebral ischemia but not necessarily responsible for the TIA symptoms. Stenotic lesions in the extracranial internal carotid artery (ICA) were assessed by carotid duplex ultrasonography, computed tomographic angiography, magnetic resonance angiography, or cerebral digital subtraction angiography. Significant stenotic lesions were defined as more than 50% stenosis observed using the North American Symptomatic Carotid Endarterectomy Trial method.[7,8] When the degree of stenosis was estimated only by area reduction with carotid ultrasonography, more than 75% reduction in artery area was applied as a significant stenosis.

Subjects were stratified into patients with TMB (TMB group) and those without TMB who had other cerebral symptoms (non-TMB group). Patients with both TMB and other cerebral symptoms were classified into the TMB group. We compared baseline, clinical characteristics, and outcomes between the TMB group and the non-TMB group.

Statistical analysis was performed using JMP 7.0 statistical software (SAS Institute, Inc., Cary, NC). Results are expressed as mean ± SD, unless otherwise specified. Differences in continuous variables between the TMB and the non-TMB groups were assessed using the Student t test or Mann–Whitney U test as applicable. Differences in categorical variables were assessed using the chi-square test and Fisher exact tests as appropriate. The category of time of arriving at stroke center was considered an ordinal variable, and Mann–Whitney U test were performed to identify the associations between the time of arrival and clinical features. P values less than .05 were considered significant.

Results

A total of 464 patients (292 men and 172 women; mean age: 69 years) were registered between January 2008 and December 2009. Of these, 20 were excluded because of incomplete data about time from onset to arrival at the stroke center. Thus, a total of 444 patients (283 men and 161 women; mean age: 68.5 ± 13.2 years) were included in the analysis. There were 13 patients (2.9%) in the TMB group.

Baseline and clinical characteristics of the TMB and non-TMB groups are shown in Table 1. There were no significant differences in sex, age, vascular risk factors, and premorbid antiplatelet or anticoagulation therapies between the groups. In the TMB group, no patient presented with unilateral weakness, and only 1 patient had dysarthria as a cerebral symptom. The frequency of ambulance use or transfer from medical practitioners was not different between the groups. Compared with patients in the non-TMB group, we found that patients with TMB were less likely to arrive at a stroke center quickly (P = .013).

No difference was observed between the TMB and non-TMB groups in the frequency of hyperintense DWI lesions (30.8% versus 21.0%, respectively; P = .488) and AF (23.1% versus 12.8%, respectively, P = .392). A total of 398 patients had imaging of the carotid arteries. Of these, 4 patients (33.3%) in the TMB group and 35 patients (9.1%) in the non-TMB group had stenotic lesions in the

Table 1. *Baseline clinical characteristics*

Characteristics	Total (n = 444)	TMB (n = 13)	Non-TMB (n = 431)	*P* value
Men, n (%)	283 (63.7)	9 (69.2)	274 (63.6)	.777
Age, y, mean (SD)	68.5 (13.2)	71.2 (7.9)	68.5 (13.4)	.456
Medical history				
Hypertension, n (%)	302 (68.0)	7 (53.9)	295 (68.5)	.364
Diabetes mellitus, n (%)	92 (20.7)	4 (30.8)	88 (20.4)	.484
Dyslipidemia, n (%)	174 (39.2)	7 (53.9)	167 (38.8)	.388
Atrial fibrillation, n (%)	58 (13.1)	3 (23.1)	55 (12.8)	.392
Premorbid ACT, n (%)	41 (9.2)	0 (.0)	41 (9.5)	.620
Premorbid APT, n (%)	125 (28.4)	3 (23.1)	122 (28.6)	1.000
Clinical symptoms				
Unilateral weakness	289 (66.3)	0 (.0)	289 (68.3)	<.001
Dysarthria	142 (32.0)	1 (7.7)	141 (32.7)	.070
Use of ambulance, n (%)	210 (48.0)	3 (23.1)	207 (48.7)	.091
Transfer from medical practitioner, n (%)	127 (28.6)	5 (38.5)	122 (28.3)	.533
Time of arriving at stroke center				.013
<3 h, n (%)	240 (54.1)	3 (23.1)	237 (55.0)	
3-6 h, n (%)	68 (15.3)	3 (23.1)	65 (15.1)	
6-12 h, n (%)	47 (10.6)	1 (7.7)	46 (10.7)	
12-24 h, n (%)	34 (7.7)	2 (15.4)	32 (7.4)	
>24 h, n (%)	55 (12.4)	4 (30.8)	51 (11.8)	
Hyperintense lesions in DWI, n (%)	93 (21.3)	4 (30.8)	89 (21.0)	.488
Stenotic lesions in the extracranial ICA, n (%)*	39 (9.8)	4 (33.3)	35 (9.1)	.022

Abbreviations: ACT, anticoagulant therapy; APT, antiplatelet therapy; DWI, diffusion-weighted imaging; ICA, internal carotid artery; TMB, transient monocular blindness.

*Data on stenotic lesions in the extracranial ICA were available in a total of 398 patients.

extracranial ICA ($P = .022$). In the TMB group, all stenotic lesions were seen in the extracranial ICA ipsilateral to the symptoms.

There were no differences in treatment after admission and clinical outcomes between the groups, as shown in Table 2. Recurrent TIA or cerebral infarction occurred in 1 patient (7.7%) in the TMB group and in 32 patients (7.4%) in the non-TMB group ($P = 1.000$).

Discussion

Previous reports from Western countries [9-11] indicated that TMB occurred in 17%-30% of all patients with TIA. Little is known about the frequency of TMB as a symptom of TIA in the Japanese population.[3,4] Inoue et al[12] reported that transient visual disturbance, including TMB, was seen in 4.7% of 898 acute TIA patients without AF and in 6.5% of 186 acute TIA patients with AF. We observed TMB in only 2.9% of all acute TIA patients, which may indicate that the frequency of TMB is quite low in Japanese TIA patients, although the possibility of admission bias cannot be completely ruled out.

In this study, as compared with patients with other TIA symptoms, patients with TMB were less likely to be admitted to the specialized stroke hospital quickly. Clinical features of TMB are described as a transient, one-sided

Table 2. *Treatment after admission and outcomes*

Characteristics	Total (n = 444)	TMB (n = 13)	Non-TMB (n = 431)	*P* value
Treatment after admission				
Oral antiplatelet, n (%)	341 (76.8)	11 (84.6)	330 (76.6)	.741
Oral anticoagulant, n (%)	93 (21.0)	2 (15.4)	91 (21.1)	1.000
Intravenous antithrombosis, n (%)	279 (62.8)	9 (69.2)	270 (62.7)	.775
Outcomes				
Length of hospital stay, mean (SD)	13.8 (18.9)	14.1 (8.6)	13.8 (19.1)	.957
Occurrence of ischemic stroke in day 0-1, n (%)	10 (2.3)	1 (7.7)	9 (2.1)	.259
Occurrence of ischemic stroke during hospitalization, n (%)	33 (7.4)	1 (7.7)	32 (7.4)	1.000

Abbreviation: TMB, transient monocular blindness.

visual disturbance, which resolves within a few minutes.[13] It is emphasized in the United States that sudden development of visual symptoms, described as "sudden trouble seeing in one or both eyes," is one of the warning signs of brain infarction.[14,15] However, previous studies reported that public awareness of TMB was low, ranging from 7% to 24%,[16,17] and patients with symptoms of visual disturbance related to acute stroke or TIA delayed seeking medical attention.[18]

Investigation of the presence of ischemic lesions on DWI,[19,20] and TIA etiology such as carotid artery atherosclerosis or AF,[21] could improve stroke risk prediction after TIA. In this study, carotid artery stenosis was more common in patients with TMB than in patients with transient cerebral ischemia, as reported in previous studies.[13,22] Hyperintense DWI lesions were seen in 30.8% of patients in the TMB group and in 21.0% of those in the non-TMB group. This is the first study to report the frequency of hyperintense DWI lesions in patients with TMB. TMB is considered to be unlikely to accompany AF.[13,23,24] In a study by Mead et al,[23] 2 (1.4%) of 138 patients with TMB had AF. Smit et al[24] reported that AF was found in only 1 (2.4%) of 41 patients with TMB. However, our result suggested that AF was not rare in TMB. This discrepancy between previous studies and ours may be explained in part by differences in patient background, the extent of diagnostic workup, or racial differences. The results of our study suggest that patients with TMB should immediately undergo brain and blood vessel imaging and cardiac evaluation.

Our study has several limitations. First, there was a risk of statistical error because of the small number of patients with TMB. Second, this was a retrospective study with missing data for some clinical characteristics. Because this retrospective study was based on the medical records, outcomes could be evaluated only within hospitalization period. Rate of recurrent stroke differs depending on the duration of hospitalization. Some previous studies reported that patients with TMB had approximately half the risk of ischemic stroke compared with those with other TIA symptoms.[25,26] Unfortunately, we were not able to determine the risk of ischemic stroke in these patients. Third, there was a selection bias in this study as subjects were TIA patients admitted to specialist stroke hospitals, and the decisions regarding hospitalization and management of TIA patients were made by an individual attending physician. Some patients with TMB might be admitted and be treated in ophthalmological specialized hospitals, not in stroke centers. A larger, prospective study is needed to confirm the risks and outcomes of patients with TMB in the Japanese population.

In conclusion, TMB was not common in our TIA inpatients. Patients with TMB were less likely to arrive early at a specialized stroke hospital than patients with other cerebral symptoms of TIA. The frequency of stenotic lesions in the carotid artery, hyperintense lesions on DWI, and AF in the present study suggested that patients with TMB could have an increased risk of ischemic stroke and should immediately undergo a diagnostic workup including brain magnetic resonance imaging, blood vessel imaging, and cardiac evaluation, as is the case in patients with other cerebral TIA symptoms.

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Factors Associated With Onset-to-Door Time in Patients With Transient Ischemic Attack Admitted to Stroke Centers

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Background and Purpose—The aim of this study was to elucidate the factors associated with the time from symptom onset to arrival at a stroke center (onset-to-door time [ODT]) in patients with classically defined transient ischemic attack using data from a multicenter, retrospective study.

Methods—The subjects were patients with transient ischemic attack admitted to 13 stroke centers in Japan within 7 days of onset between 2008 and 2009. A total of 464 patients registered (292 men, 68.5±13.2 years old), and 421 of them (268 men, 68.8±13.1 years old) were included in the analyses. ODT was classified into the following 5 categories: <3 hours, 3 to 6 hours, 7 to 12 hours, 13 to 24 hours, and >24 hours.

Results—There were 233 patients (55.3%) who visited a stroke center within 3 hours of symptom onset. Multiple ordinal logistic regression analysis revealed that motor weakness, speech disturbance, and duration of symptoms >10 minutes were independently associated with a short ODT. Furthermore, a history of transient ischemic attack and hypertension and a referral from another medical facility were independently associated with a long ODT. Patients with a higher $ABCD^2$ score were likely to arrive at a stroke center more quickly.

Conclusions—We identified several factors that were positively and negatively associated with the ODT in patients with transient ischemic attack. **(*Stroke*. 2014;45:611-613.)**

Key Words: ischemic attack, transient ■ stroke

A transient ischemic attack (TIA) is a medical emergency associated with a high risk of early recurrent stoke. Urgent assessment and management of patients in a dedicated TIA clinic were found to decrease the 90-day stroke risk by ≈80%.[1,2] Immediate medical attention is essential to reduce the risk of stroke after TIA. Although the behavior of patients after stroke has been studied extensively since the advent of thrombolysis and other potential treatments, little information is available on the behavior of patients after TIA, except for the Oxford Vascular Study.[3–5]

We investigated the factors associated with the time from symptom onset to arrival at a stroke center (onset-to-door time [ODT]) in patients with TIA admitted to stroke centers using data from a multicenter, retrospective study.

Methods

The methods of this retrospective, observational, multicenter study have already been described in detail.[6] In brief, we enrolled patients with TIA admitted to 13 stroke centers in Japan within 7 days after symptom onset between January 2008 and December 2009. The diagnosis of TIA was made if neurological symptoms and signs lasted <24 hours, regardless of the brain imaging findings.

A total of 464 patients registered (292 men, 68.5±13.2 years old), but 43 were excluded as a result of either incomplete data (n=20) or referral from another department within the same stroke center (n=23). Thus, a total of 421 patients (268 men, 68.8±13.1 years old) were included in the analyses.

Based on the study design, ODT was classified into the following 5 categories: <3 hours, 3 to 6 hours, 7 to 12 hours, 13 to 24 hours, and >24 hours. Individual $ABCD^2$ scores were calculated.[7] The clinical outcome was the occurrence of ischemic stroke during acute hospitalization.

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The ODT category was considered an ordinal variable, and ordinal logistic regression analyses were performed to identify the associations between the study variables and ODT. Variables that showed $P<0.1$ in univariate analyses were used in multiple ordinal logistic regression analysis, and this was performed using a cumulative logit model. The ABCD^2 score was excluded from the multivariable model because of confounding factors.

Results

Table 1 shows the characteristics of patients according to ODT. Patients with symptoms on arrival at stroke centers, motor weakness, speech disturbance, and duration of symptoms >10 minutes were more likely to arrive at stroke centers quickly than those without. Patients with a history of TIA and hypertension and those referred from another medical facility were more likely to have a delayed arrival at a stroke center. We found that patients with a higher ABCD^2 score were more likely to arrive at a stroke center quickly. Multiple ordinal logistic regression analysis revealed that motor weakness, speech disturbance, and duration of symptoms >10 minutes were independently associated with a short ODT. Furthermore, a history of TIA and hypertension and a referral from another medical facility were independently associated with a long ODT (Table 2).

Subsequent ischemic stroke occurred during hospitalization in 4 (1.7%) of 233 patients who visited a stroke center within 3 hours, 1 (1.5%) of 65 within 3 to 6 hours, 0 (0%) of 43 within 7 to 12 hours, 1 (3.3%) of 31 within 13 to 24 hours, and 1 (2.0%) of 49 after 24 hours. Events and ODT were not significantly associated.

Discussion

Our study revealed that motor weakness, speech disturbance, and long duration of symptoms were associated with a short ODT. Patients with a higher ABCD^2 score were more likely to arrive at a stroke center quickly. The results of our study are consistent with those of previous studies.[3,5,8] Two reports using data from the Oxford Vascular Study[3,5] demonstrated that patients with motor weakness, speech disturbance, and symptom duration >60 minutes were less likely than other patients to delay in seeking medical attention. Patients with a higher predicted stroke risk were more likely to act quickly due apparently to the influence of weakness and prolonged symptom duration on behavior, although there was no association between the recognition of symptoms and the urgency of action.[3]

We found that a history of recent TIA and hypertension, both known risk factors for stroke after TIA, was associated with delayed arrival at a stroke center. These relationships were not found in a study by Chandratheva et al.[5] They reported that prior stroke and atrial fibrillation tended to be associated with less delay. We also showed that a referral from another medical facility was associated with a longer delay in arrival at a stroke center. A systematic review found that there

Table 1. Comparison of Characteristics According to Onset-to-Door Time

		Onset-to-Door Time					
	Overall n=421	>3 h n=233	3–6 h n=65	7–12 h n=43	13–24 h n=31	>24 h n=49	*P* Value
Age, y (mean±SD)	68.8±13.1	68.8±12.4	70.9±14.3	67.0±12.6	70.0±15.3	66.5±13.0	0.566
Men, %	63.7	64.0	53.9	62.8	64.5	75.5	0.546
Symptoms, %							
Motor	68.5	76.4	59.4	59.5	50.0	62.5	<0.001
Sensory	28.0	26.8	26.6	36.8	32.3	25.5	0.591
Speech	39.2	45.9	35.4	41.9	12.9	26.5	<0.001
Visual	8.8	6.9	10.8	4.7	12.9	16.3	0.067
Presence of symptoms on arrival, %	42.8	46.8	46.2	51.2	22.6	24.5	0.005
Duration of symptoms >10 min, %	85.9	90.5	91.5	94.3	88.5	48.9	<0.001
History, %							
Stroke	23.5	24.5	21.5	27.9	16.1	22.5	0.599
TIA	18.5	15.7	13.6	13.5	26.9	40.0	0.009
Hypertension	68.2	63.1	73.9	76.7	74.2	73.5	0.017
Diabetes mellitus	20.2	18.0	21.5	25.6	19.4	24.5	0.218
Dyslipidemia	39.4	34.8	56.9	27.9	51.6	40.8	0.109
Atrial fibrillation	12.4	12.8	13.9	11.6	19.4	4.1	0.482
Median ABCD^2 score, (IQR)	4 (3–5)	5 (4–5.75)	4 (3–5)	5 (3–6)	4 (3–5)	4 (2–5)	<0.001
Referral from another medical facility, %	29.9	17.6	46.2	39.5	54.8	42.9	<0.001

IQR indicates interquartile range; and TIA, transient ischemic attack.

Table 2. Factors Associated With Onset-to-Door Time by Multivariate Analysis

	Estimate	SE	*P* Value
Motor disturbance	−0.276	0.127	0.029
Speech disturbance	−0.233	0.114	0.041
Visual disturbance	0.137	0.215	0.524
Presence of symptoms on arrival	−0.078	0.115	0.493
Duration of symptoms >10 min	−0.438	0.154	0.005
History of TIA	0.296	0.136	0.030
History of hypertension	0.258	0.122	0.034
Referral from another medical facility	0.605	0.114	<0.001

TIA indicates transient ischemic attack.

was an association between delay in seeking medical attention and referral from a general physician in patients with TIA or minor stroke.[9] The finding that patient factors are related to delayed arrival at stroke centers might be important insofar as action that could mitigate these factors. The present findings suggest that educating the general public and general physicians about TIA as a medical emergency and stroke risk factors, including hypertension, is essential to minimize the delay in arriving at a stroke center.

The present study has several limitations. First, there was a selection bias in this study because only patients with TIA admitted to a stroke center were enrolled. Second, this study had a retrospective design, and there were missing data on some baseline characteristics. Third, we were unable to investigate substantially an association between ODT and stroke risk because of the small number of patients who had stroke after TIA. Whether the hyperacute stroke treatment aphorism, time is brain, is applicable to TIA remains unclear.

In conclusion, we identified several factors that were positively and negatively associated with ODT in patients with TIA admitted to stroke centers. Further study is needed to clarify whether the same patterns of behavior after TIA would be observed in other populations.

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Disclosures

None.

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Incidence and Predictors of Ischemic Stroke Events during Hospitalization in Patients with Transient Ischemic Attack

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Key Words
Acute ischemic stroke · Diffusion-weighted image · Incidence · Predictors of outcome · Transient ischemic attack

Abstract
Background: The purpose of this study was to elucidate the incidence and predictors of ischemic stroke or recurrent transient ischemic attack (TIA) during acute hospitalization in patients with TIA. ***Methods:*** We carried out a multicenter retrospective study to clarify the characteristics of in-patients with TIA. The subjects of this study were TIA patients admitted to 13 stroke hospitals within 7 days after onset between 2008 and 2009. TIA was defined as focal neurologic symptoms ascribable to a vascular etiology lasting less than 24 h. We investigated the incidence and predictors of ischemic events including ischemic stroke or recurrent TIA during hospitalization. ***Results:*** A total of 464 patients with TIA (292 men, 69 ± 13 years) were registered. Of those, 400 (86.2%) were admitted within 24 h of TIA onset. The mean length of hospital stay was 13 days. During hospitalization, 8 patients had ischemic strokes and 26 had recurrent TIAs. The leading subtype of 8 ischemic strokes was small vessel disease (n = 3) followed by cardioembolism (n = 2). Multiple logistic regression analysis showed that hypertension (OR: 3.41; 95% CI: 1.23–12.3), MRI-diffusion-weighted image positivity (OR: 2.49; 95% CI: 1.15–5.25), and hemiparesis (OR: 2.30; 95% CI: 1.02–5.88) were independently associated with ischemic events during hospitalization. ***Conclusions:*** In this study, 1.7% of patients with TIA had ischemic stroke during acute hospitalization, and the

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most common subtype was small vessel disease. Subsequent ischemic stroke and recurrent TIA were associated with hypertension, positive DWI findings, and hemiparesis.

Introduction

Simple stratification scores are used to estimate the individual risk of subsequent stroke for patients with transient ischemic attack (TIA). The most popular tool is the $ABCD^2$ score [1]. The $ABCD^2$ score has been shown to accurately predict the risk of stroke after TIA in population- and emergency department-based studies. The presence of ischemic lesions on MRI-diffusion-weighted imaging (DWI) and large artery atherosclerosis in addition to the $ABCD^2$ score could improve stroke risk prediction after TIA [2].

We previously conducted a nationwide survey using a questionnaire to elucidate the current status of clinical practice TIA management in stroke-specialized hospitals [3]. This survey demonstrated that brain MRI was routinely performed as a diagnostic examination of recent TIA in 97% of the surveyed hospitals. Additionally, in about two thirds of the hospitals, the general policy was to immediately admit all patients with recent TIA without using risk scores. Patients were given anticoagulation or antiplatelet therapy soon after the initial work-up. In several studies from other countries, risk and predictors of stroke after TIA were reported [2, 4–12]. However, the risk of early ischemic stroke remained unclear in patients with TIA admitted to stroke centers in Japan.

The aim of this study was to retrospectively determine the incidence and predictors of ischemic stroke and recurrent TIA during acute hospitalization in TIA patients admitted to multiple stroke-specialized hospitals in Japan.

Methods

Collection of Patients

This was a multicenter, retrospective, observational study by the Japan TIA Research Group, which was organized to establish a TIA management system suitable to the healthcare environment in Japan [13]. In this study, consecutive patients with TIA admitted to 13 stroke-specialized hospitals within 7 days of symptom onset between January 2008 and December 2009 were registered. The diagnosis of TIA was made when focal neurological symptoms ascribable to a vascular etiology lasted less than 24 h, irrespective of the presence of ischemic insults on imaging. An attending physician made the ultimate diagnosis of TIA and management decisions. Patients diagnosed as TIA mimics after admission were excluded from this study. Each local ethics committee approved the retrospective collection and submission of patients' clinical data to the study office in the National Cerebral and Cardiovascular Center.

Patient Characteristics

Patient characteristics, including sex, age, risk factors, prior antithrombotic therapy, clinical symptoms of TIA, and symptom duration, were collected from medical records. For risk factors of stroke, hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medications. Dyslipidemia was defined as a low-density lipoprotein cholesterol concentration ≥140 mg/dl or current use of lipid-lowering agents. Diabetes mellitus was defined as an HbA1c ≥6.1% (Japan Diabetes Society) or the current use of hypoglycemic drugs. Current smoking was defined as present if a patient was smoking at 1 month before registration. Atrial fibrillation (AF) was considered to be present if there was a history AF or if permanent or paroxysmal AF was detected during hospitalization. We divided TIA symptoms into hemiparesis, speech disturbance, sensory disorder, amaurosis, and others. The duration of symptoms was defined as the time from onset to recovery. We also calculated the $ABCD^2$ score for each patient.

Imaging

We used the results of the DWI examination to evaluate whether acute ischemic lesions were present on admission. Extra- or intracranial arterial lesions were assessed by ultrasonography, CT angiography, MR angiography, or conventional angiography. A stenotic lesion was defined as the presence of >50% stenosis in the cervicocephalic arteries detected by any modality. An attending physician evaluated the imaging findings.

Clinical Outcomes

We used occurrence of ischemic events including ischemic stroke and recurrent TIA during acute hospitalization as clinical outcomes. The patients were divided into an ischemic event group and a nonischemic event group.

Statistical Analysis

All statistical analyses were performed using JMP 8 software (SAS Institute Inc). A χ^2 test was used, as appropriate, to compare baseline clinical characteristics between the ischemic event group and nonischemic event group. Multivariate analyses were performed to identify predictors of ischemic events during hospitalization. $p < 0.05$ was considered significant.

Results

A total of 464 patients with TIA (292 men, 69 ± 13 years) were registered. Of these, 400 (86.2%) were admitted within 24 h of TIA onset. The mean length of hospital stay was 13 days. Baseline characteristics, imaging findings, and treatment during hospitalization are listed in table 1. The leading risk factor was hypertension

Table 1. Baseline characteristics, imaging findings and treatment in the acute phase

	Overall (n = 464)	Ischemic events (+) (n = 34)	Ischemic events (–) (n = 430)	p
Demographics				
Age, years	68.5±13.2	67.6±11.6	68.6±13.3	0.452
Male	292 (63.0)	21 (61.8)	271 (63.0)	0.884
Risk factors and comorbidities				
Hypertension	344 (74.1)	30 (88.2)	314 (73.0)	0.034
Diabetes mellitus	114 (24.6)	10 (29.4)	104 (24.2)	0.504
Dyslipidemia	261 (56.3)	24 (70.6)	237 (55.1)	0.075
Current smoking	122 (26.3)	9 (26.5)	113 (27.8)	0.864
AF	79 (17.0)	5 (14.8)	74 (17.2)	0.719
Old myocardial infarction	2 (0.4)	0 (0)	2 (0.4)	0.737
Peripheral artery disease	4 (0.8)	0 (0)	4 (0.9)	0.859
Prior medication				
Anticoagulant	135 (29.1)	11 (32.4)	124 (29.1)	0.692
Antiplatelet	39 (8.4)	3 (8.9)	36 (8.4)	0.928
TIA features				
Retinal TIA	14 (3.0)	1 (2.9)	13 (3.0)	0.978
Speech disturbance	193 (41.6)	12 (35.3)	181 (42.1)	0.435
Sensory disorder	138 (29.7)	9 (26.5)	129 (30.0)	0.661
Hemiparesis	291 (62.7)	27 (79.4)	264 (61.4)	0.029
Duration of TIA ≥1 h	213 (45.9)	10 (34.5)	203 (51.7)	0.072
$ABCD^2$ score	4 (3–5)	5 (4–6)	4 (3–5)	0.218
Imaging findings				
Major artery stenosis	152 (32.8)	16 (47.1)	136 (35.4)	0.183
Positive DWI	96 (20.7)	13 (38.2)	83 (19.6)	0.017
Antithrombotic therapy				
Antiplatelet only	214 (46.1)	11 (32.4)	203 (47.2)	0.090
Anticoagulant only	75 (16.2)	5 (14.7)	70 (16.3)	0.671
Combination	157 (33.8)	18 (52.9)	139 (32.3)	0.017
None	18 (3.9)	0 (0)	18 (4.2)	0.247

Values are means ± SD, n (%), or medians (interquartile range).

(74.1%), followed by dyslipidemia (56.3%). There were 135 patients (29%) who had prior treatment (before admission) with antiplatelet agents and 39 (8%) who were treated with anticoagulant agents. The median $ABCD^2$ score was 4 (range: 3–5) in 413 patients; 51 patients did not have data about the duration of symptoms.

MRI examinations were performed in 458 patients (98.7%). Of these, 374 patients underwent MRI examinations within the initial 24 h after TIA onset. Acute ischemic lesions on DWI were found in 96 (21.0%) of the 458 patients.

Of 464 patients registered, 446 patients (96.1%) received antithrombotic therapy during acute hospitalization: 214 patients (46.1%) were treated with antiplatelet agents only, 75 (16.2%) with anticoagulant agents only, and 157 (33.8%) with a combination of antiplatelet and anticoagulant agents.

Ischemic events during acute hospitalization occurred in 34 patients. Seven patients had ischemic stroke, 26 had recurrent TIAs, and 1 had recurrent TIA episodes followed by ischemic stroke. The subtype of 8 ischemic strokes were: small vessel disease = 3, cardioembolism = 2, large artery atherosclerosis = 1, other determined etiology = 1, and undetermined etiology = 1. The timing of the ischemic events is shown in the figure 1. Most of these events occurred within the initial week, especially within 2 days after TIA onset.

As compared to patients without ischemic events, those with ischemic events were more likely to have hypertension (88.2 vs. 73.0%, p = 0.034) and hemiparesis (79.4 vs. 61.4%, p = 0.029). Furthermore, DWI-positive lesions were more common in patients with than without ischemic events (38.2 vs. 19.6%, p = 0.017). Multiple logistic regression analysis showed that hypertension (OR:

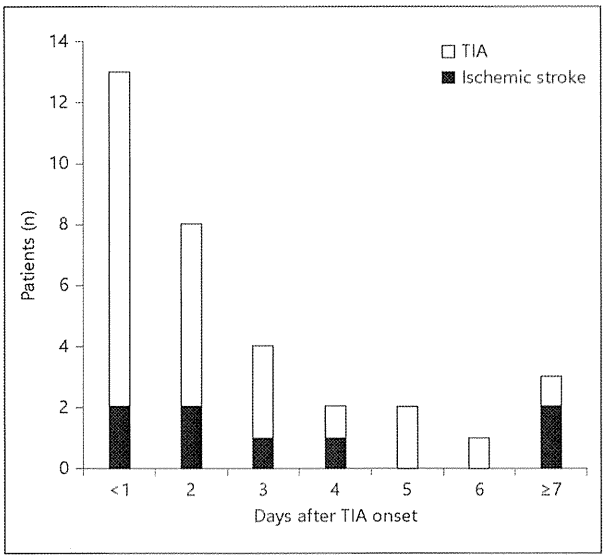

Fig. 1. Timing of ischemic events.

Table 2. Predictors of ischemic events during hospitalization by multiple regression analysis

	OR (95% CI)	p
Age	0.98 (0.96–1.01)	0.310
Male	0.80 (0.38–1.73)	0.565
Hypertension	3.41 (1.23–12.3)	0.016
Hemiparesis	2.30 (1.02–5.88)	0.045
Positive DWI	2.49 (1.15–5.25)	0.022

3.41; 95% CI: 1.23–12.3), DWI-positive lesions (OR: 2.49; 95% CI: 1.15–5.25), and hemiparesis (OR: 2.30; 95% CI: 1.02–5.88) were independently associated with ischemic events during hospitalization (table 2).

During hospitalization, myocardial infarction occurred in 1 patient and angina pectoris occurred in 3 patients.

Discussion

The first major finding of this study was that the incidence of ischemic stroke during acute hospitalization was 1.7% in patients with TIA admitted to stroke-specialized hospitals in Japan. Another important finding was that DWI-positive lesions, hypertension and hemiparesis were independent predictors of ischemic stroke or recurrent TIA during acute hospitalization. Moreover, small artery disease was the most frequent subtype of ischemic stroke after TIA.

In this study, the mean length of hospital stay was 13 days, and 1.7% of patients with TIA had ischemic stroke during this period. Similar to our study, the Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC) demonstrated that the mean length of hospital stay in TIA patients was 14 days [14]. In a recent systematic review, including 18 independent cohorts, the pooled stroke risk after TIA was 5.2% at 7 days, but ranged from 0 to 12.8%. The lowest risks were seen in studies of emergency treatment in specialist stroke services [15]. Patients with TIA registered in our study were admitted to stroke-specialized hospitals and received appropriate treatment including antithrombotic therapy. Similar low risks of stroke were reported in large population- and hospital-based studies with urgent assessment and immediate treatment of TIA [16, 17]. Although the possibility that ischemic events were underestimated due to information bias from retrospective data cannot be completely excluded, the low risks observed in our study may partially be a result of early management. Most ischemic events occurred within the initial week and were concentrated in the initial 2 days after TIA onset. This result was consistent with a previous study and suggested the importance of immediate treatment after symptom onset in TIA patients [18].

Several studies have investigated the predictors of subsequent stroke after TIA. Early stroke recurrence after TIA was reported to be associated with the $ABCD^2$ score, DWI positivity, large artery stenosis, AF, recent earlier TIA, and progression or fluctuation of TIA symptoms [1, 2, 5–12, 19–21]. The $ABCD^2$ score has been used to predict early stroke after TIA [14]. In this study, hemiparesis and hypertension, both components of the $ABCD^2$ score, were independent predictors of ischemic events. When we used 5 points as the cutoff value of the $ABCD^2$ score for acute ischemic stroke calculated by the ROC curve, patients with an $ABCD^2$ score of 5–7 had acute ischemic stroke more frequently than those with a score of 0–4 (3.0 vs. 0.47%, $p = 0.037$). This result is very compatible with previous studies. In addition, we showed that DWI positivity was associated with ischemic events. DWI positivity is well known as a predictor of ischemic stroke after TIA. Giles et al. [6] found that incorporation of an ischemic lesion on DWI into the $ABCD^2$ score ($ABCD^2I$) improved prediction of stroke in the early phase after TIA. The diagnosis of TIA is unreliable. Patients with suspected TIA require a differential diagnosis from TIA mimics.

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MRI, including DWI sequences, should be the preferred diagnostic test for patients with suspected TIA.

We were unable to confirm that large artery stenosis and AF were predictors of early stroke, as was suggested in a previous study [2, 5, 7, 8, 10]. This finding could be explained by the beneficial effect of early antithrombotic therapy in our study.

In this study, small vessel disease was the major subtype of ischemic stroke occurring after TIA. This finding is consistent with that of previous single-center studies in Japan. Mori et al. [22] reported that a half of the ischemic strokes that occurred within 7 days of TIA onset were lacunar infarctions. A study by Ohara et al. [23] showed that 6 (5.7%) of 105 patients with TIA experienced recurrent ischemic stroke after TIA during admission. Three of these 6 ischemic strokes were diagnosed as lacunar infarctions. Taken together, TIA caused by a small vessel disease may be common in Japanese patients.

Ideally, all patients with suspected TIA should be immediately hospitalized to ensure rapid diagnostic evaluation and acute stroke therapies. However, admitting all patients with suspected TIA would probably be problematic, as hospital resources including staff and beds would become insufficient and costs would soar. For acute hospitalization after suspected TIA, risk stratification in the emergency room might help triage patients (high-risk) for hospitalization and outpatient (low-risk) management [24]. On the basis of the results of the present study and previous reports, we propose risk stratification and admission policy using the ABCD^2 score and findings of initial diagnostic examinations, including DWI.

The present study has some limitations. First, this study had a retrospective design that had missing data on some baseline characteristics. Our clinical outcome measures were limited to ischemic stroke and recurrent TIA during hospitalization. Second, there was a selection bias in this study for subjects who were TIA patients admitted to stroke-specialized hospitals, and the decisions for hospitalization and management of TIA were made by attending physicians. Third, there was a possibility that some TIA patients who developed subsequent ischemic stroke very early after admission were not included in this study due to the retrospective design. This may somewhat affect the low rate of ischemic stroke in this study. Finally, when we analyzed predictors of ischemic events, we combined ischemic stroke and recurrent TIA due to the small number of ischemic strokes after TIA during hospitalization. The number of outcome events was insufficient to provide statistical power for detailed analysis of stroke predictors.

In conclusion, 1.7% of our patients with TIA had ischemic stroke during acute hospitalization, and the major subtype was small vessel disease. Subsequent ischemic stroke and recurrent TIA were associated with positive DWI lesions, hemiparesis, and hypertension.

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