EXTRA Cerebrovascular Diseases

Cerebrovasc Dis Extra 2015;5:84–90
DOI: 10.1159/000434689
Received: March 23, 2015
Accepted: May 27, 2015
Published online: July 9, 2015

1664–5456/15/0052–0084$39.50/0
www.karger.com/cee

Karger Open access

Original Paper

Clinical Characteristics of Transient Ischemic Attack Patients with Atrial Fibrillation: Analyses of a Multicenter Retrospective Study

Yuka Hama[a] Toshiyuki Uehara[a] Tomoyuki Ohara[a] Kazumi Kimura[c] Yasushi Okada[d] Yasuhiro Hasegawa[e] Norio Tanahashi[f] Akifumi Suzuki[g] Shigeharu Takagi[h] Jyoji Nakagawara[i] Kazumasa Arii[j] Shinji Nagahiro[l] Kuniaki Ogasawara[m] Takehiko Nagao[k] Shinichiro Uchiyama[k] Masayasu Matsumoto[n] Koji Iihara[b] Kazunori Toyoda[a] Kazuo Minematsu[a]

Departments of [a]Cerebrovascular Medicine and [b]Neurosurgery, National Cerebral and Cardiovascular Center, Suita, [c]Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, [d]Department of Cerebrovascular Medicine and Neurology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, [e]Department of Neurology, Nagoya Daini Red Cross Hospital, Nagoya, [f]Department of Neurology and Cerebrovascular Medicine, Saitama Medical University, Saitama International Medical Center, Hidaka, [g]Department of Stroke Science, Research Institute for Brain and Blood Vessels Akita, Akita, [h]Department of Neurology, Tokai University, Isehara, [i]Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, [j]Department of Neurology, Ebara Hospital, and [k]Department of Neurology, Tokyo Women's Medical University, Tokyo, [l]Department of Neurosurgery, Tokushima University, Tokushima, [m]Department of Neurosurgery, Iwate Medical University, Morioka, and [n]Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Hiroshima, Japan

Key Words

Transient ischemic attack · Atrial fibrillation · Diffusion-weighted imaging

Abstract

Background: Atrial fibrillation (AF) is an important risk factor for transient ischemic attack (TIA). However, little is known about the characteristics of TIA patients with AF. This study investigated the characteristics of such patients, using data from a retrospective, observational, multicenter study. ***Methods:*** TIA patients admitted to 13 stroke centers in Japan within 7 days of onset between January 2008 and December 2009 were included. The present analyses compared baseline characteristics, clinical symptoms, findings from diffusion-weighted imaging (DWI), and clinical outcomes between patients with and without AF (AF and non-AF groups). ***Results:*** A total of 464 patients (292 men; mean age 68.5 ± 13.2 years) were registered. Of these, 79 patients (17%) had AF. Patients in the AF group were older (73.9 ± 9.1 vs. 67.4 ± 13.6 years, $p < 0.001$) and more likely to show disturbance of consciousness (13 vs. 6%,

Toshiyuki Uehara, MD
Departments of Cerebrovascular Medicine and of Stroke Rehabilitation
National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai
Suita, Osaka 565-8565 (Japan)
E-Mail tuehara@ncvc.go.jp

p = 0.046) and aphasia (9 vs. 3%, p = 0.007) than patients in the non-AF group. Although no difference in the overall DWI-positive rate was seen between the groups (28 vs. 20%, p = 0.102), a single lesion (23 vs. 10%, p < 0.001), a lesion ≥15 mm (11 vs. 4%, p = 0.006), and a single lesion ≥15 mm (11 vs. 2%, p < 0.001) on DWI were more frequent in the AF group. Multivariate logistic regression analysis identified increased age [odds ratio (OR) 1.04; 95% confidence interval (CI) 1.02–1.07] and DWI single lesion ≥15 mm (OR 5.67; 95% CI 1.92–16.7) as independently associated with the presence of AF. ***Conclusions:*** In this study, 17% of our TIA patients had AF. We found an association between the acute ischemic lesion pattern on DWI of a single lesion ≥15 mm and AF in TIA patients. These results might lead to a better diagnosis of TIA patients with AF.

Introduction

Transient ischemic attack (TIA) is a medical emergency associated with a high risk of early subsequent stroke. Around 10–15% of TIA patients develop stroke within 90 days, with half of these strokes occurring within the first 48 h [1–4]. Identifying mechanisms of TIA and initiating proper treatment as soon as possible are thus important in reducing the risk of stroke after TIA. Atrial fibrillation (AF) represents an important risk factor for TIA, but little is known about the characteristics of TIA patients with AF. The purpose of this study was to investigate the characteristics of such patients using data from a multicenter, retrospective study.

Methods

The methods of this study have been described in detail elsewhere [5–7]. In brief, this retrospective, observational, multicenter study enrolled TIA patients admitted to 13 stroke centers in Japan within 7 days of symptom onset between January 2008 and December 2009. Patients were diagnosed as having TIA if neurological symptoms and signs lasted less than 24 h, regardless of brain imaging findings.

We recorded the following information on each patient: sex, age, body mass index, risk factors, past history of stroke, premorbid modified Rankin Scale (mRS), neurological symptoms, and National Institutes of Health Stroke Scale score on admission. We also calculated individual $ABCD^2$ scores. Diffusion-weighted imaging (DWI) was also performed with a 1.5-tesla system to evaluate whether acute ischemic lesions were present on admission. Acute ischemic lesions were defined as areas of signal hyperintensity on DWI. Neuroradiologists or physicians specialized in stroke evaluated the patterns of acute ischemic lesions on DWI, including their number (single or multiple) and size (largest diameter ≥15 or <15 mm). Duration of hospitalization, events including TIA recurrence, ischemic stroke, or systemic embolism during hospitalization, and mRS at day 30 were used as clinical outcomes. Each local ethics committee approved the retrospective collection and submission of patients' clinical data to the study office at the National Cerebral and Cardiovascular Center.

TIA patients were divided into two groups: patients with AF (AF group) and patients without AF (non-AF group). AF was considered present if it was previously known or newly documented on electrocardiography during hospitalization. We compared baseline characteristics, clinical symptoms, DWI findings, and clinical outcome between groups.

All statistical analyses were performed using JMP statistical software (version 9.0.2; SAS Institute, Cary, N.C., USA). Results are expressed as mean ± standard deviation (SD) or median (25th, 75th centile) and as the number of patients and percentage for categorical variables as appropriate. Baseline characteristics, symptoms, DWI lesion patterns, and clinical outcomes were compared between the groups using the χ^2 test, Student's t test, and the Wilcoxon test as appropriate. Statistical significance was set at the level of $p < 0.05$. Multivariate analyses were performed to identify predictors of the presence of AF. Sex, age, and variables showing values of $p < 0.05$ in univariate analysis were entered into the multivariate analyses.

Table 1. Baseline characteristics of the AF and non-AF groups

	All patients (n = 464)	Patients with AF (n = 79)	Patients without AF (n = 385)	p value
Male sex	292 (63)	47 (59)	245 (64)	0.487
Age, years	68.5±13.2	73.9±9.1	67.4±13.6	<0.001
BMI	23.0±3.6	23.1±3.4	23.0±3.6	0.790
Risk factors				
Hypertension	319 (69)	51 (65)	268 (70)	0.377
Diabetes mellitus	94 (20)	14 (18)	80 (21)	0.538
Dyslipidemia	181 (39)	28 (35)	153 (40)	0.476
Current smoking	121 (26)	12 (15)	109 (28)	0.016
Habitual drinker	119 (26)	16 (20)	103 (27)	0.228
Past history of stroke				
Overall	108 (23)	19 (24)	89 (23)	0.858
Ischemic stroke	101 (22)	18 (23)	83 (22)	0.810
Intracerebral hemorrhage	11 (2)	2 (3)	9 (2)	1.000
Subarachnoid hemorrhage	1 (0)	0 (0)	1 (0)	1.000
Premorbid mRS	0 (0–0)	0 (0–0)	0 (0–0)	0.553

Values are mean ± SD, n (%), or median (interquartile range). BMI = Body mass index.

Table 2. Clinical symptoms and $ABCD^2$ score in the AF and non-AF groups

	All patients (n = 464)	Patients with AF (n = 79)	Patients without AF (n = 385)	p value
Clinical symptoms				
Disturbance of consciousness	34 (7)	10 (13)	24 (6)	0.046
Gaze disturbance	6 (1)	3 (4)	3 (1)	0.065
Visual field defect	6 (1)	1 (1)	5 (1)	1.000
Facial palsy	33 (7)	5 (6)	28 (7)	0.766
Hemiparesis	100 (22)	13 (16)	87 (23)	0.227
Ataxia	13 (3)	1 (1)	12 (3)	0.706
Dysesthesia	68 (15)	6 (8)	62 (16)	0.051
Aphasia	17 (4)	7 (9)	10 (3)	0.007
Dysarthria	60 (13)	7 (9)	53 (14)	0.237
Tactile extinction	7 (2)	2 (3)	5 (1)	0.340
NIHSS score on admission	0 (0–1)	0 (0–2)	0 (0–1)	0.969
Single TIA	364 (78)	64 (81)	300 (78)	0.543
$ABCD^2$ score	5 (4–6)	5 (4–5)	5 (4–6)	0.491

Values are n (%) or median (interquartile range). NIHSS = National Institutes of Health Stroke Scale.

Results

Participants comprised 464 patients (292 men; age 68.5 ± 13.2 years). Of these, 79 patients (17%) had AF. The AF group was older (73.9 ± 9.1 vs. 67.4 ± 13.6 years, $p < 0.001$) and showed a lower frequency of current smokers (15 vs. 28%, $p = 0.016$) than the non-AF group (table 1). Table 2 presents clinical symptoms and $ABCD^2$ scores of the AF and non-AF groups. Disturbance of consciousness (13 vs. 6%, $p = 0.046$) and aphasia (9 vs. 3%, $p = 0.007$) were significantly more frequent in the AF group than in the non-AF group. Of the 464 patients,

Table 3. DWI findings of the AF and non-AF groups

	All patients (n = 458)	Patients with AF (n = 75)	Patients without AF (n = 383)	p value
DWI findings				
Overall	96 (21)	21 (28)	75 (20)	0.102
Single lesion	56 (12)	18 (24)	38 (10)	<0.001
Lesion ≥15 mm	25 (5)	9 (12)	16 (4)	0.006
Single lesion ≥15 mm	17 (4)	8 (11)	9 (2)	<0.001

Values are n (%).

Table 4. Clinical outcomes of the AF and non-AF groups

	All patients (n = 464)	Patients with AF (n = 79)	Patients without AF (n = 385)	p values
Duration of hospitalization, days	11 (8–17)	13 (9–18)	11 (7–17)	0.047
Events during hospitalization				
TIA recurrence	27 (6)	3 (4)	24 (6)	0.597
Ischemic stroke	8 (2)	2 (3)	6 (2)	0.629
Systemic embolism	4 (1)	2 (3)	2 (1)	0.136
mRS at 30 days	0 (0–0)	0 (0–1)	0 (0–0)	0.126

Values are n (%) or median (interquartile range).

458 (99%) underwent MRI of the head. Acute ischemic lesions were detected in 96 patients (21%). No difference in the overall DWI lesion rate was seen between the groups (28 vs. 20%, p = 0.102). Compared to patients in the non-AF group, patients in the AF group were more likely to show a single lesion (24 vs. 10%, p < 0.001), a lesion ≥15 mm (12 vs. 4%, p = 0.006), or a single lesion ≥15 mm (11 vs. 2%, p < 0.001) on DWI (table 3). For clinical outcomes, the median duration of hospitalization was longer in the AF group than in the non-AF group [median (interquartile range): 13 (9–18) vs. 11 (7–17), p = 0.047]. No significant differences in the incidence of TIA recurrence (4 vs. 6%), ischemic stroke (3 vs. 2%), or systemic embolism (3 vs. 1%) during hospitalization, and mRS at day 30 were evident between the groups (table 4). Multivariate logistic regression analysis identified increased age [odds ratio (OR) 1.04; 95% confidence interval (CI) 1.02–1.07] and DWI single lesion (OR 2.32; 95% CI 1.09–4.78) as independently associated with the presence of AF. When using data for the combination of DWI single lesion and lesion ≥15 mm in model 2, increased age (OR 1.04; 95% CI 1.02–1.07) and DWI single lesion ≥15 mm (OR 5.67; 95% CI 1.92–16.7) were independently associated with the presence of AF (table 5).

Discussion

In this study, 17% of TIA patients had AF, and advanced age was associated with the presence of AF. According to the Hisayama study, 16% of TIA patients in a Japanese community had AF or valvular heart disease [8]. In the Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC) registry of 1,084 TIA patients, the frequency of AF was 17%, and TIA patients

Table 5. Multivariate logistic regression analysis for the factors associated with presence of AF

	Multivariate-adjusted model 1			Multivariate-adjusted model 2		
	OR	95% CI	p value	OR	95% CI	p value
Male sex	0.93	0.55–1.60	0.80	0.93	0.55–1.60	0.79
Age	1.04	1.02–1.07	<0.001	1.04	1.02–1.07	<0.001
Current smoking	0.59	0.28–1.15	0.13	0.56	0.26–1.09	0.09
Clinical symptoms						
Consciousness disturbance	1.56	0.64–3.57	0.32	1.45	0.59–3.32	0.40
Aphasia	2.32	0.75–6.81	0.14	2.38	0.77–6.92	0.13
DWI single lesion	2.32	1.09–4.78	0.03			
DWI lesion ≥15 mm	2.13	0.74–5.84	0.16			
DWI single lesion ≥15 mm				5.67	1.92–16.7	0.002

Model 1: adjusted for sex, age, and factors with $p < 0.1$ in univariate analysis. Model 2: integration of DWI single lesion ≥15 mm in addition to factors from model 1.

with AF were likely to be older compared to those without AF [9]. Our results were consistent with those of previous studies in Japan. On the other hand, a previous study of 1,429 TIA patients registered in Germany reported AF in 11% of patients [10]. Another study in northern California demonstrated that 9% of 1,707 TIA patients had AF [11]. These results indicate that the frequency of AF in patients with TIA is higher in Japanese populations than in European or American populations. This difference may be explained in part by differences in patient background, extent of diagnostic workup, and ethnicity.

This study determined the association between acute ischemic lesion patterns on DWI and AF in TIA patients. In the abovementioned J-MUSIC study, multiple logistic regression analysis revealed disturbance of consciousness and speech disturbance as factors independently associated with AF in TIA patients. This may be because cardioembolic TIA tends to involve the cortical region. The J-MUSIC study mentioned that these results may support the hypothesis that TIA patients with AF have larger emboli originating from the left atrium than patients without AF and that ischemic lesions are also larger in TIA patients with AF than in those without [8, 9]. We actually found that a single lesion ≥15 mm in size was associated with the presence of AF. Similar to our results, Purroy et al. [12] showed that a single cortical lesion was associated with cardioembolism in a study of 254 TIA patients.

In this study, patients in the AF group showed a longer duration of hospitalization than those in the non-AF group. This may be attributable to patients with AF needing a number of days for adjustment of warfarin dosages. No significant differences in the frequency of ischemic stroke or recurrent TIA during hospitalization were identified between the groups. In the same cohort, DWI-positive lesions, hypertension, and hemiparesis were reported as independent predictors of ischemic stroke or recurrent TIA during acute hospitalization [7].

Some limitations must be considered when interpreting the study results. First, a selection bias was present in this study, since only TIA patients admitted to stroke centers were enrolled. In addition, decisions regarding hospitalization and management of TIA patients were made by the individual attending physicians. Second, this study utilized a retrospective design, and data were missing for some baseline characteristics. Third, we did not have additional monitoring data on patients in whom AF was not detected before or during hospitalization. Holter monitors after hospitalization detect about 5% of cryptogenic stroke patients as having AF, and 30-day monitors up to 20% [13]. Fourth, there are no data regarding events within 30 or 90 days. Given the potential continuous risk of AF, this represents a limitation in

this study. Finally, an adequate analysis of clinical outcome was difficult due to the small number of events encountered during hospitalization.

In conclusion, 17% of our TIA patients showed AF. Increased age and a single lesion ≥15 mm on DWI were associated with the presence of AF. The present results might lead to a better diagnosis of TIA patients with AF.

Appendix

Chief Investigator

K. Minematsu, National Cerebral and Cardiovascular Center.

Investigators and Institutions

Y. Hama, T. Uehara, T. Ohara, R. Suzuki, J. Fujinami, T. Miyagi, K. Tanaka, H. Matsushima, R. Shimomura, T. Matsushige, K. Iihara, and K. Minematsu, National Cerebral and Cardiovascular Center; T. Iwanaga, J. Uemura, and K. Kimura, Kawasaki Medical School; M. Mori, T. Uwatoko, S. Yoshimura, and Y. Okada, National Hospital Organization Kyushu Medical Center; K. Yasui and Y. Hasegawa, Nagoya Daini Red Cross Hospital; N. Tanahashi, Saitama Medical University; T. Nakase, S. Yoshioka, and A. Suzuki, Research Institute for Brain and Blood Vessels Akita; S. Takagi, Tokai University Tokyo Hospital; K. Ueyama and J. Nakagawara, Nakamura Memorial Hospital; K. Arii and T. Nagao, Ebara Hospital; J. Satomi and S. Nagahiro, Tokushima University; K. Ogasawara, Iwate Medical University; S. Mizuno, T. Hoshino, and S. Uchiyama, Tokyo Women's Medical University; N. Hosomi, T. Ohtsuki, and M. Matsumoto, Hiroshima University.

Acknowledgement

This study was supported in part by Grants-in-Aid (H21-Junkanki-Ippan-017 and H24-Junkanki-Ippan-011) from the Ministry of Health, Labor and Welfare of Japan (MHLW-Japan).

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease: Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276–2293.
2 Giles MF, Rothwell PM: Risk of stroke early after transient ischemic attack: a systematic review and meta-analysis. Lancet Neurol 2007;6:1063–1072.
3 Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA: Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med 2007;167:2417–2422.

4 Redgrave JN, Coutts SB, Schulz UG, Briley D, Rothwell PM: Systematic review of associations between the presence of acute ischemic lesions on diffusion-weighted imaging and clinical predictors of early stroke risk after transient ischemic attack. Stroke 2007;38:1482–1488.
5 Miyagi T, Uehara T, Kimura K, Okada Y, Hasegawa Y, Tanahashi N, Suzuki A, Takagi S, Nakagawara J, Arii K, Nagahiro S, Ogasawara K, Nagao T, Uchiyama S, Matsumoto M, Iihara K, Toyoda K, Minematsu K: Examination timing and lesion patterns in diffusion-weighted magnetic resonance imaging of patients with classically defined transient ischemic attack. J Stroke Cerebrovasc Dis 2013;22:e310–e316.
6 Uehara T, Kimura K, Okada Y, Hasegawa Y, Tanahashi N, Suzuki A, Takagi S, Nakagawara J, Arii K, Nagahiro S, Ogasawara K, Nagao T, Uchiyama S, Matsumoto M, Iihara K, Minematsu K: Factors associated with onset-to-door time in patients with transient ischemic attack admitted to stroke centers. Stroke 2014;45:611–613.
7 Fujinami J, Uehara T, Kimura K, Okada Y, Hasegawa Y, Tanahashi N, Suzuki A, Takagi S, Nakagawara J, Arii K, Nagahiro S, Ogasawara K, Nagao T, Uchiyama S, Matsumoto M, Iihara K, Minematsu K: Incidence and predictors of ischemic stroke events during hospitalization in patients with transient ischemic attack. Cerebrovasc Dis 2014;37:330–335.
8 Ueda K, Kiyohara Y, Hasuo Y, Yanai T, Kawano H, Wada J, Kato I, Kajiwara E, Omae T, Fujishima M: Transient cerebral ischemic attacks in a Japanese community, Hisayama, Japan. Stroke 1987;18:844–848.
9 Inoue T, Kimura K, Minematsu K, Yamaguchi T; Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC): Clinical features of transient ischemic attack associated with atrial fibrillation: analysis of 1,084 TIA patients. J Stroke Cerebrovasc Dis 2004;13:155–159.
10 Weimar C, Kraywinkel K, Rödl J, Hippe A, Harms L, Kloth A, Diener HC; German Stroke Data Bank Collaborators: Etiology, duration, and prognosis of transient ischemic attacks: an analysis from the German Stroke Data Bank. Arch Neurol 2002;59:1584–1588.
11 Johnston SC, Gress DR, Browner WS, Sidney S: Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901–2906.
12 Purroy F, Begué R, Gil MI, Quílez A, Sanahuja J, Brieva L, Piñol-Ripoll G: Patterns of diffusion-weighted magnetic resonance imaging associated with etiology improve the accuracy of prognosis after transient ischemic attack. Eur J Neurol 2011;18:121–128.
13 Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Côté R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M; EMBRACE Investigators and Coordinators: Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med 2014;370:2467–2477.