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Clinical Study

Factors associated with early recurrence at the first evaluation of patients with transient ischemic attack

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ABSTRACT

We aimed to identify factors easily collected at admission in patients with transient ischemic attack (TIA) that were associated with early recurrence, so as to guide clinicians' decision-making about hospitalization in routine practice. From September 2011 to January 2013, all TIA patients who were referred to the University Hospital of Dijon, France, were identified. Vascular risk factors and clinical information were collected. The etiology of the TIA was defined according to the results of complementary examinations performed at admission as follows: large artery atherosclerosis (LAA-TIA) TIA, TIA due to atrial fibrillation (AF-TIA), other causes, and undetermined TIA. Logistic regression analyses were performed to identify factors associated with any recurrence at 48 hours (stroke or TIA). Among the 312 TIA patients, the etiology was LAA-TIA in 33 patients (10.6%), AF-TIA in 57 (18.3%), other causes in 23 (7.3%), and undetermined in 199 (63.8%). Early recurrence rates were 12.1% in patients with LAA-TIA, 5.3% in patients with AF-TIA, 4.3% in patients with another cause of TIA, and 1.0% in patients with undetermined TIA. In multivariable analysis, the LAA etiology was independently associated with early recurrence (odds ratio [OR]: 12.03; 95% confidence interval [CI]: 1.84–78.48, $p = 0.009$). A non-significant trend was also observed for AF-TIA (OR: 3.82; 95% CI: 0.40–36.62, $p = 0.25$) and other causes (OR: 3.73; 95% CI: 0.30–46.26, $p = 0.31$). A simple initial assessment of TIA patients in the emergency room would be helpful in targeting those with a high risk of early recurrence and who therefore need to be hospitalized.

1. Introduction

The emergency management of patients presenting with transient ischemic attack (TIA) is a major challenge because of the risk of early ischemic stroke in the few days following the TIA [1]. In routine practice, clinicians are faced with a dilemma, namely to hospitalize or not to hospitalize patients presenting with TIA. On the one hand, hospitalization may be justified as it provides the opportunity to identify stroke early and therefore to provide thrombolysis within the therapeutic time window. On the other hand, systematic hospitalization of all TIA patients is economically inefficient [2], and may be problematic in terms of access to beds. As an alternative, the management of TIA patients in a dedicated same-day TIA clinic has been demonstrated to be both effective and safe [3–5]. However, despite these positive findings, such services remain very limited in France, and French guidelines for the management of TIA patients have not changed and still recommend hospitalization after TIA [6]. As a result, the mean length of stay of TIA patients is 5 days, and this has not greatly improved in recent years [7].

Predicting the risk of early recurrence after TIA would be useful so as to guide physicians in their decisions concerning the need to hospitalize their patients. Prognostic scores have been established to stratify the risk of stroke after TIA, but several limitations make them difficult to use in routine practice. For example, the Age, Blood Pressure, Clinical Features, Duration, and Diabetes plus Dual TIA (ABCD(3)-I) score is not applicable in many settings because MRI is unavailable [8], especially in France where CT scan is the most frequent diagnostic procedure performed in TIA patients.

Therefore, the aim of this study was to identify factors in patients with TIA that were easy to collect at admission and associated with early recurrence, so as to guide clinicians' decision-making about hospitalization in routine practice.

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2. Methods

2.1. Study population and case ascertainment

Data for all patients with TIA who were referred to the University Hospital of Dijon, France, from September 2011 to January 2013 were retrieved using procedures similar to those used by the Dijon Stroke Registry [9]. The University Hospital of Dijon is the only tertiary center with a neurology department and a stroke unit in a geographical area of approximately 520,000 inhabitants. Patients with suspected TIA are usually referred by their general practitioner or by emergency medical dispatchers at the call center when they or their relatives call the national emergency number. They are admitted to the emergency department of the hospital, where they are first managed by an emergency doctor. When a TIA or a stroke is suspected, the emergency doctor immediately calls a stroke-trained neurologist who is available 24 hours a day, 7 days a week to examine the patient, make the diagnosis and decide on complementary examinations and treatment. This procedure takes place in a dedicated specialized stroke/TIA network with management prioritization. Depending on the results of the investigations performed in the emergency department, patients are subsequently admitted as priorities to either the stroke unit or the department of clinical neurology, or another medical department of the hospital if no beds are available in these units, or are discharged to home.

For the few cases of patients who present symptoms compatible with a stroke or TIA while they are hospitalized in clinical departments for another reason, the doctors of these departments refer to the neurologist, who also ensures the management of the patients.

For this study, multiple overlapping sources of information were used to identify TIA patients. (a) A review of computerized hospital diagnostic codes provided by all the departments of the Dijon University Hospital was carried out. The International Classification of Diseases, tenth revision was used. The following codes were initially searched for: I60 (subarachnoid hemorrhage), I61 (intracerebral hemorrhage), I62 (non-traumatic intracranial hemorrhage), I63 (ischemic stroke), I64 (non-determined stroke), G45 (vascular syndromes), G46 (transient ischemic attack) and G81 (hemiplegia). (b) A review of computerized emergency department registers was carried out using the same procedure. (c) A review of computer-generated lists of all requests for brain and cerebral vascular imaging, and all referrals for ultrasound Doppler of cervical arteries was carried out. All queries, including the referral diagnosis and the results of the imaging procedure, were reviewed by study investigators.

TIA was defined according to the World Health Organization criteria as sudden signs and symptoms affecting motor, sensory, sensorial, speech, brainstem and cerebellar functions lasting less than 24 hours [10]. Patients who received intravenous thrombolytic therapy or mechanical revascularization were diagnosed with ischemic stroke even though total recovery was observed within 24 hours. Since all stroke and TIA patients are managed by a neurologist specifically trained in stroke, it was expected that only a small number of patients were misdiagnosed. However, for this study, investigators systematically consulted the medical records of identified patients with suspected TIA or stroke so as to confirm the reported diagnosis or to reclassify the patients if a misdiagnosis was noted. This procedure was applied particularly to avoid the confusion due to the fact that patients with clinical TIA who had a positive diffusion-weighted (DWI) MRI may have been subsequently classified as stroke instead of TIA. Similarly, the review of all medical records by study investigators prevented the misclassification of patients as TIA when symptoms lasted more than 24 hours. Finally, patients with symptom fluctuations defined as complete remitting and relapsing of TIA symptoms for $\geqslant$ two times in the acute phase within the first 24 hours, and those with a previous TIA <1 month were excluded from this study.

2.2. Data collection

The following vascular risk factors were collected: hypertension (high blood pressure noted in a patient's medical history or patients on antihypertensive treatment), diabetes mellitus (glucose level $\geqslant$7.8 mmol/l reported in the medical record or patients on insulin or oral hypoglycemic agents), hypercholesterolemia (total cholesterol level $\geqslant$5.7 mmol/L reported in the medical history or patients treated with lipid-lowering therapy), and history of atrial fibrillation, coronary heart disease, heart failure, peripheral artery disease, smoking, stroke, and TIA. Treatments prior to the TIA, including antiplatelet agents, anticoagulants, antihypertensive treatments and statins were recorded. Vital signs at admission and clinical features (including neurological signs and duration of the TIA) were collected. The ABCD(2) score was calculated for each patient [11].

2.3. Initial assessment of the etiological mechanism of TIA and treatment

At admission, all patients underwent a brain imaging examination. A brain CT scan and brain CT angiography were routinely performed in the first instance at the University Hospital of Dijon for all TIA and stroke patients. In some patients, especially if there was a contra indication, a brain MRI with magnetic resonance angiography (MRA), or a brain CT scan completed with an ultrasound Doppler scan of the cervical arteries was performed. Electrocardiogram (ECG) and biological tests were systematically done. According to the results of these examinations, TIA were initially classified into four etiological categories: large artery atherosclerosis TIA (LAA-TIA) if there was stenosis of more than 50% of a cervical or intracranial artery that could explain the clinical symptoms of the TIA; TIA due to atrial fibrillation (AF-TIA) if atrial fibrillation was detected on the ECG or if patients had a history of known paroxysmal atrial fibrillation; other causes of TIA; and TIA from an undetermined cause after the initial assessment.

Patients were treated according to the current recommendations. Of note, none of the patients with TIA due to large artery atherosclerosis had carotid surgery within 48 hours of their admission.

2.4. Outcome

The outcome was an early recurrent event defined as any TIA or stroke that occurred within the first 48 hours following the admission of TIA patients.

2.5. Statistical analysis

Proportions and mean values of baseline characteristics were compared between groups using the Chi-squared and Wilcoxon test when appropriate. Logistic regression analyses were performed so as to identify factors associated with early recurrence. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. In multivariate models, we introduced age, sex and all variables with a p value <0.20 in unadjusted models. p values <0.05 were considered statistically significant. STATA 10.0 software (StataCorp LP, College Station, TX, USA) was used for the statistical analyses.

2.6. Ethics

This study was conducted in the context of the Dijon Stroke Registry and was approved by the Comité National des Registres (French National Committee of Registers) and the French Institute for Public Health Surveillance (InVS). Authorization of the Commission Nationale de l'Informatique et des Libertés (National Commission for the Protection of the Privacy of Electronic Data) was obtained.

3. Results

A total of 12,539 files were reviewed according to our procedures. Among these, TIA was confirmed in 312 patients (Fig. 1). Baseline characteristics of these patients are shown in Table 1. At admission, 268 (85.9%) patients had a brain CT scan associated with brain CT angiography, nine (2.9%) patients had brain MRI with MRA, 22 (7.0%) patients had a brain CT scan with an ultrasound Doppler scan of the cervical arteries, and 13 (4.2%) patients had a brain CT scan with no exploration of the vessels. Of note, 111 patients had DWI MRI of whom 28 (25.2%) had an ischemic lesion. All of the patients had an ECG and a biological assessment. Based on these examinations, the etiological diagnosis of TIA made at the first assessment was LAA-TIA in 33 patients (10.6%), AF-TIA in 57 (18.3%), other causes in 23 (7.3%), and was undetermined in the remaining 199 (63.8%) patients.

Within the first 48 hours following admission, 10 (3.2%) patients had a recurrent event including five patients with stroke and five with TIA. Recurrence rates were 12.1% (4/33) in patients with LAA-TIA, 5.3% (3/57) in patients with AF-TIA, 4.3% (1/23) in patients with another cause of TIA, and 1.0% (2/199) in patients with undetermined TIA. For these two latter patients, the recurrent event was a TIA. Patients with a recurrent event differed from those without recurrence only with regard to the distribution of the etiological mechanism of the TIA (Table 2). Of note, the ABCD(2) score was similar in the two groups.

In multivariable analysis, the LAA-TIA mechanism was strongly and independently associated with recurrence at 48 hours (OR: 12.03; 95% CI: 1.84–78.48, $p = 0.009$) (Table 3). In addition, a non-significant trend was also observed for AF-TIA (OR: 3.82; 95% CI: 0.40–36.62, $p = 0.25$) and other causes (OR: 3.73; 95% CI: 0.30–46.26, $p = 0.31$).

Table 1
Baseline characteristics of transient ischemic attack patients (n = 312)

	n	%	95% CI
Demographics			
Age, mean ± SD	70.0 ± 15.6		
Age, median (IQR)	72.9 (59.9–82.4)		
Male sex	159	51.0	45.4–56.5
Medical history			
Hypertension	201	64.2	59.1–67.8
Diabetes	56	18.0	13.7–22.2
Hypercholesterolemia	135	42.3	37.7–48.8
Smoking	42	13.5	9.6–17.3
Atrial fibrillation	46	14.7	10.8–18.7
Coronary heart disease	45	14.2	10.5–18.3
Previous stroke	41	13.8	9.4–16.9
Previous TIA	44	14.1	10.2–18.0
PAD	26	8.3	5.2–11.4
Premorbid treatment			
Antiplatelet agent	99	32.7	27.4–40.0
Anticoagulants	35	11.6	7.9–15.2
Antihypertensive therapy	193	61.9	56.4–67.3
Statins	102	33.7	28.3–39.0
TIA mechanism			
LAA-TIA	33	10.6	7.1–14.0
AF-TIA	57	18.3	13.9–22.6
Other causes	23	7.3	4.4–10.3
Undetermined	199	63.8	58.4–69.1

AF-TIA = transient ischemic attack due to atrial fibrillation, CI = confidence interval, IQR = interquartile range, LAA-TIA = transient ischemic attack due to large artery atherosclerosis, PAD = peripheral artery disease, SD = standard deviation.

4. Discussion

This study demonstrated that LAA-TIA was predictive of early recurrence in patients admitted for TIA. Patients with AF-TIA and

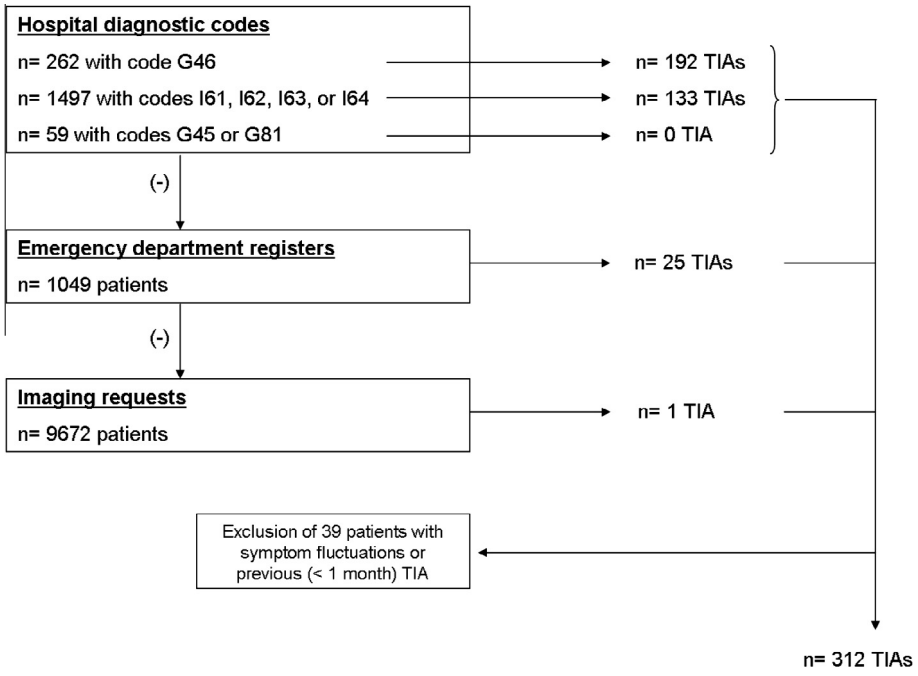

Fig. 1. Flow chart of the study. TIA = transient ischemic attack.

Table 2
Characteristics of transient ischemic attack patients according to recurrence at 48 hours

	No recurrence (n = 302)			Recurrence (n = 10)			
	n	%	95% CI	n	%	95% CI	*p* value
Demographics							
Age, mean ± SD	69.94 ± 15.7			72.1 ± 12.3			0.83
Age, median (IQR)	72.7 (59.8–82.4)			75.4 (61.5–83.0)			0.22
Male sex	152	50.3	44.7–56.0	7	70.0	35.4–100	
Medical history							
Hypertension	194	64.2	58.8–69.7	7	70.0	35.4–100	0.71
Diabetes	55	18.2	13.8–22.6	1	10.0	0.0–32.6	0.51
Hypercholesterolemia	129	42.7	37.1–48.3	6	60.0	23.1–96.9	0.28
Smoking	40	13.3	9.4–17.1	2	20.0	0.0–50.2	0.54
Atrial fibrillation	43	14.2	10.3–18.2	3	30.0	0.0–64.6	0.17
Coronary heart disease	43	14.2	10.3–18.2	2	20.0	0.0–50.2	0.18
Previous stroke	40	13.3	9.4–17.1	1	10.0	0.0–32.6	0.77
Previous TIA	42	13.9	10.0–17.8	2	20.0	0.0–50.2	0.59
PAD	24	8.0	4.9–11.0	2	20.0	0.0–50.2	0.18
Premorbid treatments							
Antiplatelet agents	94	32.1	26.7–37.4	5	50.0	12.3–87.7	0.24
Anticoagulants	32	10.9	7.3–14.5	3	30.0	0.0–64.6	0.063
Antihypertensive therapy	186	61.6	56.1–67.1	7	70.0	35.4–100	0.59
Statins	98	32.5	27.1–37.8	4	40.0	3.1–76.9	0.62
TIA mechanism							0.006
LAA-TIA	29	9.6	6.3–12.9	4	40.0	3.1–76.9	
AF-TIA	54	17.9	13.5–22.2	3	30.0	0.0–64.6	
Other causes	22	7.3	4.3–10.2	1	10.0	0.0–32.6	
Undetermined	197	65.2	59.8–70.6	2	20.0	0.0–50.2	
ABCD(2) score, mean ± SD	4.05 ± 1.49			4.3 ± 1.64			0.56

ABCD(2) = Age, Blood Pressure, Clinical Features, Duration, and Diabetes, AF-TIA = transient ischemic attack due to atrial fibrillation, CI = confidence interval, IQR = interquartile range, LAA-TIA = transient ischemic attack due to large artery atherosclerosis, PAD = peripheral artery disease, SD = standard deviation.

Table 3
Predictors of early recurrence in transient ischemic attack patients in multivariable analysis

Variable	OR	95% CI	*p* value
Age	0.99	0.94–1.04	0.97
Male sex	1.65	0.37–7.35	0.51
Anticoagulants	2.46	0.35–17.34	0.37
Atrial fibrillation	1.15	0.13–3.83	0.90
PAD	1.46	0.24–9.01	0.68
TIA mechanism			
Undetermined	REF	–	–
LAA-TIA	12.03	1.84–78.48	0.009
AF-TIA	3.82	0.40–36.62	0.25
Other causes	3.73	0.30–46.26	0.31

AF-TIA = transient ischemic attack due to atrial fibrillation, CI = confidence interval, LAA-TIA = transient ischemic attack due to large artery atherosclerosis, OR = odds ratio, PAD = peripheral artery disease, REF = reference, TIA = transient ischemic attack.

those with another cause of TIA also had a greater risk of recurrence than did patients with TIA due to an undetermined mechanism, although the difference was not significant. These findings suggest that a simple initial assessment of TIA patients performed at the emergency room would be helpful in targeting those who need to be hospitalized.

Our findings about recurrence rates were consistent with those from the literature. Indeed, a meta-analysis concluded that the risk of stroke within the 48 hours following TIA is 3.1% [1]. Moreover, our study showed that large artery atherosclerosis was strongly associated with the risk of very early new TIA or stroke. Other studies identified this mechanism as an independent risk factor for recurrence at 7 day follow-up [12,13]. Similarly, the risk of recurrence at 7 days in patients with ischemic stroke was shown to be higher for those with large artery atherosclerosis [14]. We chose to focus on the very early risk of recurrence, i.e. recurrence that may occur while the patient is still hospitalized, since our objective was to identify factors in TIA patients that could be easily collected at admission and could help in making the decision about whether or not to hospitalize the patients. This objective was justified for two reasons. Firstly, it has been suggested that currently available clinical scores for predicting recurrent events after TIA may not be accurate enough [15]. For example, in our study, the ABCD(2) score did not differ between patients with and those without a recurrent event. This finding is consistent with results from recent studies, which concluded that this score was unable to predict early stroke after TIA [15–17], while other works suggested that it was a useful predictor [18–20], especially in patients with TIA suspected by non-specialists [21]. Secondly, it has been shown that when brain infarction on MRI is incorporated into the ABCD(2) system, the system is better able to predict early stroke following TIA [22], and that adding carotid imaging improves this ability even further [8]. However, because MRI is not available everywhere, such scores are not always feasible.

In the present study, AF-TIA and other causes of TIA were not significant predictors, but tended to be associated with an increased risk of early recurrence. Conflicting results about the association between AF and the risk of early recurrence after TIA have been published [11,21,23], and to the best of our knowledge, no study has demonstrated an association between other causes of TIA and early recurrence.

We did not include patients with symptom fluctuations. This choice was justified by the fact that it has been already well established that these patients are at high risk of early recurrence, and the decision-making about hospitalization is usually easy in routine practice [13,16].

This work has major clinical implications. The demonstration that a simple initial assessment of TIA patients that includes brain and vessels imaging, ECG and biological tests, and can be performed in the emergency room is able to identify those at high risk of recurrence strongly encourages the implementation of a same-

day TIA clinic in our setting, so as to reduce unnecessary hospitalizations of TIA patients. Only two of the 199 patients in whom the TIA etiology was undetermined at the first evaluation had an early recurrent event. Of note, in these two patients, the recurrent event was a new TIA.

The major strength of this study was the use of well-established procedures similar to those used in the Dijon Stroke population-based registry, which ensured that case-ascertainment of TIA patients admitted to hospital was exhaustive. Moreover, the fact that in our study sample 25% of TIA patients had a positive DWI MRI is a strong argument to support the assumption that our retrospective multimodal procedure to identify TIA patients was unbiased by the exclusive use of discharge diagnostic codes. In addition, the fact that patients were assessed using readily available examinations means that our findings can be generalized to other settings, including non-tertiary centers for stroke and TIA management. However, our study was limited by the small number of patients included. It therefore lacked sufficient power to draw any definite conclusions about the association between either AF-TIA or other causes of TIA and recurrent events.

To conclude, patients presenting with TIA due to large artery atherosclerosis identified at the initial evaluation, and to a lesser degree those with either AF-TIA or another cause of TIA, are at a high risk of a recurrent cerebral ischemic event within the first 48 hours. An easy-to-do assessment that includes brain and vessel imaging, ECG, and biological tests would be of use in the rapid triage of TIA patients so as to identify those who need to be kept in hospital.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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