

Attack Interval Is the Key to the Likely Pathogenesis of Multiple Transient Ischemic Attacks

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Keywords

Transient ischemic attack · Capsular warning syndrome ·
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Abstract

Introduction: The aim of this study was to test the hypothesis that the attack interval of multiple transient ischemic attacks (TIAs) is correlated with the underlying pathogenesis of ischemia. **Methods:** Patients with multiple TIAs, defined as 2 or more motor deficits within 7 days, were studied. The attack interval between the last 2 episodes was classified into 3 groups: 2 episodes within an hour (Hour group), over hours within a day (Day group), and over days within a week (Week group). Patients with a lacunar syndrome, no cortical lesions, and no embolic sources were recognized as having a small vessel disease (SVD) etiology for their multiple events. **Results:** Of 312 TIA patients admitted over a 9-year period, 50 (37 males, 13 females, mean 67.6 years) had multiple TIAs. Twelve patients were classified as being within the Hour group, 23 within the Day group, and 15 within the Week group. Lacunar syndromes were observed in 30 (75%, 35%, and 67%), embolic sources were detected in 28 (25%, 65%, and 67%), and a high signal lesion on diffusion-weighted imaging was depicted in 30 (75%, 48%, and 67%) patients (18 cortical, 11 subcortical, and one cerebellar). Patients in the

Hour group had a significantly higher prevalence of SVD etiology (75%) than those in the Day and Week groups (30%, $p = 0.0165$; 27%, $p = 0.0213$, respectively). Four patients had a subsequent stroke within 7 days. **Conclusion:** Attack intervals of multiple TIAs may be correlated with the underlying pathogenesis of ischemia. Two motor deficits within an hour are more likely to suggest a SVD etiology.

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Introduction

Patients with transient ischemic attacks (TIAs) are recognized to be at high risk of early stroke and recent studies have shown that early treatment is effective in subsequent stroke prevention. Practical guidelines, therefore, recommend triage of patients by ABCD2 score (age, blood pressure, clinical features, duration, and diabetes) [1]. In addition to the ABCD2 items, some clinical variables have been proposed to enhance the prediction of stroke. For example, multiple TIAs, also called crescendo TIAs, or dual TIAs when the attacks occur twice, have been recognized as contributors to early stroke risk [2, 3].

Capsular warning syndrome (CWS) is a particular example of multiple TIAs, in which 3 or more events of motor, sensory, or sensorimotor symptoms affecting the

face, arm, and leg simultaneously, with no cortical signs, occur within 24 h. The probability of subsequent early capsular stroke is high [4]. While multiple TIAs have a heterogeneous underlying pathogenesis including artery-to-artery or cardiogenic embolism, as well as small vessel disease (SVD), CWS is a pathophysiologically and prognostically distinct form of TIA due to ischemia within the territory of a single penetrating artery.

In this study, we aimed to determine whether the attack interval of patients presenting with multiple TIAs is correlated with the underlying ischemic pathogenesis. We also wished to delineate the characteristics of CWS among those of multiple TIAs.

Methods

We retrospectively reviewed the clinical records of consecutive patients who presented with TIA and admitted to our hospital within 7 days after onset, between April 2007 and March 2016. TIA was defined as a brief episode of a focal neurological deficit due to cerebral ischemia lasting for 24 h or less, regardless of neuroimaging evidence of acute infarction [5]. Patients with multiple TIAs were defined as having 2 or more attacks of limb weakness within 7 days and were included in this study. It was required that for those patients with multiple events, limb weakness should be completely resolved between each episode. Isolated sensory symptoms were not included as a form of multiple TIA. Patients who had a deficit at the time of administration of any specific therapy for ischemia were excluded from this study, even if they had completely recovered within 24 h. An attack interval between the last 2 episodes of multiple TIAs was classified into 3 groups: when the last 2 episodes had occurred within an hour (Hour group), over hours within a day (Day group), and over days within a week (Week group). In accord with standard departmental screening protocols to determine the underlying etiology of the event, blood tests, chest X-ray, ECG, echocardiography, carotid duplex sonography, and brain CT were performed routinely upon admission. Multimodal MRI, including diffusion-weighted imaging (DWI) and MR angiography, were also performed on admission or on the first business day after unless patients were noncompliant. If the initial scan was negative, MRI or CT was repeated within 14 days. All patients had continuous ECG monitoring for 3 or more days and a Holter ECG monitoring unless atrial fibrillation had been previously recorded. Transesophageal echocardiography (TEE) was carried out when no relevant embolic sources were detected by the above routine investigations. Atrial fibrillation on ECG, ipsilateral intracranial arterial occlusive diseases (>50% stenosis or occlusion determined by either CT or MR angiography, or digital subtraction angiography), ipsilateral carotid disease (>50% or occlusion determined by either CT or MR angiography, or digital subtraction angiography), a complicated aortic arch atheroma on TEE, and patent foramen ovale on TEE with deep venous thrombosis were identified as a potential embolic source. The pathogenesis of the TIA was categorized into SVD and non-SVD, depending on symptoms, imaging findings, and concomitant embolic sources. If patients presented with a lacunar syndrome, that is, clinical

features suggesting subcortical ischemia [4], had a subcortical lesion or no lesions on DWI and no concomitant embolic sources, they were categorized as having a SVD etiology. Otherwise, those with a nonlacunar syndrome, a cortical lesion, or an embolic source were categorized as having a non-SVD etiology.

Results

Clinical Characteristics

During a 9-year period of study between April 2007 and March 2016, 3,118 patients were admitted to our hospital due to ischemic stroke or TIA within 7 days of onset, and 312 were diagnosed with TIA. Of these, 50 (16.0%) had multiple TIAs. Clinical characteristics of the patients are shown in Table 1. Only 9 (2.9%) had 3 or more attacks within 24 h. According to an attack interval, 12 patients were classified into the Hour group, 23 into the Day group, and 15 into the Week group. No significant differences between the groups were observed in age, sex, risk factors, and stroke history. Thirty patients had lacunar syndromes with motor deficits, while the remaining 20 had nonlacunar syndrome. The latter included symptoms of arm or leg monoparesis in 14, cortical symptoms in 2, and vertebrobasilar symptoms in one. In all groups, motor deficits involving both arm and leg were the most common pattern.

Embolic Sources

Potential sources of embolism were detected in 28 patients, 25 of which were in the Day and Week groups (Table 1). Two patients had ipsilateral arterial disease together with atrial fibrillation. Of 19 patients who had TEE examination, one had complicated aortic arch atheroma as well as an intracranial arterial disease. Patients without embolic sources had shorter attack intervals than those without (median, interquartile range: 2, 1–20 vs. 11, 3–48 h; mean \pm standard deviation: 21.4 \pm 39.7 vs. 30.0 \pm 39.5 h).

MRI Findings

All 50 patients had multimodal MRI, which was performed on the day of admission in 41, on the second day in 7, and on the third day in 2. Lesion topography is shown in Table 2 and Figure 1.

Pathogenesis of TIA

SVD etiology was significantly more frequent in the Hour group (75%) than in the Day and Week group (30%, $p = 0.0165$; 27%, $p = 0.0213$; by Fisher's exact test, respectively) (Table 1).

Table 1. Clinical characteristics of patients with multiple TIAs

	Total (n = 50)	Hour group (n = 12)	Day group (n = 23)	Week group (n = 15)
Mean age, year	67.6±11.4	65.1±10.0	68.7±12.4	68.0±11.3
Male	37 (74)	10 (83)	16 (70)	11 (73)
Hypertension	38 (76)	10 (83)	16 (70)	12 (80)
Diabetes	11 (22)	0	6 (26)	5 (33)
Dyslipidemia	27 (54)	5 (42)	14 (61)	8 (53)
Smoking	26 (52)	5 (42)	12 (52)	9 (60)
Stroke history	4 (8)	1 (8)	2 (9)	1 (7)
Median duration of TIA				
The last attack, min	10 (1–180)	20 (2–60)	5 (1–150)	30 (5–180)
The second last attack, min	18 (1–720)	6 (2–50)	10 (1–720)	30 (2–480)
Interval between the last 2 attacks				
Median, hour	5 (0.3–168)	0.6 (0.3–1)	5 (1.3–24)	60 (30–168)
Mean, hour	26.2±39.4	0.7±0.3	7.6±7.7	75.2±40.5
Lacunar syndrome	30 (60)	9 (75)	8 (35)	10 (67)
Cortical symptoms	2 (4)	0	1 (4)	1 (7)
Motor deficits				
Face + arm + leg	6 (12)	4 (33)	2 (9)	0
Face + arm	3 (6)	0	3 (13)	0
Arm + leg	27 (54)	5 (42)	12 (52)	10 (67)
Arm	11 (22)	1 (8)	5 (22)	5 (33)
Leg	3 (6)	2 (17)	1 (4)	0
Embolic sources	28 (56)	3 (25)	15 (65)	10 (67)
Atrial fibrillation	3 (6)	0	2 (9)	1 (7)
Carotid occlusive disease	10 (20)	0	6 (26)	4 (27)
Intracranial arterial occlusive disease	13 (26)	1 (8)	8 (35)	4 (27)
Complicated aortic arch atheroma	4 (8)	2 (17)	0	2 (13)
Patent foramen ovale with DVT	1 (2)	0	1 (4)	0
Pathogenesis of TIA				
SVD	20 (40)	9 (75)	7 (30)	4 (27)
Non-SVD	30 (60)	3 (25)	16 (70)	11 (73)
Seven-day stroke risk	4 (8)	3 (25)	1 (4)	0

Data are number (%) of patients, mean ± SD, or median (range). DVT, deep venous thrombosis; SVD, small vessel disease; TIA, transient ischemic attack; SD, standard deviation.

Table 2. MRI findings in patients with multiple TIAs

Lesion site	Total (n = 50)	Hour group (n = 12)	Day group (n = 23)	Week group (n = 15)
Cortical	18 (36)	2 (17)	7 (30)	9 (60)
Subcortical	11 (22)	7 (58)	3 (13)	1 (7)
Cerebellar	1 (2)	0	1 (4)	0
No lesions	20 (40)	3 (25)	12 (52)	5 (33)

Data are number (%) of patients. TIA, transient ischemic attack.

Treatment

As initial treatment, anticoagulants were used in 45 patients and antiplatelet agents were 44 (dual in 29 and single in 15). One patient who had a subsequent stroke during the initial evaluation was given intravenous recombinant tissue plasminogen activator, and only one

had no antithrombotic therapy. Dual antiplatelet therapy with an anticoagulant was the most popular treatment (27 patients), following single antiplatelet agents with anticoagulant (14 patients). Twenty-five patients were taking antihypertensive treatment and 36 patients statins.

Seven-Day Risk of Stroke

Four patients had a subsequent stroke within 7 days (Table 1). Of these, 3 patients in the Hour group developed stroke on Day 1, and one in the Day group had a stroke on Day 3. When the subsequent event happened, 2 had dual antiplatelet therapy with an anticoagulant, one had an anticoagulant only, and one had no antithrombotic therapy due to incomplete initial evaluation. All had an ischemic lesion on the first MRI in the penetrating artery territory (2 in the anterior choroidal artery and 2 in the lenticulostriate artery) and infarct growth in the same artery territory on the follow-up MRI. A representative case is reported in Figure 2.

Discussion

We have shown that among patients with multiple TIAs, those with 2 attacks within an hour (the Hour group) had a significantly high prevalence of SVD as an etiology and a considerable risk of early penetrating artery territory infarction. Conversely, when 2 attacks occurred over hours (the Day group) or days (the Week group), embolic sources were more frequently detected (two-thirds of cases), and the early risk of stroke was quite low. These results suggested that the attack interval of multiple TIAs may reflect its underlying pathogenesis.

The pathophysiological mechanism underlying multiple TIAs varies. A number of investigators have suggested that cardioembolism may be the presumed cause in 10–17%, large-artery atherosclerosis in 18–25%, and SVD in 14–37% of cases [2, 3, 6, 7]. Some have suggested that a SVD etiology was more likely in patients with multiple TIAs in comparison to those with a single TIA [3, 6], while this finding was not supported by others [2]. This discrepancy may be due to difficulty in the etiological classification of all many patients with TIA. The Trial of Org 10,172 in Acute Stroke Treatment classification is often used to determine etiological subtypes of TIA [2, 3, 7], in which diagnoses of SVD are based on clinical lacunar syndromes and CT or MRI findings corresponding to small subcortical infarcts [8]. According to DWI-based studies using the 24 h time-based definition of TIA, the frequency of positive DWI findings ranged from 9 to 67% [9]. It is known that without imaging, the phenotypic expression of lacunar syndromes is less reliable in diagnosing lacunar infarction [10, 11]. Furthermore, diagnostic errors are unavoidable when clinicians are assessing lacunar syndromes with transient symptoms described by patients rather than by neurological examination.

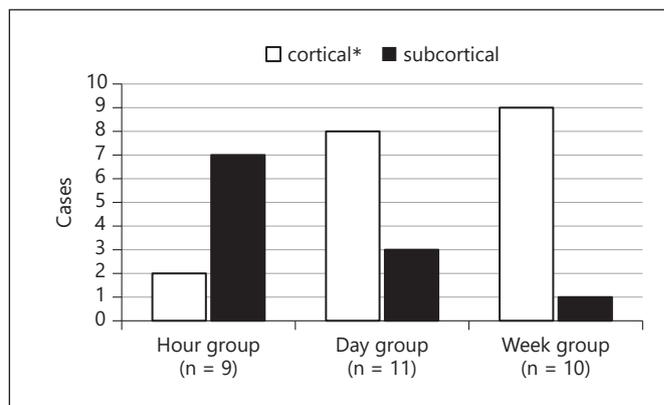


Fig. 1. Lesion topography on DWI in patients with multiple TIAs. The number of cases with cortical lesions (white column) and with subcortical lesions (black column) is shown by the groups of different attack intervals. The shorter the attack interval of multiple TIAs is, the more prevalent are subcortical lesions. *Including one patient with a cerebellar lesion. DWI, diffusion-weighted imaging; TIA, transient ischemic attack.

The most dramatic and stereotypic example of multiple TIAs with a SVD etiology is known as CWS. CWS was first postulated in early 1980s as pathophysiologically and prognostically distinct form of multiple TIAs, where the ischemia was restricted to the region of the internal capsule due to single penetrating vessel disease, leading to early capsular infarction [4, 12, 13]. The original definition of CWS was 3 or more events of motor, sensory, or sensorimotor symptoms affecting face, arm, and leg simultaneously, with no cortical signs, all within 24 h [4]. Due to the infrequency of CWS; however, the original definition has been modified by a number of investigators to extend the time period beyond 24 h [3, 14, 15] or reduce number of events [7, 16]. Even so, the prevalence of CWS is less than 10% among all TIAs (Table 3). Some authors have proposed the concept of dual or multiple TIAs consisting of repetitive focal neurological deficits regardless of lacunar syndrome or other phenotypic expressions [2, 3, 6, 7, 17, 18]. Overall, multiple TIAs are more common as a form of TIA than CWS, the latter of which form only a small subset. Multiple TIAs are pathophysiologically heterogeneous with a range of mechanisms including cardiac sources of embolism or large-artery occlusive disease as we have shown in this study [2, 3, 6, 7].

Although the exact mechanism of CWS remains unclear, it is supposed that hemodynamic factors secondary to high-grade stenoses within penetrating arteries or at their orifices at the parent artery are the most likely mech-

Fig. 2. MRI findings of a 66-year-old man with repetitive episodes of left face, arm, and leg weakness. The first episode lasting 30 min completely resolved shortly after arriving at the emergency room. **a** Twenty-five minutes later, the second 30-min episode occurred while preparing MRI scans, which shows mild DWI restriction in the right corona radiata. After a complete resolution of the second attack, he again developed a dense left hemiplegia and was given intravenous recombinant tissue plasminogen activator. The symptoms fluctuation was observed over the next 3 days, and moderate left face, arm, and leg weakness remained. **b** DWI on day 10 demonstrates higher restriction and lesion enlargement in the same lenticulostriate artery territory. DWI, diffusion-weighted imaging.

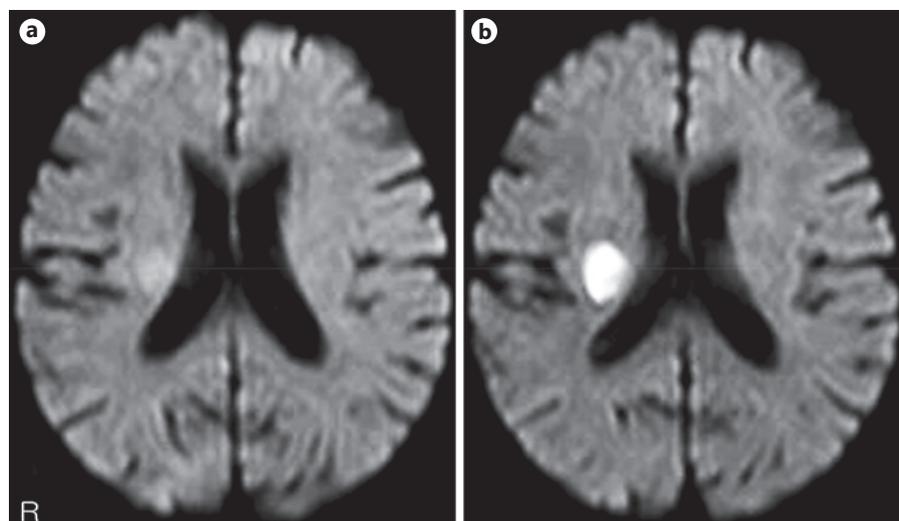


Table 3. Comparison of clinical characteristics of multiple TIAs by different definitions

Definitions	Author	Cases, <i>n</i>	Prevalence in TIA, %	Cardiac sources of embolism, %	Large-artery occlusive disease, %	Early risk of stroke, %
Lacunar syndrome						
≥3 episodes, ≤24 h	Donnan et al. [4, 13]	50	4.5	2.0	2.0	32
≥3 episodes, ≤48 h	He et al. [15]	72	1.7*	0	0	72
≥2 episodes, ≤48 h	Tassi et al. [16]	18	8.3	0	0	78
≥3 episodes, ≤7 days	Foschi et al. [3]	33	3.3	n.a.	n.a.	>60 [†]
Motor or sensorimotor lacunar syndrome						
≥3 episodes, ≤24 h	Staaf et al. [21]	8	n.a.	0	0	50
≥3 episodes, ≤72 h	Camps-Renom et al. [14]	42	n.a.	9.5	12	31
≥2 episodes, ≤7 days	Paul et al. [7]	15	1.5	0	0	60
Focal neurological deficits						
≥2 episodes, ≤24 h	Crespo et al. [6]	70	n.a.	10	17	30
	Chatzikonstantinou et al. [17]	67	29	n.a.	n.a.	19
≥2 episodes, ≤7 days	Paul et al. [7]	170	17	13	18	11
	Purroy et al. [2]	274	24	17	25	5.8
	Lim et al. [18]	77	15	n.a.	n.a.	9.1 [†]
	Foschi et al. [3]	213	21	16	27	7.1
Motor deficits						
≥2 episodes, ≤1 h	Present study	12	3.8	0	0	25
≥3 episodes, ≤24 h	Present study	9	2.9	11	22	22
≥2 episodes, ≤24 h	Present study	35	11	8.6	17	11
≥2 episodes, ≤7 days	Present study	50	16	8.0	20	8.0

TIA, transient ischemic attack; h, hour; n.a., not applicable. * Prevalence in acute ischemic stroke and TIA. [†] 90-day risk.

anisms [4, 6, 19, 20]. Because a penetrating artery supplying the region of the internal capsule has poor collateral flow, subtle hemodynamic changes due to blood pressure fluctuations, changes in blood viscosity, platelet aggregation or adhesion, superimposed microthrombosis, or a combination of these may lead repetitive motor deficits

within a quite brief time period. Another suggested mechanism was the generation of peri-infarct depolarizations adjacent to the internal capsule, thus causing intermittent motor symptoms [21]. Conversely, embolic artery-to-artery phenomena cause events more widely separated in time [4]. Given that such a clinical time course may reflect

a different pathogenesis of multiple TIAs, categorization by attack intervals of multiple TIAs may be reasonable and practical.

Multiple TIAs have been validated as an independent predictor of early subsequent ischemic stroke in several large cohort studies [2, 3], where the early risk of stroke in multiple TIAs is around 10%, and much less than the risk reported after CWS [3, 4, 7, 13–16, 21] (Table 3). Within the entire cohort of this study, the 7-day stroke risk of 8.0% was comparable to previous studies of multiple TIAs [2, 3, 7, 18]. When the attack interval was limited to 1 h time span, the 7-day risk of stroke increased to 25%, which is, however, still not as high as the risk described in the original CWS cohort.

Therapeutic resistance was mentioned as a consistent feature of CWS [4]. Since then, various strategies, such as blood pressure augmentation [22], anticoagulation [21, 22], antiplatelet therapy [15, 16, 23], and these in combination [21, 24] have been administered to attenuate crescendo attacks and to prevent a subsequent stroke. In the presence of an attack with disabling symptom not resolving within minutes, intravenous thrombolysis may be considered, as occurred in one patient in this study [15]. Recently, dual antiplatelet therapy with a loading dose has been established as an effective early management of patients with TIA [25], which is may also be a promising therapeutic approach in CWS [24]. In this study, 29 of 50 patients had dual antiplatelet therapy, mostly with a loading dose, and 41 patients had a combination of antiplatelet and anticoagulant therapy. Since a subsequent stroke rarely happened in the Day or Week group, this combination therapy may be more effective to patients with non-SVD etiology, such as artery-to-artery or cardiogenic embolism, than to patients with a SVD etiology [26]. It may be also true that patients in the Day or Week group have longer therapeutic time window than in the Hour group. Indeed, 3 patients in the Hour group developed stroke on Day 1. Among 30 patients with a DWI-positive lesion, 26 did not have permanent neurological deficits, and even 4 patients with a subsequent stroke had a favorable functional outcome at 90 days (modified Rankin Scale one in 2 patients and 2 in 2 patients). In a recent study of CWS in which patients were frequently treated with combination antithrombotic therapy, it was shown that these patients had a favorable prognosis in spite of the high frequency of a DWI-positive lesion [15]. Hence, an aggressive therapeutic intervention such as this may reduce the risk of subsequent stroke in CWS patients.

There are some limitations to this study. First, this is a single-center style with retrospective analysis and, there-

fore, can induce bias into the results. Especially, initial treatment was not standardized, although a combination therapy of an antiplatelet agent with an anticoagulant was the major treatment in all 3 groups. The result should be confirmed by multicenter prospective studies. Second, among patients without a DWI lesion, TIA mimics might be included. To minimize diagnostic errors, we used our hospital stroke registry, in which all patients were assessed by a stroke neurologist, and a final diagnosis was made after a diagnostic workup.

Conclusions

We have shown that attack time intervals were correlated with the underlying pathogenesis of patients presenting with multiple TIAs. Two motor deficits within an hour may be an important feature to suggest a SVD etiology to the events, such as in seen in the exemplar CWS among patients with multiple TIAs. Conversely, when 2 episodes occur over hours, this is more likely to suggest a non-SVD etiology, most commonly cardiac or artery-to-artery embolism.

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Statement of Ethics

The use of human subjects for this study has been approved by the institutional review board of Kyoto Second Red Cross Hospital (the reference No: Sp2020-15). Because this is a retrospective cohort study where the deidentified clinical records were reviewed without any interventions to participants, our institutional review board waived the need for written informed patients consent in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yoshinari Nagakane designed and conceptualized study, analyzed the data, and drafted the manuscript for intellectual content. Tomoyuki Ohara had a major role in acquisition of data, interpreted the data, and revised the manuscript for intellectual content. Eijirou Tanaka, Takehiro Yamada, Shinji Ashida, Yuta Kojima, Keiko Maezono, Shiori Ogura, Daisuke Nakashima, and Takamasa Kitaoji had a major role in acquisition of data. Yasumasa Yamamoto revised the manuscript for intellectual content.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369(9558):283–92.
- 2 Purroy F, Jiménez Caballero PE, Gorospe A, Torres MJ, Alvarez-Sabin J, Santamarina E, et al. Recurrent transient ischaemic attack and early risk of stroke: data from the PROMAPA study. *J Neurol Neurosurg Psychiatry*. 2013 Jun;84(6):596–603.
- 3 Foschi M, Pavolucci L, Rondelli F, Spinardi L, Favaretto E, Filippini M, et al. Prospective observational cohort study of early recurrent TIA: features, frequency, and outcome. *Neurology*. 2020 Sep 22;95(12):e1733–44.
- 4 Donnan GA, O'Malley HM, Quang L, Hurley S, Bladin PF. The capsular warning syndrome: pathogenesis and clinical features. *Neurology*. 1993 May;43(5):957–62.
- 5 Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke*. 1990 Apr;21(4):637–76.
- 6 Crespo M, Melo TP, Oliveira V, Ferro JM. Clustering transient ischemic attacks. *Cerebrovasc Dis*. 1993;3(4):213–20.
- 7 Paul NL, Simoni M, Chandratheva A, Rothwell PM. Population-based study of capsular warning syndrome and prognosis after early recurrent TIA. *Neurology*. 2012 Sep 25;79(13):1356–62.
- 8 Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke*. 1993 Jan;24(1):35–41.
- 9 Brazzelli M, Chappell FM, Miranda H, Shuler K, Dennis M, Sandercock PA, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Ann Neurol*. 2014 Jan;75(1):67–76.
- 10 Arboix A, Massons J, García-Eroles L, Targa C, Comes E, Parra O. Clinical predictors of lacunar syndrome not due to lacunar infarction. *BMC Neurol*. 2010 May 18;10:31.
- 11 Potter G, Doubal F, Jackson C, Sudlow C, Dennis M, Wardlaw J. Associations of clinical stroke misclassification ('clinical-imaging dissociation') in acute ischemic stroke. *Cerebrovasc Dis*. 2010;29(4):395–402.
- 12 Donnan GA, Tress BM, Bladin PF. A prospective study of lacunar infarction using computerized tomography. *Neurology*. 1982 Jan;32(1):49–56.
- 13 Donnan GA, O'Malley HM, Quang L, Hurley S. The capsular warning syndrome the high risk of early stroke. *Cerebrovasc Dis*. 1996;6(4):202–7.
- 14 Camps-Renom P, Delgado-Mederos R, Martínez-Domeño A, Prats-Sánchez L, Cortés-Vicente E, Simón-Talero M, et al. Clinical characteristics and outcome of the capsular warning syndrome: a multicenter study. *Int J Stroke*. 2015 Jun;10(4):571–5.
- 15 He L, Xu R, Wang J, Zhang L, Zhang L, Zhou F, et al. Capsular warning syndrome: clinical analysis and treatment. *BMC Neurol*. 2019 Nov 13;19(1):285.
- 16 Tassi R, Cerase A, Acampa M, D'Andrea P, Guideri F, Lo Giudice G, et al. Stroke warning syndrome: 18 new cases. *J Neurol Sci*. 2013 Aug 15;331(1–2):168–71.
- 17 Chatzikonstantinou A, Wolf ME, Schaefer A, Hennerici MG. Risk prediction of subsequent early stroke in patients with transient ischemic attacks. *Cerebrovasc Dis*. 2013;36(2):106–9.
- 18 Lim JS, Hong KS, Kim GM, Bang OY, Bae HJ, Kwon HM, et al. Cerebral microbleeds and early recurrent stroke after transient ischemic attack: results from the Korean transient ischemic attack expression registry. *JAMA Neurol*. 2015 Mar;72(3):301–8.
- 19 Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. *Neurology*. 1989 Sep;39(9):1246–50.
- 20 Xu X, Wei Y, Zhang X, Yang L, Cui Z, Yan J. Value of higher-resolution MRI in assessing middle cerebral atherosclerosis and predicting capsular warning syndrome. *J Magn Reson Imaging*. 2016 Nov;44(5):1277–83.
- 21 Staaf G, Geijer B, Lindgren A, Norrving B. Diffusion-weighted MRI findings in patients with capsular warning syndrome. *Cerebrovasc Dis*. 2004;17(1):1–8.
- 22 Lalive PH, Mayor I, Sztajzel R. The role of blood pressure in lacunar strokes preceded by TIAs. *Cerebrovasc Dis*. 2003;16(1):88–90.
- 23 Li W, Wu Y, Li XS, Liu CC, Huang SH, Liang CR, et al. Intravenous tirofiban therapy for patients with capsular warning syndrome. *Stroke Vasc Neurol*. 2019 Mar;4(1):22–7.
- 24 Kawano H, Nakajima M, Inatomi Y, Yonehara T, Ando Y. Loading dose of clopidogrel in combination with other antithrombotic therapy for capsular warning syndrome. *J Stroke Cerebrovasc Dis*. 2014 May–Jun;23(5):1265–6.
- 25 Amarenco P. Transient ischemic attack. *N Engl J Med*. 2020 May 14;382(20):1933–41.
- 26 Ohara T, Uehara T, Sato S, Hayakawa M, Kimura K, Okada Y, et al., PROMISE-TIA Study Investigators. Small vessel occlusion is a high-risk etiology for early recurrent stroke after transient ischemic attack. *Int J Stroke*. 2019 Dec;14(9):871–7.