Stroke Mimics and Accuracy of Referrals Made by Emergency Department Doctors in Japan for Patients with Suspected Stroke

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Background: Stroke mimics (SMs)are medical conditions that are at first considered to be of cerebrovascular etiology but turn out to be a condition other than stroke. While many reports on SMs have been published, there have been none from Japan. Thus, we sought to assess the current state of SMs in a Japanese population. *Methods:* We collected data of patients referred with suspicion of stroke to neurosurgeons by emergency department (ED) doctors, and we retrospectively evaluated the diagnosis concordance rate between the ED doctors and the neurosurgeons. We also assessed the plausible causes leading to misdiagnosis of stroke. *Results:* Of the 226 consecutive referrals with suspicion of stroke, only 71.7% were accurate. Furthermore, 75% of the SMs were disorders unrelated to neurosurgery, such as psychiatric disorders, peripheral dizziness/vertigo, and cardiovascular events. In other words, referring those patients to neurosurgeons was inappropriate. We found that perceived notion or premature assumption of stroke accounted for 43.8% of the stroke mimic patients and was the most important reason for the misdiagnosis. *Conclusions:* This is the first report on SMs in a Japanese population. About one-third of all referrals with suspicion of stroke made by ED doctors were inappropriate. Including more information on stroke diagnosis in the educational program for young doctors in Japan would be beneficial for improving the quality of the initial medical examination of patients with suspected stroke.

Key Words: Stroke mimics—accuracy of referrals—emergency department—Japanese community hospital—neurosurgery—burnout—perceived notion of stroke—consultation

Introduction

Japan is a rapidly aging country, with an increasing number of stroke patients. In medical care for stroke patients, it is indispensable to coordinate work with emergency department (ED) doctors; however, the diagnosis of suspected stroke by ED doctors is not always accurate. Many medical conditions initially considered to be of cerebrovascular etiology turn out to be conditions other than stroke; these misdiagnosed strokes are called stroke mimics (SMs). Since ED doctors are usually not stroke specialists, they might not easily recognize some SMs, and consequently, before vascular neurologists or neurosurgeons are called, not a few SM patients are misdiagnosed with stroke and even given recombinant tissue-plasminogen activators (rt-PA).[1-4]

Although a number of articles on SMs have been published, articles from Japan have been limited to single case reports or case series. We believe that analyzing the current status of SMs and the possible reasons for this problem and ways to solve it is crucial for Japanese society. In Japan, several issues may influence

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misdiagnosis of stroke. The first is the availability of imaging tests: the number of computed tomography (CT) and magnetic resonance imaging (MRI) devices per capita is much larger in Japan than in any other country,[5] which allows Japanese patients to undergo imaging tests easily, even at night. Another issue is the medical care system organization with its insufficient numbers of emergency doctors, no shift-work system, and nonspecialists as rotating doctors on duty.[6] Additionally, the universal health insurance coverage system in Japan, called "*Kokumin-Kai-Hoken-Seido*" in Japanese, allows Japanese citizens to access medical facilities easily and independently in terms of both place and time and with relatively low personal charges to be paid, which may also play a role in the number of SMs.

Furthermore, after the *Japanese Guidelines for the Management of Stroke 2015* was updated in 2017,[7] interventional radiology became a standard treatment for hyperacute stroke patients along with administration of rt-PA. Since these treatments have tight time constraints, ED doctors must consider the differential diagnosis in a shorter time than ever before, which may result in an increased rate of misdiagnosis.[8] In parallel, as the population continues to age, the number of stroke patients along with that of SM patients is expected to increase. Given that as many as 40% of Japanese stroke physicians or vascular neurologists have already been reported to be suffering from burnout,[9] this increase may lead to a heavier burden for doctors working in stroke care and exacerbate their exhaustion further. Therefore, to enhance the quality of medical practice for stroke patients, it is important to elucidate the causes of or backgrounds leading to misdiagnoses of strokes.

In this study, we aimed to assess the current state of SMs and the accuracy of referrals for suspected stroke patients by ED doctors and to analyze the factors associated with SMs in Japanese community hospitals.

Materials and Methods

Patients and Hospitals

Patients referred by ED doctors to a neurosurgeon (in most cases, the first author) because of suspected stroke or transient ischemic attack (TIA) from April 2015 to March 2017 were enrolled in the study. Owing to the first author's relocation, the study was conducted first in Ibaraki Seinan Medical Center Hospital (Sakai, Ibaraki, Japan) and later in Kobari General Hospital (Noda, Chiba, Japan). Both hospitals are located in rural or suburban areas near the borders between the Ibaraki, Chiba, and Saitama prefectures. Although they have no stroke specialists among the ED doctors, both hospitals play an important role in providing secondary emergency medical services to the surrounding medical districts.

Study Design

We collected data on patients with suspected stroke or TIA who were referred to a board-certified neurosurgeon by ED doctors, and we evaluated the diagnosis concordance rate between the ED doctors and the neurosurgeon and retrospectively analyzed the factors associated with SMs. To avoid selection biases and to ensure the accuracy of the data collection, we limited the patients to those who were directly referred to the first author. We excluded referrals for suspected conditions other than stroke or TIA, inpatient referrals, transfers from other hospitals, and nonurgent consultations. When referrals were accepted, patients of interest were examined by at least 1 board-certified neurosurgeon (including the first author) and the diagnosis was based on the clinical, laboratory, and neuroimaging findings. When the diagnosis was thought to be difficult at the moment of the initial examination, the patients were hospitalized or followed up and reexamined for appropriate diagnosis through discussion with other neurosurgeons and physicians. A number of factors were evaluated in this study: age, sex, focal symptoms (eg, hemiparesis, aphasia, and dysarthria), history of stroke, history of vascular risk factors (eg, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary artery disease, and chronic kidney disease on hemodialysis), risk factors associated with living conditions (welfare recipients, patients without family support, patients living alone, age >40 years without marriage), unclear history of the present illness (difficulty in taking the history of the present illness owing to preexisting conditions such as dementia, mental retardation, and psychiatric disorder), whether the referral was made within 4.5 hours of the onset (defined as *hyperacute*), whether MRI was taken before the referral, and whether the referral was in the daytime (8 AM-5 PM).

Stroke Mimics (SMs)

We defined SM cases as those in which the final diagnosis was a disorder other than stroke or TIA. We divided the SMs into 2 main groups: nonneurosurgical disorders and neurosurgical disorders. The nonneurosurgical disorders included cardiovascular events/collapses (aortic dissection, myocardial infarction, neurally mediated syncope, and heart failure), hypoglycemia, hyponatremia, intoxication/adverse drug effects (alcohol/organophosphate intoxication, overdose administration), peripheral dizziness/vertigo, peripheral neuropathy/artery disease (carpal tunnel syndrome, sciatic neuralgia), psychiatric/psychogenic disorder, spinal disorder (spondylosis, spinal canal stenosis, and spinal injury), systemic infection/sepsis, and other/unclear conditions. The neurosurgical disorders were as follows: brain tumor, cranial nerve palsy, epileptic seizures, migraine, transient global amnesia, and traumatic intracranial hemorrhage. We also assessed the possible causes leading to SMs based on the medical

records and the comments of the involved doctors or staff members.

Ethical Standards

The present study was approved by the ethics review boards of both hospitals involved in the study (approval numbers: 35 in Kobari General Hospital; 1801 in Ibaraki Seinan Medical Hospital) and performed in accordance with the principles of the Declaration of Helsinki.

Statistical Analyses

All information was handled anonymously. To assess associations between patients' baseline characteristics and each evaluated factor, we used the Mann−Whitney *U* test for continuous variables and the Fisher exact test for categorical variables. Multivariate analysis with logistic regression analysis was conducted to determine the factors associated with SMs. All statistical analyses were performed with EZR version 1.36 (R commander version 2.4-0), a graphical user interface for R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).[10] Probability values below .05 were considered significant.

Results

Patient Demographics and Accuracy of Referrals

Altogether, 338 patients were referred by ED doctors during the study period, and after 112 ineligible patients (referrals for suspected conditions other than stroke or TIA) were excluded, 226 patients (66.9%) with suspected stroke or TIA were enrolled (Fig 1). Of those, only 15 patients (6.6%) were suspected of having TIA, with the others suspected of having stroke. In 64 of the 226 enrolled patients, the suspected stroke/TIA turned out to be an SM according to the final diagnosis and the accuracy of the referrals for suspicion of stroke/TIA was 71.7%. Comparison of the baseline characteristics of the stroke/TIA and SM groups showed that the characteristics were statistically similar, except for the focal symptoms and immediate admission rate (ie, the stroke patients were more likely to be hospitalized than were the SM patients) (Table 1). Almost all the patients (92.9%) underwent CT scans before the referral, and in 81 patients (35.8%), the diagnosis (eg, subarachnoid hemorrhage) could be made on the basis of the CT findings only. Most MRI examinations (85.0%) were taken in combination with CT after negative CT findings, and 51 (37.5%) of the 136 patients with negative CT findings underwent MRI. The diagnoses of the stroke patients were as follows (data not shown in the Table): intracranial hemorrhage, 55 (34.0%); subarachnoid hemorrhage, 15 (9.3%); and ischemic stroke or TIA, 92 (56.8%). We gave rt-PA to 12.2% of the ischemic stroke patients.

Breakdown List of SMs

Three-quarters of the SMs had little or no relation to neurosurgical disorders: the most prevalent diagnoses were psychiatric/psychogenic disorders (15.6%), followed by peripheral dizziness/vertigo (12.5%), and cardiovascular events/collapses (9.4%). All the hypoglycemia patients were on 1 or more oral antihyperglycemic drugs. The remaining one-quarter of the SM patients were those with neurosurgical disorders, with epileptic seizures being the most common etiology (10.9%), 85.7% of which (6 of 7) were nonconvulsive seizures. The 2 patients who complained of sudden onset of headache turned out to have migraine. The 2 traumatic intracranial hemorrhage patients were elderly and had dementia, and their histories of head injury were overlooked before their referral to the neurosurgeon (Table 2).

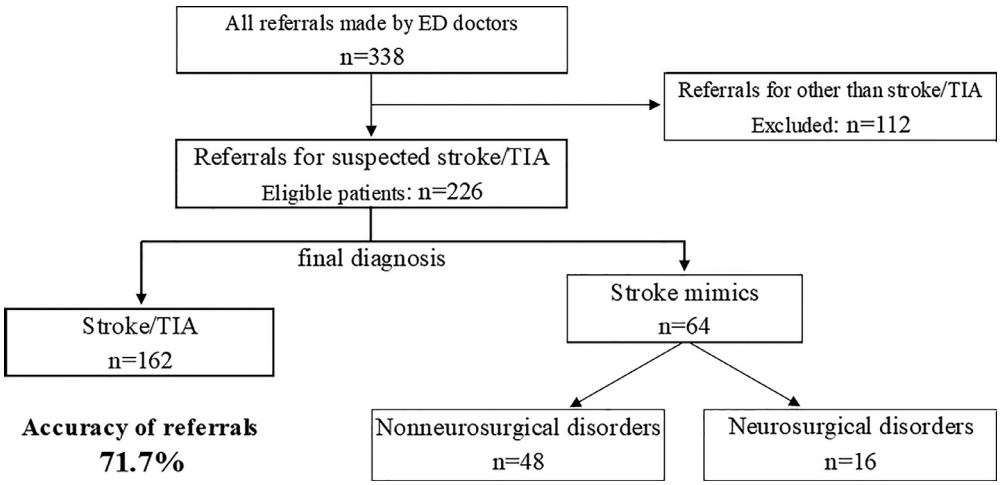

Figure 1. ***Flowchart of patient inclusion and final diagnosis.***
Abbreviations: ED, emergency department; TIA, transient ischemic attack.

Table 1. *Patient demographics*

	All n = 226	Stroke/TIA 162 (71.7%)	Stroke mimics 64 (28.3%)	*P* value
Mean age (range)	73.0 (11-95)	74.0 (11-95)	71.5 (22-95)	.443
Age <49	24 (10.6%)	15 (9.3%)	9 (14.1%)	.338
Male patients	142 (62.8%)	99 (61.1%)	43 (67.2%)	.447
Previous stroke	54 (23.9%)	33 (20.4%)	21 (31.8%)	.057
Vascular risk factors	159 (70.4%)	118 (72.8%)	41 (64.1%)	.200
Living conditions risks	37 (16.4%)	31 (19.1%)	6 (9.4%)	.109
Unclear HPI	31 (13.7%)	18 (11.1%)	13 (20.3%)	.086
Hyperacute condition	76 (33.6%)	58 (35.8%)	18 (28.1%)	.348
Day (8 AM-5 PM)	140 (61.9%)	102 (63.0%)	38 (59.4%)	.650
Night (5 PM-0 AM)	65 (28.8%)	42 (25.9%)	23 (35.9%)	.145
Morning (0 AM-8 AM)	21 (9.3%)	18 (11.1%)	3 (4.7%)	.202
Focal symptoms	129 (57.1%)	111 (68.5%)	18 (28.1%)	<.001**
CT image	210 (92.9%)	154 (95.1%)	56 (87.5%)	.079
MRI	60 (26.5%)	43 (26.5%)	17 (26.6%)	1.000
Admission rate	189 (83.6%)	156 (96.3%)	33 (51.6%)	<.001**

Abbreviations: CT: computed tomography; HPI: history of present illness; MRI: magnetic resonance imaging; TIA: transient ischemic attack.

We used the Mann−Whitney *U* test for continuous variables and the Fisher exact test for categorical variables.

**$P < .01$.

Factors Associated with SMs

The multivariate analysis revealed that a history of stroke (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.01-4.85; $P = .048$) and an unclear history of the present illness (OR, 3.28; 95% CI, 1.29−8.31; $P = .013$) were significantly related to SMs. On the other hand, the factor of focal symptoms was negatively associated with SMs (OR, .16; 95% CI, .08−.32; $P < .01$) (Table 3).

Possible Reasons for Stroke Misdiagnoses

We assessed the causes leading to SMs, which were categorized into 4 major groups (Fig 2): lack of knowledge (ED doctors were not aware of the differential diagnosis or could not interpret the imaging findings correctly), oversights in simple tests (eg, blood glucose level, body temperature, and electrocardiogram), perceived notion of stroke (premature assumption of a stroke diagnosis), and inadequate history-taking or medical examination. The perceived notion was the most prevalent reason for stroke misdiagnoses (43.8%), followed by inadequate history-taking (32.8%). Two or more reasons for the misdiagnosis were found in nearly half of the SM cases.

Discussion

In 226 consecutive referrals from ED doctors in which the diagnosis was suspected stroke/TIA, the accuracy was 71.7%. Furthermore, 75% of the SMs were totally unrelated to neurosurgical disorders; in other words, referring those patients to a neurosurgeon was inappropriate. We attributed the results to 4 major reasons (Fig 2). Among them, we considered perceived notion or premature assumption of a diagnosis of stroke to be the most influential factor for SMs, which was related to the cause for oversights in terms of needed tests or biased and

Table 2. *Misdiagnoses of strokes*

Nonneurosurgical disorders	48 (75.0%)	Neurosurgical disorders	16 (25.0%)
Psychiatric/psychogenic disorder	10 (15.6%)	Epileptic seizure	7 (10.9%)
Peripheral dizziness/vertigo	8 (12.5%)	Migraine	2 (3.1%)
Cardiovascular event/collapse	6 (9.4%)	Brain tumor	2 (3.1%)
Systemic infection/sepsis	5 (7.8%)	Cranial nerve palsy	2 (3.1%)
Hypoglycemia	4 (6.3%)	Traumatic ICH	2 (3.1%)
Intoxication/adverse drug effect	3 (4.7%)	Transient global amnesia	1 (1.6%)
Spinal disorder	3 (4.7%)		
Peripheral neuropathy/PAD	2 (3.1%)		
Hyponatremia	1 (1.6%)		
Other/unknown	6 (9.4%)	Total number of stroke mimics	n = 64

Abbreviations: ICH: intracranial hemorrhage; PAD: peripheral artery disease.

Table 3. *Factors associated with stroke mimics*

	Odds ratio (95% CI)	*P* value
Age <49	1.52 (.55-4.24)	.422
Male patients	2.08 (1.00-4.35)	.051
Previous stroke	2.21 (1.01-4.85)	.048*
Vascular risk factors	.57 (.26-1.24)	.155
Living conditions risks	.36 (.12-1.02)	.055
Unclear HPI	3.28 (1.29-8.31)	.013*
Hyperacute condition	.79 (.38-1.61)	.511
Daytime (8 AM-5 PM)	.82 (.41-1.63)	.562
Focal symptoms	.16 (.08-.32)	<.001**
MRI	1.51 (.68-3.34)	.308

Abbreviations: CI: confidence interval; HPI: history of present illness; MRI: magnetic resonance imaging.

We used multivariate analysis with logistic regression analysis.

*$P < .05$.

**$P < .01$.

inadequate history-taking, eventually resulting in misdiagnosis. Therefore, this suggests that diagnostic procedures can be improved through excluding perceived notion. If SM patients with the misdiagnosis due to 2 or more of the possible reasons had been diagnosed correctly, the accuracy of referrals for suspicion-of-stroke patients would be 82.2% (162/ [226-29]); a 10.5% increase. To achieve this improvement, doctors in the ED must continue their efforts to examine patients in unbiased ways with decent history-taking and needed tests. As an additional possible solution, a stroke-related course might be included in the educational program for young doctors working in EDs.

In previous studies conducted in countries other than Japan, the accuracy of referrals from ED doctors was 61%-74%,[2,11-17] which was approximately the same as the results of the present study (71.7%). However, medical circumstances differ from country to country, and so this concordance must be interpreted with caution. Japan has the world's largest number of CT/MRI devices per inhabitant,[5] which allows Japanese patients to undergo CT/MRI examinations in most emergency hospitals, even at nighttime. From this perspective, the accuracy of referrals in Japan should have been higher than that in other countries. On the other hand, because of the country's health insurance system that covers all of its citizens (the universal health insurance coverage system), Japanese people can see doctors whenever and wherever they want with minimal personal charges to pay. This increases the number of unnecessary consultations, as many people with relatively insignificant symptoms decide to visit medical institutions, and the fact that they can go there themselves raises the probability that the symptoms are in fact not those of stroke, resulting in a relative decrease in diagnostic accuracy as the number of patients is large. Moreover, the shortage of emergency physicians in Japan means that emergency care is provided by nonspecialists on duty, especially in hospitals providing second-line medical care.[6] Therefore, this may be one of the reasons for the difficulty in maintaining decent levels of medical care for stroke patients. We hope that the rate of diagnostic accuracy for stroke will rise in the future after ED doctors gain sufficient experience in managing patients with stroke.

A variety of disorders have been reported to be causes of SMs, including migraine, syncope, seizures, and metabolic disorders,[4,14-15] but the proportions of the disorders have varied from report to report. In the present study, three-quarters of the SM patients had disorders unrelated to the field of neurosurgery. Most of these disorders could have been differentiated from stroke with simple tests or

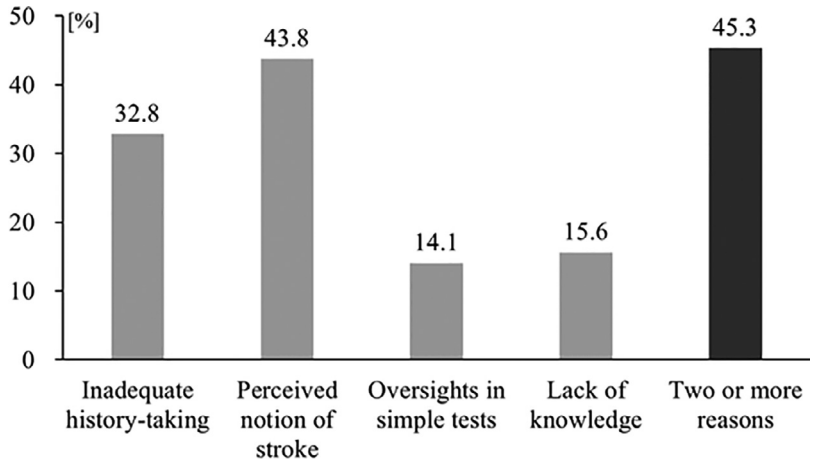

Figure 2. ***Possible reasons leading to stroke misdiagnosis and stroke mimics.***

Four major reasons leading to stroke mimics. Perceived notion was the most prevalent. Lack of knowledge: emergency department doctors were not aware of the differential diagnosis of stroke or could not interpret the imaging findings correctly; oversights in simple tests: doctors did not thoroughly evaluate simple and essential test results such as blood glucose level, body temperature, and electrocardiogram; perceived notion of stroke: premature assumption of diagnosis of stroke; inadequate history-taking: history-taking or medical examinations were not performed correctly.

focused history-taking; hence, we have to say that the referrals in this group were inappropriate. Among the SMs related to neurosurgical diseases, which accounted for one-quarter of the SM patients, the most prevalent disorders were epileptic seizures, followed by brain tumors, migraine, cranial nerve palsy, and traumatic intracranial hemorrhage. Almost all the epilepsy patients (6 of 7) presented with nonconvulsive seizures or postictal states, which are epileptic attacks difficult to diagnose by general physicians. In the same way, both of the patients with migraine presented with sudden headache onset, and both of the cranial nerve palsy patients manifested evident diplopia; accordingly, they needed to see a specialist. Although stroke was misdiagnosed in those patients, the referrals to neurosurgeons were thought to be appropriate.

In the multivariate analysis, we found that focal symptoms were negatively associated, and unclear history of present illness and history of stroke were positively associated, with SMs. These results agreed with the existing data showing that focal symptoms increase and preexistent dementia/cognitive impairment decreases the chance of stroke[4,15,18]; on the other hand, the impact of stroke history on diagnosis is controversial.[4,19] We speculate that perceived notion correlated somewhat with the odds of the history of stroke because ED doctors' rash assumption that they were seeing recurrent stroke could lead to misdiagnosis. It was surprising to us that undergoing MRI had no significant correlation. When we excluded the patients who could be diagnosed only by CT (ie, those with hemorrhagic stroke), which was 41.7% (60 of 144) of the patients who underwent MRIs at the time of referral, the factor of undergoing an MRI showed a better tendency toward proper diagnosis of stroke but was insignificant (data not shown). MRI is generally considered to be the most powerful imaging modality for diagnosing acute ischemic stroke; however, a false-negative result is not uncommon during the first few hours of stroke onset. Furthermore, Japanese doctors may be so dependent on imaging tests that they may order unnecessary MRI irrespective of the preexamination probability of stroke. Understandably, no one can overestimate the importance of clinical diagnosis based on the clinician's experience and knowledge of neuroanatomy.

This study has some limitations. It was conducted in only 2 institutions and was limited to the patients who were examined at the EDs of both hospitals and referred to the neurosurgeon, which might have led to selection bias. The retrospective design may also have introduced information bias. We assessed the factors relevant only to the patients and their conditions, but not to the physicians involved. Furthermore, we did not follow-up all the patients for an extended period of time, so misdiagnoses could have been possible.

The present study revealed that the accuracy of referrals from ED doctors for patients with suspected stroke or TIA was 71.7% in Japanese community hospitals, and 75% of these patients turned out to have conditions totally unrelated to neurosurgery. Room for improvement in the accuracy of referrals remains. Therefore, it might be beneficial to include more information on stroke diagnosis in the educational program for young doctors in Japan to improve the quality of the initial medical examination of patients suspected of having stroke through decent history-taking and unbiased evaluation of medical tests.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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