Different Pattern of Clinical Deficits in Stroke Mimics Treated with Intravenous Thrombolysis

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Key Words

Intravenous thrombolysis • Ischemic stroke • Stroke mimics • Adverse events

Abstract

Background: Guidelines recommend intravenous thrombolysis (IVT) to be applied as early as possible in ischemic stroke (IS), while clinical presentation is often assessed by using the National Institutes of Health Stroke Scale (NIHSS). However, diagnostic workup under time pressure bears the risk of misdiagnosis. Little is known about whether NIHSS could help to differentiate between IS and stroke mimics (SM) in patients being evaluated for IVT. **Methods:** Prospectively collected data of 326 consecutive patients treated with IVT were analyzed. Baseline characteristics and NIHSS subscores were compared between SM and IS. **Results:** Among 326 patients, 23 (7%) had a final diagnosis other than IS. Age and vascular risk factors were comparable in both groups. Patients with SM less often had oculomotor disturbance (0 vs. 37%, $p < 0.001$), dysarthria (9 vs. 51%, $p < 0.001$), hemineglect (0 vs. 30%, $p < 0.01$), hemianopia (0 vs. 22%, $p < 0.01$) and facial palsy (33 vs. 70%, $p < 0.01$). On the other hand, global aphasia without hemiparesis was more prevalent in SM patients (43 vs. 6%, $p < 0.001$). **Conclusion:** Our study suggests that patients with SM undergoing IVT present with a different pattern of clinical deficits than patients with IS.

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Introduction

Patients presenting with an acute onset of neurological symptoms need to be quickly evaluated because they may have a stroke for which immediate treatment is mandatory. Intravenous thrombolysis (IVT) can only be delivered within 4.5 h of symptom onset, with the likelihood of good outcome decreasing with time to treatment [1]. Therefore, history and examination remain short and focused in the emergency setting, while clinical stroke severity is often assessed using the National Institutes of Health Stroke Scale (NIHSS) [2]. Acute brain imaging is often restricted to computed tomography (CT), which can exclude intracranial hemorrhage but, in most cases, cannot prove ischemia. These constraints pose the risk of misdiagnosis and administering IVT to patients who present with symptoms suggestive of ischemic stroke (IS) but finally have a different diagnosis at discharge (so-called ‘stroke mimic’, SM). It has not been evaluated whether patients with SM differ from those with IS in NIHSS subscores, which could help physicians to suspect SM clinically. Furthermore, little is known about the frequency of SM in the extended 4.5-hour treatment time window. We aimed to assess the frequency, clinical characteristics and the risk for adverse events in SM patients treated with IVT within 4.5 h after symptom onset.

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Patients and Methods

We analyzed data collected prospectively as part of the Zurich Observational Registry of Rehabilitation Outcomes (ZORRO). In total, 326 consecutive patients who were treated with intravenous recombinant tissue plasminogen activator (r-tPA) in the University Hospital Zurich from October 2008 to May 2011 were included. SM was diagnosed when all of the following 3 criteria were met: (1) clinical condition at admission suggesting acute IS; (2) normal diffusion-weighted magnetic resonance imaging (MRI) of the brain, and (3) specific diagnosis at discharge other than IS. The specific diagnosis was based on the clinical course and additional investigations if needed (e.g. characteristic findings in electroencephalography; history of migraine, epilepsy or conversion disorder; specific laboratory or imaging findings). Patients with normal diffusion-weighted MRI but unclear diagnosis at hospital discharge were excluded, as were patients with clinically probable stroke or transient ischemic attack and normal MRI. Normal neuroimaging in the setting of unknown cause as well as probable stroke or transient ischemic attack was excluded from the definition. Baseline investigations included neurologic and physical examination, assessment of stroke severity at admission using the NIHSS [2], routine blood analysis, 12-lead electrocardiography (ECG) and brain CT. The following variables were prospectively collected: age, gender, baseline NIHSS score, vascular risk factors according to predefined criteria [3], time to treatment and history for coronary heart disease or prior IS, and the NIHSS subscores. Thrombolysis was applied according to current guidelines with r-tPA 0.9 mg/kg to a maximum of 90 mg, 10% of the total dose given as a bolus and the remaining dose over the next hour [4]. Based on the results of the European Cooperative Acute Stroke Study (ECASS) III, we regularly extended the time window for all IVT to 4.5 h after symptom onset from October 2008 onwards [5]. All patients treated with IVT were admitted to intermediate or intensive care units for at least 24 h.

Outcome Parameters

All intracranial hemorrhages were ascertained on follow-up CT or MRI routinely performed at 24 h after IVT and additional scans in case of clinical deterioration. Symptomatic intracranial hemorrhage (sICH) was defined as any intracranial bleed temporally related to a neurological deterioration [6]. Furthermore, we assessed the NIHSS and modified Rankin Scale (mRS) score at discharge in patients with a final diagnosis of SM [2, 7].

Literature Search

Two independent observers (A.R.G., H.S.) performed a detailed literature search in the PubMed, Embase and Cochrane databases for any reports on IVT in patients presenting with SM (search period defined from January 1995 to August 2011). First, we searched for the terms ('stroke mimic' OR 'stroke misdiagnosis') AND ('thrombolysis', 'alteplase' OR 'rtPA'). We also screened reference lists of all retrieved reports. There were no restrictions regarding language or publication status.

Statistical Analysis

Baseline and demographic data were examined with descriptive statistics. For the comparison of the group of SM versus IS, Fisher's exact test was used for the dichotomous variables, and the

Wilcoxon rank-sum test was used for the continuous variables. Significance was assumed at $p < 0.05$. All tests were performed with the statistical software R 2.13 (2011).

Results

Study Population

Within the study period, a total of 326 patients with suspected IS were treated with IVT. Of these, 23 (7%) patients (13 males, 10 females) with a mean age of 63 years (range 26–86) presented with SM. There were no significant differences in demographic characteristics and vascular risk factors as compared to patients with IS (table 1). Stroke severity at admission was less severe in patients with SM (NIHSS 6 vs. 10, $p = 0.003$) (table 1). Furthermore, on average, patients with SM were treated 52 min later than patients with IS (208 vs. 156 min). Table 2 shows a detailed description of clinical and imaging findings in the 23 patients with SM. Before thrombolysis, 21 patients underwent neuroimaging by CT and CT angiography (CTA), 1 patient (No. 1) by CT without contrast agent and 1 patient (No. 8) by CT, CTA and perfusion CT. All CTA and the perfusion CT were normal. MRI was performed in all 23 patients with SM at 24 h after IVT, and the diffusion-weighted imaging sequences were normal in all of them. SM were most frequently diagnosed as epileptic seizures ($n = 14$), migraine with aura ($n = 3$) and conversion disorder ($n = 3$). The remaining 3 patients had less frequent causes for SM: hypoglycemia (blood glucose of 2.6 mmol/l at admission), sinusitis with systemic infection and multiple sclerosis with a demyelinating lesion in the cervical spinal cord.

We assessed the NIHSS subgroups in the two cohorts at admission. As compared to IS, no patient with SM presented with oculomotor disturbance (0 vs. 37%, $p = 0.0001$), hemianopia (0 vs. 22%, $p = 0.0093$) or hemineglect (0 vs. 30%, $p = 0.0013$). Dysarthria and facial palsy were less often observed in these patients (9 vs. 51%, $p = 0.0003$ and 33 vs. 70%, $p = 0.0012$, respectively). Furthermore, a marginal difference was observed in the frequency of arm paresis, which was slightly higher in the IS group (78 vs. 52%, $p = 0.0166$). On the other hand, no significant differences were evident between the SM and IS groups when comparing common stroke findings such as leg paresis (48 vs. 66%, $p = 0.0984$), sensory disturbances (38 vs. 53%, $p = 0.252$), problems in answering questions (57 vs. 34%, $p = 0.053$) or performing tasks (24 vs. 22%, $p = 1.0$). However, the combined occurrence of global

Table 1. Comparison of baseline characteristics in thrombolized patients with SM (n = 23) or IS (n = 303)

	SM	IS	p value
Age, years	63.0 ± 19.2	69.9 ± 14.0	0.19*
Male gender	13/23 (56.5%)	202/303 (66.7%)	0.36
Arterial hypertension	13/23 (56.5%)	209/296 (70.6%)	0.16
Diabetes mellitus	4/21 (19.0%)	41/262 (15.6%)	0.76
Current smoking	7/22 (31.9%)	60/270 (22.2%)	0.30
History of IS	2/22 (9.1%)	58/288 (20.1%)	0.27
Coronary artery disease	2/22 (9.1%)	59/296 (19.9%)	0.27
NIHSS score	6.43 ± 5.21	9.89 ± 6.0	0.003*
OTT, min	208.3 ± 43.7	156.1 ± 68.0	<0.001*

Values are mean ± SD, unless otherwise indicated. OTT = Onset to treatment time.

p values from Fisher's exact test, unless otherwise indicated (* Wilcoxon rank-sum test).

aphasia without hemiparesis was much more frequent in the SM group (43 vs. 6%, $p = 0.00003$).

None of the 23 patients with SM experienced sICH, systemic bleeding or death. At discharge, 16 (70%) patients were without any neurological symptoms (NIHSS score 0, mRS score 0), whereas 7 (30%) patients had persisting residual deficits due to the condition that caused the acute neurological deficit but without any worsening of the symptoms after IVT.

Literature Review

Our literature search resulted in 13 reports (10 cohort studies, 3 case reports) fulfilling the predefined criteria [8–20]. These included a total of 209 patients with SM (mean frequency 6%) treated with IVT, 200 (96%) of them within the 3-hour treatment time window. sICH was reported in 1 of 209 (0.5%) cases [10].

Discussion

Although time constraints in the diagnostic workup and administration of IVT for patients with suspected IS are prone to misdiagnosis, this study demonstrates that IVT carries minimal risks of serious adverse events in these patients. In our cohort, 7% of thrombolized patients had a misdiagnosis of IS. Similar to our findings, Giraldo et al. [19] reported that 9 of 89 (10%) patients undergoing IVT within 4.5 h were misdiagnosed as having IS. For the 3-hour treatment time window, SM rates of 1–13% (mean 6%) have been reported [8, 11–14, 16, 18, 20]. The wide range of SM rates in these studies probably relates to several factors such as study size, definition of SM,

treatment protocol and experience of the respective center. Patients with SM underwent IVT later than patients with IS in this series. In the absence of data about door-to-needle time, we do not know whether this difference was caused by a pre-hospital or an in-hospital delay, hence whether this delay was related to the uncertainty of the patient or primary/emergency physician to send the patient to the hospital or a longer diagnostic workup in the hospital. Our data suggest that age and the presence of vascular risk factors do not predict SM. In fact, epileptic seizures mimicking IS typically occurred in older patients with higher vascular risk profiles. In contrast, young patients with IS often have no cardiovascular risk factors and stroke of non-atherosclerotic etiology, e.g. due to cervical artery dissection [21].

The main strength of our study is the comparison of NIHSS subscores in patients with SM and IS. Our results show that the presence of oculomotor disturbance, hemianopia, facial palsy, dysarthria or hemineglect strongly suggests IS. In contrast, global aphasia in the absence of hemiparesis should raise the suspicion of SM, which is in line with the findings of Winkler et al. [12]. It is noteworthy that the frequency of common stroke symptoms such as aphasia, leg paresis or sensory disturbances was similarly distributed in the two groups, whereas arm paresis was slightly more often observed in IS patients. However, the latter finding may be coincidental in view of the small sample size and marginal statistical difference.

Epileptic seizure was the most common cause for SM in our cohort, followed by migraine and conversion disorder. These findings are in line with the literature [12, 14, 20]. Among less frequent etiologies, multiple sclerosis, hypoglycemia and systemic infection mimicked IS in our

Table 2. Characteristics of SM patients undergoing IVT

Pa- tient No.	Gender/ age	Signs at Admission	NIHSS score	OTT min	Neuroimaging at admission	Radiological finding at admission	EEG	Comorbidities	Final diagnosis	NIHSS/ mRS scores at discharge
1	F/78	Aphasia, confusion	3	190	CT (without contrast agent)	Subcortical hypodense lesion	Irritative focus	DM	Glioblastoma with symptomatic seizure	4/3*
2	F/76	Left hemiparesis	5	150	CT, CTA	Meningioma, normal CTA	Irritative focus	Meningioma, M. Sjögren	Epileptic seizure	2/1*
3	M/78	Aphasia	3	210	CT, CTA	Normal CT/CTA	–	DM, HT, DL, CAD	Hypoglycemia	0/0
4	M/34	Right hemiparesis	6	230	CT, CTA	Normal CT/CTA	–	M. Hodgkin	Multiple sclerosis	6/2*
5	M/41	Speech arrest, left sensory hemisindrome	5	220	CT, CTA	Normal CT/CTA	Epileptic focus	Smoking	Epileptic seizure	0/0
6	F/86	Aphasia	5	235	CT, CTA	Meningioma, normal CTA	Irritative focus	Meningioma, HT, CAD	Epileptic seizure	0/0
7	M/76	Left sensory hemisindrome	3	260	CT, CTA	Chronic infarct, normal CTA	Temporal focal slowing	Prior stroke, HT, smoking	Epileptic seizure	0/0
8	M/30	Aphasia	2	240	CT, CTA, PCT	Normal CT/CTA/PCT	–	MwA, smoking	MwA	0/0
9	F/55	Vertigo, right sensory hemisindrome	4	210	CT, CTA	Normal CT/CTA	Normal	HT, DL	Conversion disorder	2/2*
10	F/59	Nausea, right hemisindrome	9	225	CT, CTA	Normal CT/CTA	Temporal focal slowing	–	Epileptic seizure	0/0
11	F/83	Aphasia, confusion, headache	2	225	CT, CTA	Sinus obliteration, normal CTA	Normal	HT	Sinusitis with systemic infection	0/0
12	M/46	Aphasia, tetraplegia	19	110	CT, CTA	Normal CT/CTA	Normal	Depression, MwA, HT, DL	Conversion disorder	0/0
13	F/74	Aphasia	3	185	CT, CTA	Normal CT/CTA	–	DM, HT, DL	Epileptic seizure	0/0
14	M/75	Speech arrest, right hemiparesis	7	255	CT, CTA	Chronic infarct, normal CTA	Temporal focal slowing	DL, prior stroke	Epileptic seizure	0/0
15	M/77	Aphasia, facial paresis	8	240	CT, CTA	Normal CT/CTA	–	DL, DM	Epileptic seizure	0/0
16	F/77	Aphasia, facial paresis	6	170	CT, CTA	Normal CT/CTA	Irritative focus	DM, HT	Epileptic seizure	0/0
17	M/27	Left sensory hemisindrome	5	180	CT, CTA	Normal CT/CTA	Normal	Smoking	MwA	0/0
18	M/75	Right hemiparesis	6	150	CT, CTA	Subdural hematoma, normal CTA	Irritative focus	HT, DL, smoking, CAD	Subdural hematoma with symptomatic seizure	2/1*
19	F/76	Left hemiparesis	6	135	CT, CTA	Normal CT/CTA	Normal	RLS, HT, dizziness	Conversion disorder	1/1
20	M/71	Aphasia, tetraplegia	23	270	CT, CTA	Leukoaraiosis, chronic infarct, normal CTA	Status epilepticus	HT, DM, AF, schizophrenia	Status epilepticus	5/2*
21	F/66	Aphasia	3	195	CT, CTA	Chronic infarct, normal CTA	Irritative focus	HT	Epileptic seizure	0/0
22	M/27	Left sensory hemisindrome	3	265	CT, CTA	Normal CT/CTA	Normal	MwA	MwA	0/0
23	M/62	Aphasia, right hemiparesis	12	240	CT, CTA	Normal CT/CTA	Irritative focus	HT, smoking	Glioblastoma with symptomatic seizure	0/0

OTT = Onset to treatment time; EEG = electroencephalography; DM = diabetes mellitus; HT = arterial hypertension; DL = dyslipidemia; CAD = coronary artery disease; MwA = migraine with aura; RLS = restless legs syndrome; AF = atrial fibrillation; PCT = perfusion computed tomography.

study. Perfusion CT, which has a broad availability and short processing time, may be an alternative diagnostic tool to detect epileptic seizures mimicking acute IS: while cerebral regional hyperperfusion has been reported to be characteristic for non-convulsive status epilepticus [22, 23], focal hypoperfusion in atypical vascular distributions was reported for post-ictal neurological deficits [24]. CTA was performed in 22 of 23 patients with SM and showed normal findings in all of them. Retrospectively, the obvious discrepancy between patent cerebral arteries in CTA and high NIHSS scores (e.g. patient No. 10, 12, 20 and 23) should suggest SM. Furthermore, neurologists should carefully consider the CT findings prior to thrombolysis. Reviewing the CT images, 3 patients (No. 1, 11 and 18) had subtle but visible lesions that retrospectively should have raised the suspicion of SM. In patient No. 18, treatment with alteplase was stopped 15 min after bolus application when a subdural hematoma was detected after reviewing the CT images.

To assess the risk of adverse events after IVT, our meta-analysis includes 232 patients with SM treated with IVT. None of the patients died. Grimm and DeAngelis [10] reported 1 patient (case report) experiencing sICH after IVT due to underlying glioblastoma multiforme. In two other studies, 1 patient suffered from gastrointestinal hemorrhage and 2 patients from cervical epidural hemorrhage [16, 17]. In one of these patients, it is unclear whether spinal hematoma was pre-existing, hence the cause of stroke-like symptoms and not a complication of IVT [16]. In the other case, the hematoma may also have existed before IVT, as suggested by the clinical presentation with acute shoulder pain and face-sparing hemiparesis [17]. Though our data suggest that the risk of hemorrhage seems to be low, a direct comparison of the bleeding risk attributable to IVT in SM versus IS in a large data set is

warranted. Furthermore, caution is needed when interpreting these findings as the low complication risk may be valid only for experienced stroke centers.

Some limitations should be considered in this study. The sample size of the SM group was small, thus the analysis is prone to type II errors. We therefore included a meta-analysis of published SM series to better ascertain the risk of hemorrhage in patients with SM after IVT – with the caveat that the definition of SM and sICH was not identical in all studies. Further support for low sICH risks in patients without IS is derived from studies that assessed intravenous r-tPA for acute myocardial infarction. The sICH risk in these patients is less than 1% despite the addition of intravenous heparin to the treatment protocol [25]. Another limitation is the use of the NIHSS for assessing the neurological outcome at discharge from the hospital. While the NIHSS is applicable to IS, its value for assessing the symptoms of conditions other than stroke is limited.

In conclusion, our study suggests that the pattern of clinical deficits measured by the NIHSS differs between SM and IS, whereas common stroke predictors such as age and vascular risk factors were similarly distributed in both groups.

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Disclosure Statement

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