Full title

The frequency, characteristics and aetiology of stroke mimic presentations: a narrative review.

Short title

A narrative review of stroke mimics

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Abstract

A significant proportion of patients with acute stroke symptoms have an alternative “mimic” diagnosis. A narrative review was conducted to explore the frequency, characteristics and aetiology of stroke mimics. Prehospital and thrombolysis treated patients were described separately.

9,972 studies were identified from the initial search and 79 studies were included with a median stroke mimic rate of 19% (range 1-64%). The prehospital median was 27% (range 4-43%) and the thrombolysis median 10% (range 1-25%).

Seizures, migraines and psychiatric disorders are the most frequently reported causes of stroke mimics. Several characteristics are consistently associated with stroke mimics; however, they do not fully exclude the possibility of stroke.

19% of suspected stroke patients had a mimic condition. Stroke mimics were more common with younger age and female gender. The range of mimic diagnoses, a lack of clear differentiating characteristics and the short treatment window for ischaemic stroke creates challenges for early identification.

Keywords

Stroke mimic, narrative review, prehospital, thrombolysis

Introduction

Twenty-six percent of patients with suspected stroke are reported to have a stroke mimic (SM)(1) condition as the final diagnosis, which reflects the challenging nature of clinical diagnosis. In order to maximize prehospital identification of stroke patients, assessment tools (2-4) focus upon positive identification of common stroke symptoms (sensitivity) at the expense of specificity, and so contribute further towards the high rate of SM (4). Failure to identify SM patients could lead to inappropriate treatment and inefficient use of specialist stroke services. This might be most important in centralised service configurations (5, 6) where prehospital suspected stroke cases bypass local hospitals, thereby increasing ambulance transfer times for SM patients and displacing them from appropriate local care.

Even with specialist input and improving access to neuroimaging, SM patients receive thrombolysis (7). Due to the time dependent nature of thrombolysis, the limited availability of advanced imaging and the low risk of intracerebral haemorrhage amongst SM patients (8, 9) current practice favours treatment of eligible suspected stroke patients due to the perceived risk benefit balance.

A number of studies have developed tools to identify SM (10-12). These tools use characteristics associated with SM diagnosis, such as patient age or presence of seizures, along with the absence of factors associated with stroke diagnosis, such as atrial fibrillation or hypertension.

This narrative review was conducted to summarise the literature describing SM frequency, characteristics and aetiology and explore the issues relating to identifying SM patients at an early stage.

Methods

A systematic search was performed with the results reported using narrative synthesis. The review protocol was prospectively registered on PROSPERO registration number 42015026457 (13). This review is reported following the PRISMA statement (14).

Inclusion criteria

To be eligible for inclusion studies had to fulfil the following criteria:

- Primary studies describing adult (18 years and above) patients with initial diagnosis of stroke and final non-stroke diagnosis
- Reported a number and/or rate of SM
- Reported the clinical and/or demographic characteristics of a SM population
- Published in the English language

Case reports were excluded from the review.

Database search strategy

A simple but structured search strategy (supplemental digital content 1) was developed with input from an information specialist. This was applied to the following databases up to February 2017: MEDLINE; EMBASE; PsycInfo; CINAHL; Cochrane Database of Systematic Reviews and Database Of Research In Stroke. Grey literature was identified using the first 30 pages of Google and Google Scholar (15).

Study selection process

Studies were screened based upon title and abstract by one reviewer (GM) with uncertainties discussed with another member of the review team. Abstracts which

appeared relevant were assessed for eligibility in full text format by the same reviewer (GM). The reference lists of all studies included were hand searched. Citation searching of included studies was undertaken using ISI Web of Science.

Data extraction and analysis

Data were extracted using a structured form to capture the following: title; authors(s); journal; year; country; setting; proportion of SM; stroke assessment tool; method of stroke diagnosis; method of SM diagnosis; presence of SM final diagnosis; demographics or clinical characteristics.

Clinical Classification Software (CCS) codes were used to combine SM diagnoses reported within studies using variable terminology into clinically relevant groups (16).

Due to the descriptive aims of the review, variability in the definition of stroke and SM and the anticipated heterogeneity of studies with variable quality there was no pre-specified meta-analysis.

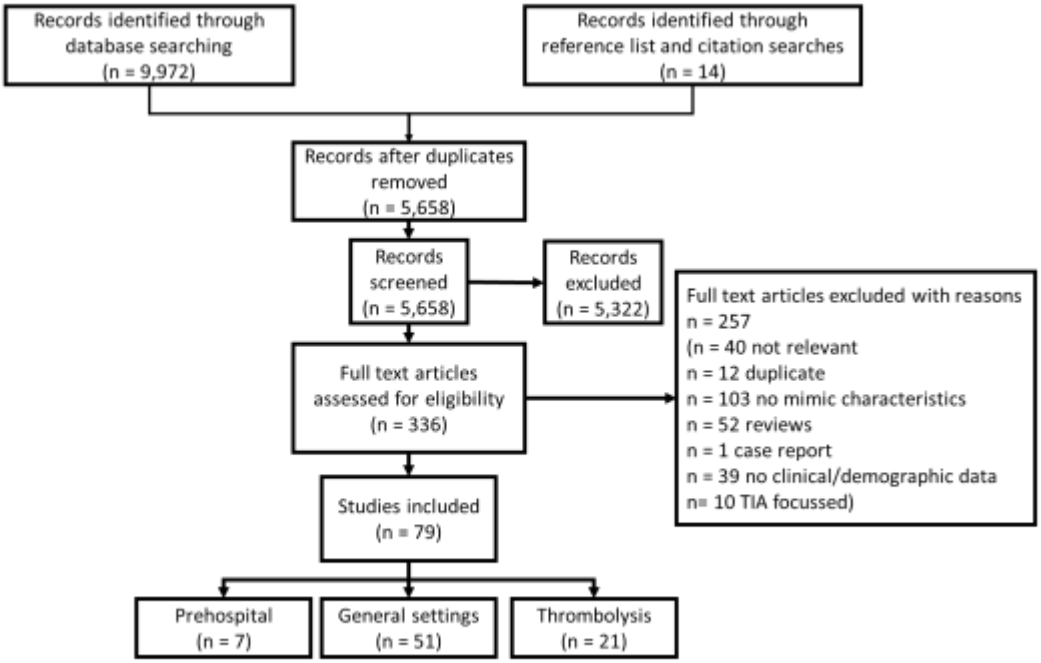
Quality assessment

Due to anticipated heterogeneity within the literature the QATSDD tool for reviewing studies with diverse designs was preselected for assessing study quality (17). This tool was not applied to abstracts.

Results

The search strategy yielded 9,972 references (Figure 1). After initial screening 336 full text articles were reviewed.

Figure 1.



Flow chart describing the study selection process.

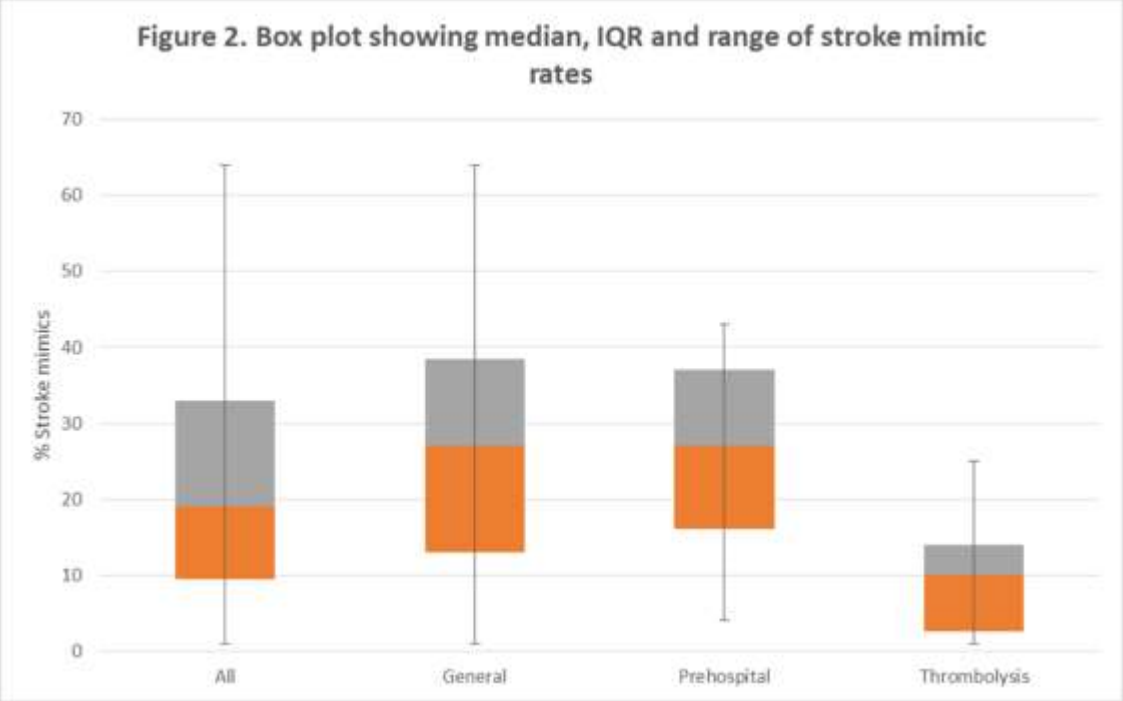
Seventy-nine studies (full details and references in supplemental digital content 2) were included in the review.

The median year of publication was 2013 (range 1982-2017). The majority of studies originated from North America (n=34, 43%) or Europe (n=29, 37%). The majority (n=78, 99%) of studies were cohort studies with 41 (53%) collecting data prospectively, 36 (46%) retrospectively and in 1 (1%) study the direction of data collection was unclear.

The overall population include 147,779 patients. SM patients were younger than stroke patients (pooled mean age 61.7 vs 69.6 years) with a higher percentage of females (pooled female gender 53.3% vs 47.7%). Included studies were described as three groups. Those with populations confined to prehospital settings (n=7) reflect the early identification of

suspected stroke patients, usually through application of specific tools and protocols. Thrombolysis studies (n=21) are separately described as these have a clearly defined sub-population based upon the criteria for administration of a specific treatment. All other studies (n=51) were not uniquely prehospital or thrombolysis focussed.

The pooled mean and median SM rates were 22% (SD 16%) and 19% (IQR 9.5-33%) respectively. The median SM rates were 27% (IQR 13-38.5%) in the general group, 27% (IQR 16-37%) in the prehospital group and 10% (IQR 2.5-14%) in the thrombolysis group. These SM rates are summarised in figure 2.



QATSDD scoring was converted into an overall percentage for each study to simplify comparison. Included studies scored a median 60% (IQR 52-69) on the QATSDD (see supplemental digital content 3). The three subgroups had similar pooled mean scores on the QATSDD: prehospital 64%; mixed 59% and thrombolysis 59%. As a sensitivity analysis the studies scoring below the lower QATSDD quartile were compared with studies scoring above

the upper quartile. The lowest quartile studies (n=17) reported a pooled mean SM rate of 21% (SD 17.5) based on 5,601 patients and the highest quartile studies (n=11) reported a pooled mean SM rate of 28% (15.1) based on 6,680 patients.

Stroke mimic final diagnosis

Sixty-three studies (80%) reported the SM underlying diagnoses. Methods of identifying the diagnosis of SM included: discharge/final diagnosis (40%); neurologist or stroke specialist assessment (17%); expert panel (14%); registry (6%); and other/unclear (22%).

SM diagnoses were summarised using CCS codes.(16) This resulted in 103 initial CCS codes, which were reported using level 1 CCS (broad disease categories) and level 2 CCS (more specific disease areas) codes (Figure 3).

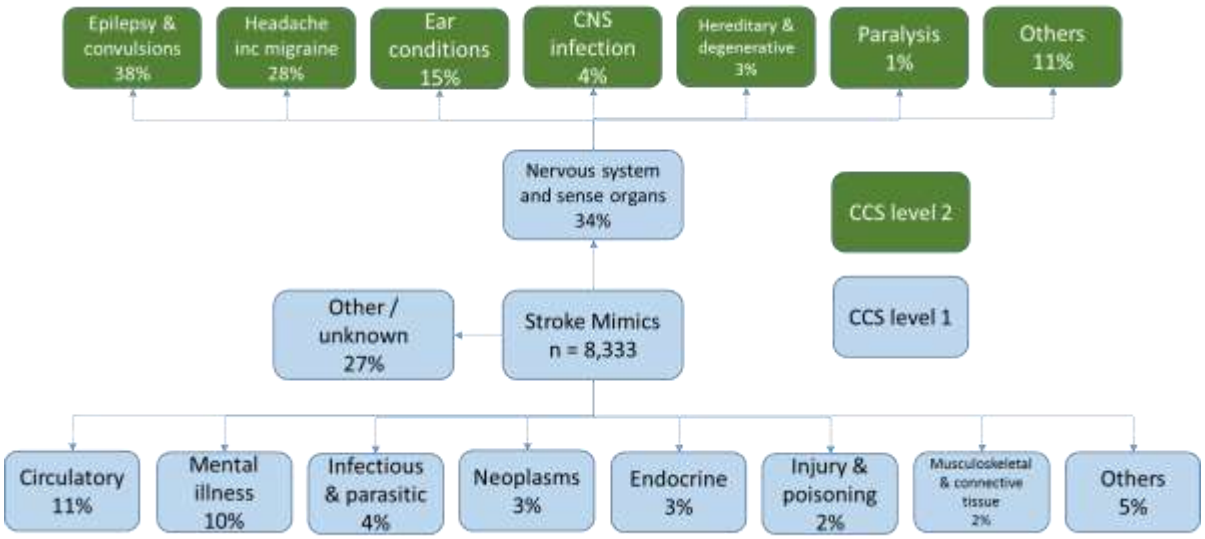


Figure 3. Taxonomy of stroke mimics using Clinical Classification Software (CCS) codes.

Prehospital

Seven (9%) studies clearly described prehospital settings: 6,870 patients, mean SM rate 26% (SD 14%). SM patients were younger than stroke (67 vs 73 years pooled mean age) with a higher proportion of females (SM 58% female vs stroke 49% female).

The most frequent level 1 CCS diagnostic groups in the pure prehospital setting were: diseases of the nervous system and sense organs (29%); symptoms, signs and ill-defined conditions and factors influencing health status (9%) and unknown (43%). The most frequent level 2 CCS diagnostic groups were: epilepsy and convulsions (19%); symptoms, signs and ill-defined conditions (9%) and ear conditions (5%).

Thrombolysis

Twenty-one (26%) studies described SM in patients treated with thrombolysis: 103,731 patients, mean SM rate 9% (SD 7%). SM patients were younger than stroke patients (57 vs 68 years mean age). More SM patients were female (SM pooled mean 57% vs stroke 46%).

The most frequent level 1 CCS diagnostic groups in the thrombolysis cohorts were: diseases of the nervous system and sense organs (37%); mental illness (18%) and unknown (42%). The most frequent level 2 CCS diagnostic groups were: miscellaneous mental disorders (17%); headache including migraine (17%); and epilepsy and convulsions (16%).

General studies

Fifty-one (65%) studies described cohorts that were not specifically identified as pre-hospital or receiving thrombolysis: 37,178 patients, mean SM rate 27% (SD 16%). These settings included: hospital (41%); Emergency Department (ED) (35%); stroke unit/hyper acute stroke unit (HASU) (18%); telemedicine (4%); and general practice (2%). The total population was 50% male with a pooled mean age of 68 years. SM patients were younger

than stroke (63 vs 70 years pooled mean age) with a higher proportion of females (SM 51% female vs stroke 48% female).

The most frequent level 1 CCS diagnostic groups were: diseases of the nervous system and sense organs (34%); diseases of the circulatory system (15%); mental illness (10%) and unknown (17%). The most frequent level 2 CCS diagnostic groups were: epilepsy and convulsions (10%); cerebrovascular disease e.g. transient ischemic attack; subdural haemorrhage (9%); and headache including migraine (9%).

Clinical characteristics

Studies reporting clinical characteristics associated with SM are described in table 2 (see supplemental digital content 4 for table with references). Associations between clinical characteristics and diagnosis were reported as positive for SM or stroke ($p<0.05$ or stated within text as significant) or non-significant.

Table 2. Number of studies reporting characteristics associated with stroke mimic diagnoses

	Characteristics	Associated with SM (n, %)	No association (n, %)	Associated with stroke (n, %)
Past medical history	Diabetes	2 (6%)	23 (68%)	9 (26%)
	Hypercholesterolemia	3 (27%)	6 (55%)	2 (18%)
	Migraine	5 (71%)	2 (29%)	0
	Seizure	9 (75%)	3 (25%)	0
	Smoker	1 (4%)	21 (81%)	4 (15%)
	Stroke	7 (29%)	12 (50%)	5 (21%)
	Transient Ischemic Attack (TIA)	1 (25%)	2 (50%)	1 (25%)
Symptoms (negative)	Abnormal admission neurological examination	1 (100%)	0	0
	Altered level of consciousness / mental status	9 (60%)	5 (33%)	1 (7%)
	Aphasia	1 (50%)	0	1 (50%)
	Cognitive impairment	3 (75%)	1 (25%)	0
	Confusion	3 (75%)	1 (25%)	0
	Dysphagia	1 (100%)	0	0
	General weakness	1 (100%)	0	0
	Sensory deficit	4 (100%)	0	0
Symptoms (positive)	Diabetic symptoms	1 (100%)	0	0
	Dizziness / vertigo	5 (63%)	3 (38%)	0
	Headache	1 (14%)	5 (71%)	1 (14%)
	Pain	1 (100%)	0	0
	Psychiatric / somatic disorder	6 (86%)	1 (14%)	0
	Seizure	6 (100%)	0	0

Other	Can walk now	1 (100%)	0	0
	Neuro symptoms inconsistent with vascular territory	1 (100%)	0	0
	No lateralising symptoms	1 (100%)	0	0
	No motor or speech deficit	1 (100%)	0	0
	No neurological signs	1 (100%)	0	0
	Normal extraocular movements	1 (100%)	0	0
	Normal Glasgow Coma Score	1 (100%)	0	0

Discussion

This review identified SM studies with heterogeneous aims, settings and reporting methods. The studies included had a wide range of QATSDD scores, however the subgroup mean scores were similar. As there were no pre-specified exclusion criteria based on quality assessment all identified studies were included. The QATSDD identified that very few studies discussed sample size or considered the accuracy of the final diagnoses therefore an element of selection bias must be acknowledged.

Our findings build on earlier work (1) by showing that despite advancing technology and better availability of specialist assessment, SM continues to be a diagnostic challenge. To inform the development of screening processes with improved specificity, we have described typical characteristics that may aid with SM diagnosis and discuss tools that have been developed to aid identification.

Frequency

The reported rate of SM was influenced by the clinical definition of stroke used at the time of the study and therefore varied across the literature (18). SM accounted for 22% of all suspected stroke cases, which is lower than 26% previously reported (1). This discrepancy may be the result of recent large thrombolysis cohorts being included (7, 19). Thrombolysis studies have a lower SM frequency because of the specialist assessment, treatment criteria and neuroimaging required to make treatment decisions. However, the pooled SM rate for prehospital and general populations was similar at 27%. Studies in the upper quartile based on QATSDD scoring reported a higher SM rate (28%) than studies in the lower quartile (21%) so the combined figure may be an under-estimate.

The high frequency of SM in prehospital care may be due to a number of factors: most prehospital services are paramedic led; application of high sensitivity stroke identification instruments; availability of information about past medical history; and the lack of imaging. Nevertheless, SM rates were similar in prehospital and hospital groups. This may reflect that a significant portion of the general group were also unfiltered prehospital patients, and that the initial diagnosis made in the prehospital setting is not over-ruled until later stroke specialist assessment and brain imaging.

The presence of SM in thrombolysis populations reflects the challenging nature of acute stroke treatment. The drive to reduce door-to-needle (DTN) time may be linked with increased SM thrombolysis (20). Thrombolysing SM has relatively low risks (19, 20) but does have financial implications (21). Using current diagnostic processes this is a challenging area to address because of the lack of clear clinical characteristics differentiating stroke from SM; and the need to treat patients early to get the most benefit. Developments and investment in rapid advanced imaging to reveal positive evidence of acute ischaemia would help avoid thrombolysis for some patients in this group (22).

Characteristics

SM patients tended to be younger than stroke patients and were more likely to be female. The mean age falls as patients move from prehospital care, to non-specialist care (general group) and on to specialist care (thrombolysis group). This may reflect the increasing rigour of the assessment process.

Clinical characteristics (Table 2) were reported under a variety of overlapping terms. Due to methodological concerns we did not create a weighted average or conduct a meta-analysis. The distribution of clinical characteristics across studies was used as a crude measure of

association. Seizures, history of migraine and psychiatric disorders were the characteristics with the clearest association with SM diagnosis. There was disagreement between studies as to the direction of association for some characteristics e.g. history of stroke is associated with stroke (5 studies), SM (7 studies) and non-significant (12 studies). This reflects that although vascular risk factors are more likely to be present amongst stroke patients, their presence was a reason for clinicians to wrongly suspect stroke as a cause for new symptoms. However as a stronger risk factor, AF had a clearer relationship with stroke (26 studies positive association; 7 non-significant association).

Focal neurological deficits used by most identification scores maintained their relationship with stroke e.g. facial palsy/weakness (1 non-significant, 13 associated with stroke)(23, 24). The absence of these characteristics could be an indicator of SM, and has been used in SM identification tools (10).

Aetiology

Many conditions present as SM and diagnostic methods, including the use of brain imaging, were highly variable in the literature. The definition of stroke, and therefore SM, varied and conditions such as TIA and sub-arachnoid haemorrhage were variably classified as stroke or SM. It is important that investigators transparently present data so that services can decide upon the relevance of the results.

The use of CCS codes allowed the findings of this heterogeneous dataset to be summarised. Disorders of the nervous system and sense organs were the most common cause of SM, particularly seizures which mirrors previous findings (1). Some prehospital stroke tools used seizures to indicate a reduced likelihood of stroke (3, 25) and some SM identification tools also included seizures (10, 11). Accurate history taking is crucial, but seizures can be

unwitnessed and it is only the gradual recovery, lack of acute changes on imaging, clarification of previous medical history and further investigations which reveal the diagnosis. As 2% of acute stroke patients experience a seizure (26), this is an area where development of rapid diagnostics may be helpful.

Clinical implications

Although SM have short stays on HASUs (mean 2.8 days), the frequency of SM admissions accounts for 8-17% of HASU bed occupancy, which could be otherwise used treating stroke patients (27). Prehospital identification of SM may help to ensure that patients access appropriate pathways of care, especially in centralised service configurations which require a prehospital redirection decision.

Application of a SM identification tool, such as those described earlier (10-12), would support creation and evaluation of a two stage process. The initial stage is suspicion of stroke based on triggering a high sensitivity tool at dispatch (28) and/or during clinical assessment such as FAST(2), and the second stage is refinement of this initial diagnosis based upon a SM assessment with high specificity. This two stage assessment does not include the initial suspicion of stroke by the ambulance dispatch centre where high sensitivity to potential stroke is paramount. A recent study using CPSS guided dispatch of ambulances was able to identify 2/3 of patients suitable for thrombolysis simply through structured telephone description of symptoms (28), but there is currently no formalised prehospital equivalent score at dispatch to then identify patients who could be a SM.

Due to the lack of clinical characteristics that clearly differentiate strokes and SM, this second stage provides an opportunity to apply novel point of care diagnostic technologies (29, 30) to improve the overall assessment performance. A SM assessment could also be

used to help target specialist resources such as mobile stroke units (31). These may also assist in an early decision about whether patients being assessed for thrombolysis should have additional imaging, other than CT, in order to minimize inappropriate treatment, particularly as migraine was more common amongst the thrombolysis SM population.

In the meantime, clinician knowledge of common SM characteristics could inform the differential diagnoses considered when assessing suspected stroke patients. Training programmes should encourage clinicians to seek additional information which might broaden the diagnosis for key demographic groups.

Limitations

Meta-analysis was not attempted due to the narrative nature of this review and study heterogeneity. A quality assessment tool tailored for cohort studies may have been more appropriate than the QATSDD tool which was chosen prior to study identification. The initial screening and identification was performed by a single reviewer so relevant studies could have been missed. We did not include non-English studies. CCS coding simplified cases to a single diagnostic category to aid reporting, but this does not represent the multiple problems some patients possess. The prehospital population was small reflecting the lack of clearly described prehospital research. The representation of clinical characteristics is crude but could be used to inform the focus of future studies.

Conclusion

Twenty-two percent of all suspected stroke patients had a SM condition. SM patients included a higher proportion of females and tended to be younger than stroke patients. Many conditions present as SM but seizures and migraines are the most frequent

aetiologies. It is challenging to identify clinically useful characteristics that differentiate SM from stroke, however a combination of stroke and SM assessment tools during the acute phase of emergency stroke care might reduce the number of false positive identifications created by commonly used symptom checklists.

Acknowledgements

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Supplemental Digital Content available on request

Structured search strategy. Supplemental Digital Content 1.doc

Description of included studies with references. Supplemental Digital Content 2.doc

Table showing full quality assessment scoring. Supplemental digital content 3.xlsx

References for table 2. Supplemental Digital Content 4.doc