Review article

Ischemic stroke mimics: A comprehensive review

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Article history:
Received 1 June 2021
Accepted 12 September 2021

Keywords:
Stroke
Thrombolysis
Mimic
Etiology
Clinical findings
Outcome

A B S T R A C T

Background: Ischemic stroke is the leading cause of disability and one of the leading causes of death. Ischemic stroke mimics (SMs) can account for a notable number of diagnosed acute strokes and even can be thrombolysed.

Methods: The aim of our comprehensive review was to summarize the findings of different studies focusing on the prevalence, type, risk factors, presenting symptoms, and outcome of SMs in stroke/thrombolysis situations.

Results: Overall, 61 studies were selected with 62,664 participants. Ischemic stroke mimic rate was 24.8% (15,044/60,703). Most common types included peripheral vestibular dysfunction in 23.2%, toxic/metabolic in 13.2%, seizure in 13%, functional disorder in 9.7% and migraine in 7.76%. Ischemic stroke mimics have less vascular risk factors, younger age, female predominance, lower (nearly normal) blood pressure, no or less severe symptoms compared to ischemic stroke patients (p < 0.05 in all cases). 61.7% of ischemic stroke patients were thrombolysed vs. 26.3% among SMs (p < 0.001). Overall intracranial hemorrhage was reported in 9.4% of stroke vs. 0.7% in SM patients (p < 0.001). Death occurred in 11.3% of stroke vs 1.9% of SM patients (p < 0.001). Excellent outcome (mRS 0–1) was reported in 41.8% ischemic stroke patients vs. 68.9% SMs (p < 0.001). Apart from HINTS manouvre or Hoover sign there is no specific method in the identification of mimics. MRI DWI or perfusion imaging have a role in the setup of differential diagnosis, but merit further investigation.

Conclusion: Our article is among the first complex reviews focusing on ischemic stroke mimics. Although it underscores the safety of thrombolysis in this situation, but also draws attention to the need of patient evaluation by physicians experienced in the diagnosis of both ischemic stroke and SMs, especially in vertigo, headache, seizure and conversional disorders.

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1. Introduction

Ischemic stroke is the leading cause of disability and one of the leading causes of death. Enormous efforts have been recently made to improve the clinical outcome of stroke patients including testing up comprehensive stroke units and the introducing endovascular procedures [1]. The benefit of revascularisation procedures (both intravenous thrombolysis and endovascular procedures) is time-dependent, therefore shortening door-to-needle time is crucial in the emergency department [2]. Ischemic stroke is usually an exclusionary clinical diagnosis in the emergency room, usually supported by noncontrast computed tomography (NCCT), which is the first step in the evaluation of ischemic stroke patients due to its widespread availability and relatively short imaging time [3,4].

However, the increased availability of systemic thrombolysis and shortened door-to-needle time have lead to inappropriate inclusion and treatment of so-called ischemic stroke mimics (ie. non-stroke patients) [3,5]. Ischemic stroke mimics can account for approximately one in five clinically diagnosed acute ischemic strokes and the rate of thrombolysed mimics can be as high as 17% [6]. Based on literature data mimics are most likely to be identified as seizures, complicated migraines or conversion disorders [6–9].
Multimodal patient imaging (both CT and MR perfusion techniques) is an important part of acute ischemic stroke imaging to delineate the infarct from ischemic penumbra in specific situations such as stroke of unknown time of onset (SUTO) or in endovascular intervention with extended time window [6,10]. Perfusion techniques may play a vital role in diagnosing SMs in the stroke/thrombolysis pathway (if the etiology is doubtful) [6,10].

Despite of increasing number of publications in the last three decades, no comprehensive review has summarized the complex etiology, potential maltreatment and outcome of ischemic stroke mimics, especially in emergency situations. The aim of our review article was to summarize the findings of different studies focusing on the prevalence, type, risk factors, presenting symptoms, and outcome of mimics in ischemic stroke/thrombolysis situations.

2. Methods

We searched PubMed, MEDLINE, and the Cochrane Library restricted to English language publications to January 2020. We used these search items in the following combinations: stroke, ischemic stroke, mimic, thrombolysis, rt-PA, alteplase, imaging, outcome, and mortality. After reviewing the abstracts, we obtained and reviewed the full text and reference lists of relevant articles.

3. Statistical analysis

Participants of the relevant studies were divided into two groups: (1) ischemic stroke patients, and (2) ischemic stroke mimics. Ischemic stroke mimic types, clinical findings, risk factors, thrombolysis rates and outcomes were compared between the two groups. Data were evaluated as means ± SD (standard deviation) by Student’s t-test or chi square test to detect significant differences among the examined parameters. Data analysis was performed using SPSS (version 22.0, IBM, New York, NY, USA).

4. Results

Overall, 61 studies were selected with 62,664 participants [11–71]. There were five prospective multicenter, one observational prospective, 17 prospective single center, 9 retrospective multicenter and 30 retrospective single center study (Supplementary Table 1).

Stroke mimic rate was 24.9% overall (15595/62664). Stroke mimic rate based on study type can be seen in Supplementary Table 1.

4.1. Mimic types

Ischemic stroke mimic types were the following: peripheral vestibular dysfunction in 23.2% (1109/4769 based on 15 studies [11, 16, 22, 26, 30, 32, 44, 46, 51, 61, 65, 66, 69, 70, 71]), toxic/metabolic in 13.2% (1053/7985 based on 15 studies [11, 16, 22, 26, 30, 32, 44, 46, 51, 61, 65, 66, 69, 70, 71]), seizure in 13% (1257/9629) [11,17,19,20,22,25–27,30,32,33–47,71], transient global amnesia etc. (Fig. 1).

9.69% had non defined etiology which was not entirely clarified including Susac syndrome, obtrusive hydrocephalus, transient global amnesia etc. (Fig. 1).

4.2. Clinical findings

SM patients had significantly lower NIHSS (4.99 ± 5.65 vs. 8.06 ± 6.37, p < 0.001 [11, 14, 15, 19, 20–22, 24, 26, 28, 30, 34, 37, 41, 42, 45, 47, 49, 52, 53, 55, 58, 59, 61, 63–67, 69, 70]), acute confusion in 1.9% (84/3444 [11, 14, 16, 34, 38, 44, 59, 70]), dementia in 1.2% (54/4577 [11, 16, 23, 33, 34, 38, 43, 46, 51, 54, 55, 61, 69, 70]) and spinal lesion in 0.7% (22/2939 [11, 16, 20, 25, 43, 61]) (Fig. 2). 9.69% had non defined etiology which was not entirely clarified including Susac syndrome, obtrusive hydrocephalus, transient global amnesia etc. (Fig. 1).

4.3. Risk factors

Hypertension 66.8% (20074/30035) vs. 41.1% (3434/8347) [11,14,15,19,20,21,23,24,28,30–34,37,38,40–42,47,48,50,52,53,55,56,61,64,65,66,67,68,70,71], dyslipidaemia 38% (9891/26005) vs. 24.3% (6970/28689) vs. 17.8% (373/2173) [14,15,19,20,23,28,32–34,37,40,41,48,50,52,53,55–57,59,61,64,65,67,68,70,71], smoking 25.7% (5002/19433) vs. 23.6% (1585/6717) [14,15,19,20,23,28,32–34,37,40,41,48,50,52,53,55–57,59,61,64,65,67,68,70,71], dyslipidaemia 38% (9891/26005) vs. 24.3% (6970/28689) vs. 17.8% (373/2173) [14,15,19,20,23,28,32–34,37,40,41,48,50,52,53,55–57,59,61,64,65,67,68,70,71], unconfirmed AF on admission was 15.6% (17/109) in SM and 24.6% (55/224) in ischemic stroke patients based on one study (p = 0.06) [11] (Table 1).

Stroke mimic rate was 24.9% overall (15595/62664). Stroke mimic rate based on study type can be seen in Supplementary Table 1.

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were more common in ischemic stroke patients (p < 0.001 in all cases) (Table 2).

Ischemic heart disease (IHD) 15.9 % (3388/21237) vs. 9.1% (507/5542) [11,14,15,20,23,31,33,34,38,50,52,56,57,59,61,64,65,68] previously known atrial fibrillation 23% (6611/28723) vs. 8.4% (670/7929) [11,14,15,19,20,23,24,28,31–35,37,38,40,41,45,47,50,52,53,56–59,61,64–68,70] and peripheral vascular disease (PVD) 9.9% (468/4719) vs. 6.7% (45/669) [11,33,59,67] were more common in ischemic stroke patients also (p < 0.01 in all cases) (Table 2).

### Table 1
Clinical findings in the examined subgroups.

|                     | Stroke | Stroke mimic | p value |
|---------------------|--------|--------------|---------|
| NIHSS (points)      | 8.06 ± 6.37 | 4.99 ± 5.65 | <0.001  |
| Age (years)         | 68.4 ± 9.7  | 60.9 ± 10.4  | <0.001  |
| Female gender (%)   | 56%     | 68%          | <0.001  |
| Median time (min)   | 134.45 ± 58.27 | 116.75 ± 53.03 | 0.5     |
| Blood pressure (Hgmm) | 153.75/86.45 | 140.25/83.1 | <0.001  |
| Unrevealed atrial fibrillation (%) | 24.6 | 13.6 | 0.06 |

### Table 2
Distribution of risk factors in the study subgroups.

|                     | Stroke | Stroke mimic | P values |
|---------------------|--------|--------------|----------|
| Smoking             | 25.7   | 22.2         | <0.001   |
| Hypertension        | 66.8   | 41.1         | <0.001   |
| Dyslipidaemia       | 38     | 23.6         | <0.001   |
| Diabetes            | 24.3   | 17.8         | <0.001   |
| IHD                 | 15.9   | 9.1          | <0.001   |
| AF                  | 23     | 8.4          | <0.001   |
| PVD                 | 9.9    | 6.7          | <0.001   |
| Previous stroke     | 19.3   | 19.7         | 0.42     |
| Cognitive impairment| 11.1   | 25.4         | <0.001   |
| Migraine in anamnesis| 11.3   | 16.5         | <0.001   |
| Seizure in anamnesis| 1.5    | 2.3          | 0.23     |
| Known malignancy    | 8.7    | 9.1          | 0.88     |

Abbreviations: IHD: ischemic heart disease, AF: atrial fibrillation, PVD: peripheral vascular disease.

(PVD) 9.9% (468/4719) vs. 6.7% (45/669) [11,33,59,67] were more common in ischemic stroke patients also (p < 0.01 in all cases) (Table 2).
The prevalence of previous ischemic stroke was not statistically different between the two groups (19.3%, 4906/25481 vs. 19.7%, 1412/7141, p = 0.42) \[11,14,15,19–21,23,25,28,31,33,34,38,40,41, 50,52,53–55,59,61,63,65,67,68,71\].

Cognitive impairment 25.4% (31/122) vs. 11.1% (40/359) \[11,14\], and history of migraine 16.5% (151/916) vs. 11.3% (215/1900) \[11,14,15,28,46,68\] were more common in SM patients (p < 0.001 in both cases).

History of seizures/epilepsy (1.5%, 13/871 vs. 2.3%, 15/643, p = 0.23) \[11,14,15,28\] and malignancy (8.7%, 21/241 vs. 9.1%, 10/109, p = 0.88) \[11\] were not different in the two groups.

Pre-existing psychological disturbance was more common in ischemic stroke vs. SM patients (12.5%, 233/1857 vs. 9.2%, 121/1318, p = 0.003) \[11,14,68\].

4.4. Thrombolysis

20 studies reported thrombolysis rates between ischemic stroke and SM patients \[18–22,24,26,28,31,41,47,49,53,55,59,63,64,65,70,71\]. 61.7% (10232/16586) of ischemic stroke patients were thrombolysed vs. 26.3% (635/2407) among SMs (p < 0.001). Three studies reported thrombectomy rates, 12.2% of ischemic stroke patients (140/1150) had revascularisation procedure, while no SM had thrombectomy (0/607) \[26,28,63\].

Overall intracranial hemorrhage was reported in 9.4% of stroke (786/8403) vs. 0.7% in SM patients (4/524) (p < 0.001) \[14,20,21,24,41,53,64,65,70\]. Death occurred in 11.3% (953/8472) of ischemic stroke vs 1.9% (15/789) of SM patients (p < 0.001) \[14,24,30,33,41,53,61,64,65\]. Excellent outcome was (mRS 0–1) was reported in 3806/9095 (41.8%) ischemic stroke patients vs 646/937 (68.9%) SMs (p < 0.001) \[22,41,53,64,65,71\] (Fig. 3).

5. Discussion

Ischemic stroke is a potentially treatable medical emergency with a limited time window \[11\]. Its assessment requires immediate management, and decision-to-treat is an exclusionary diagnosis based on clinical findings and normal non-contrast CT or showing early ischemic changes based on the current AHA guidelines \[4\]. MRI can also be used but it has limited availability and perfusion imaging is recommended only for certain patients, which may be helpful in the differential diagnosis of ischemia versus other etiologies \[4,10\].

The differential diagnosis of ischemic stroke (so called ischemic stroke mimics) is an umbrella term rather than a single disease \[72\]. As rapid diagnostic accuracy is required due to the „time-is-brain” concept, MRI or multimodal brain imaging are sparse even in pending situations to avoid significant delay in revascularisation \[72\]. Based on review articles, about one-third of stroke admissions can be labelled as mimics \[5–7\].

In our comprehensive review including more than 60,000 patients, the rate of stroke mimics was approximately 25% which is in concordance to the above-mentioned findings; it means one out of four ischemic stroke unit admissions is unnecessary and could be avoided. These findings apart from rapid assessment are attributable to the involvement of emergency staff as first contact who are not properly trained in the detection of stroke mimics, and the relatively low specificity of currently used stroke scales \[43,72\]. Stroke mimic prediction scales as well as education of staff involved in stroke management can be useful \[73\].

Seizure, syncope, sepsis, migraine, functional disorders, space-occupying lesions and metabolic conditions were the most frequently diagnosed stroke mimics \[5–7,72,73\]. Interestingly, our findings showed that peripheral vertigo is the main challenge for stroke/emergency physicians accounting ~ 25% of all mimics. Vertigo/dizziness is a common complain of patients seeking medical attendance, however, stroke syndromes are responsible for only 3–5% of all emergency cases \[74,75\]. Acute dizziness/vertigo is most often caused by benign otovestibular origins, including benign paroxysmal positional vertigo, vestibular neuritis (viral infection of the vestibular nerve), labyrinthitis (infection of the labyrinthine organs), and Meniere disease (increased endolymphatic fluid in the inner ear), but vestibular migraine is also worth noting \[76\]. After orthostatic hypotension benign paroxysmal positional vertigo (BPPV) seems to be the second most common cause of acute vestibular syndromes, accounting for up to 10% of acute dizziness cases \[75\]. Its clinical diagnosis is based on canal-specific positional testing maneuvers and the detection of a canal-specific nystagmus and usually does not require head imaging \[75,76\]. Patients with atypical nystagmus forms (eg, persistent positional downbeat or horizontal nystagmus; no latency between the head reaching the target position during positional testing and nystagmus onset) may have mimics known as central paroxysmal...
positional vertigo. Central paroxysmal positional vertigo may result from benign central causes, such as alcohol intoxication or vestibular migraine, but other cases are caused by posterior fossa structural lesions [75].

Hearing loss and duration of symptoms may help in the differential diagnosis of vertigo. The presence hearing loss is usually caused by Meniere disease or labyrinthitis, whereas lack of it is more likely caused by BPPV or vestibular neuritis [77]. Episodic vertigo tends to be caused by BPPV or Meniere disease, whereas persistent vertigo can be caused by vestibular neuritis or labyrinthitis [75–77].

Diagnosis of migrainous vertigo (which affects 3% of the whole population and 10% of migraineurs) is established in patients with a history of episodic vertigo with a current migraine or history of migraine and one of the following symptoms during at least two episodes of vertigo: migraine headache, photophobia, phonophobia, or aura [77].

In cerebrovascular disorders, the dizziness/vertigo usually accompanies other neurological symptoms and signs, but there are exceptions as recent studies have shown that stroke in the distribution of the posterior circulation may mimic acute peripheral vestibular disorders. Furthermore, patients with infarction in the territory of anterior inferior cerebellar artery (AICA) may have isolated recurrent vertigo, fluctuating hearing loss, and/or tinnitus (similar to Meniere’s disease) as the initial symptoms 1–10 days prior to the permanent infarction [79].

Plain CT is usually non-informative, MRI can be helpful, but can be negative in a small, but significant proportion of posterior stroke patients [6,75]. A three-step bedside oculomotor exam (H.I.N.T.S.: Head-Impulse—Nystagmus—Test-of-Skew) appears to be more sensitive to stroke than early MRI in the detection of stroke [79]. The acronym refers to HI: Head Impulse, N: Nystagmus direction and TS: Testing Skew. In addition, a second acronym and mnemonic: INFARCT summarises the application of HINTS: IN: Impulse normal, FA: Fast Alternates (referring to the nystagmus fast phase) and RCT: Reflexation on cover test (skew deviation) [79] (Fig. 4).

Metabolic/toxic disturbances were the second most common cause of stroke mimics in this comprehensive review. Hypoglycaemia is easily detectable with a bedside test, however, only INR and blood glucose measurement is recommended before thrombolysis based on the current guidelines, the lack of blood test results is not an exclusionary criteria [4]. In one prospective study, metabolic disorders accounted for a significant proportion of ischemic stroke mimics and severe hyponatraemia accounted for one-third of these [80,81]. Symptoms include lethargy and confusion at mild levels of hyponatraemia to seizures, coma and respiratory arrest at significantly lower levels, but focal neurological symptoms can also occur [81]. Hypokalaemia or intoxication with alcohol or drugs can also result in transient focal neurological symptoms. Furthermore, intoxication may cause delay in the management of acute ischemic stroke [82]. So in doubtful cases detailed blood tests and bedside toxicology is strongly recommended (Fig. 4).

Seizures were responsible for 13% of all mimics. Seizure has been recognized as a cause of focal paresis since the 19th century and duration of this Todd’s paresis can be quite short, mimicking a TIA [51]. Deficits may persist longer in the case of generalized seizure, with reports of postictal deficits lasting days. Postictal dysphasia has also been reported to follow dominant hemisphere seizures [6]. If a previous seizure is unwitnessed postictal paresis or aphasia is easy to misdiagnose as a stroke or a transient neurological symptoms of vascular origin.

Although seizures can occur due to ischemic stroke, especially in cortical lesions, early seizures can occur in 3.8% of all cases and only 1.5% had seizure at the onset of stroke symptoms [6,83]. Therefore the presence of a seizure implies other etiology than ischemic stroke.

On the other hand, population based data have shown that stroke is the underlying cause of epilepsy in older adults in more than 30% [6]. After having a post-stroke seizure recovery is rapid in most patients (see above) although rarely non-convulsive status epilepticus may present with prolonged aphasia or motor weakness [84].

MRI diffusion-weighted imaging and multimodal brain imaging may help in the differentiation of ischemia vs. seizure (see details below) [6]. The widely available CT perfusion is a quick, fast imaging modality which plays a role not only on the detection of infarct size and penumbra but also delineate conditions mimicking stroke. However, its limitations are exposure to additional radiation (also intravenous contrast), additional delay (15 min) in care, and cost of the procedure [85] (Fig. 4).

Functional neurological disorder is also a great imitator of ischemic stroke responsible for ~ 10% of SMs. These patients are younger and seem to be more likely to be female, usually presenting with more weakness/numbness than speech disturbance (aphasia, dysarthria) or reduced consciousness based on a recent analysis [8]. Previous psychiatric history is common, symptoms are usually atypical and fluctuating [85]. Physical examination shows inconsistent findings with repeated examinations. Furthermore, Hoover sign - weakness of voluntary hip extension with normal involuntary hip extension during contralateral hip flexion against resistance – can be very specific in the diagnosis of functional stroke mimics [86]. Imaging is normal or reveals no DWI/MRI lesions [71] (Fig. 4). The prognosis for full recovery is unfortunately not very good with more than one-third of patients reporting same or worse deficits during follow up as levels of physical disability and psychological comorbidity were high if the diagnosis was delayed [87].

Migraines account for ~8% of mimics. Aura symptoms may be multiple, for example, a combination of visual (hemianopsia) and hemiparesthetic aura (especially if occurs without headache) may suggest infarction in the posterior cerebral artery territory [88]. Basilar migraine is an uncommon, but devastating condition, which can present with vertigo, dysarthria, ataxia and decrease loss of consciousness [85]. Hemiplegic migraine, any migraine with aura including motor weakness, is perhaps the primary headache disorder most likely to be mistaken for stroke. It is very rare, with a prevalence estimated at 0.01%. Among patients with hemiplegic migraine, motor symptoms typically last up to 72 h, but may persist for weeks [88,89].

Although an updated meta-analysis involving more than one million individuals showed higher risk of stroke among migraineurs, migrainous stroke could be classified in 0.3–0.5% [90]. Long lasting aura (>60 min) draws attention to symptoms of cerebrovascular origin [91]. History of migraine and detailed anamnesis can be helpful including enquiring about similar previous symptoms.

Plain CT is not helpful, MRI DWI may help to identify migraineurs as ischemic stroke mimics, but can be negative in rare cases [92]. Perfusion techniques (CT or MR perfusion) show atypical stroke perfusion abnormalities usually not limited to one vascular territory in these patients [93] (Fig. 4).

Sudden onset of neurological symptoms can develop in 4.3% of patients with intracranial tumors based on our results raising the possibility of acute stroke. A brain CT can usually distinguish between stroke and malignancy in the vast majority of cases, however, primary intracranial malignancies may require extensive diagnostic workup including contrast-enhanced MRI, as plain CT can be misinterpreted as normal [94,95].

Other etiologies included collapsing/presyncope, mononeuropathy, sepsis, acute confusion, dementia and spinal lesion.
Anamnestic data, sophisticated neurological examination, presence of febrile and blood test results usually help to identify mimics, but it can be very difficult in the minority of cases [96].

The mechanism of neurological signs in syncope and sepsis is not always hypoperfusion. Careful collateral histories obtained from carers or details from previous medical records can differentiate this from recurrent stroke. In the case of sepsis, there are often clues from the history, signs of systemic illness on examination and raised inflammatory markers. However, both sepsis and stroke are common and dual pathology can exist, sepsis can also induce a hypercoagulable state and predispose to cerebral infarction. Loss of consciousness is, as a general rule, unusual in stroke [72].

Bell’s palsy, radial palsies or other neuropathies usually do play a role in the differential diagnosis of ischemic stroke. Peripheral facial paresis can be the consequence of brainstem stroke, but it is usually associated with other neurological signs. Distinct radial neuropathy in a relatively old patient with vascular risk factors, stroke should be considered as the possible aetiology until proven otherwise, but these are rare etiologies [97]. Miller Fisher syndrome (MFS) is a rare acquired polyneuropathy precipitated by an acute infection, more commonly respiratory than gastrointestinal (GI) or meningeal source, and it is recognized as a variant of Guillain-Barre syndrome (GBS) [98]. It is characterized by areflexia, ataxia and ophthalmoplegia without significant sensory loss, but can be associated with facial droop, slurring of speech and gait instability, which can be easily misdiagnosed as a stroke [98].

Strokes affecting the non-dominant inferior parietal lobe, non-dominant temporal gyrus or occipital lobe can present with confusion, agitation or restlessness and can be mistaken for delirium [72,99]. Similarly, vertebrobasilar ischaemia causing thalamic infarcts can lead to sudden onset confusion with memory loss [72,99]. The key to diagnosis here is that few other causes of delirium present so acutely; witnesses may report the patient being asymptomatic one moment and then confused the next [72] (Fig. 4).

It is worth noting the term stroke recrudescence, which refers to the re-emergence of the previous stroke-related deficits in the settings of metabolic, infectious and toxic dysfunction. The diagnosis requires an MRI which shows the old stroke and reveals no new DWI-MRI deficits. Symptoms are mostly short-lived and show improvement within 24 h in most subjects. Recrudescence can develop within weeks to years after the previous stroke [84,100]. The recrudescence under metabolic, infection, fatigue or sedative medications is likely due to functional suppression of compensatory cerebral networks [84,100] (Fig. 4).

Stroke mimic patients are usually younger, tend to be female and have less severe symptoms (interestingly, no neurological
abnormalities could be detected in 1/3 of them) compared to stroke patients in the emergency room and they usually have lower (nearly normal) blood pressure based on our results. Loss of consciousness, vomiting and headache are also more frequent among mimics. However, there are no definite diagnostic criteria of mimics, age, gender and the lack of obvious neurological abnormalities do not exclude stroke syndromes neither do headache and vomiting. Verteobasilar stroke patients usually have no or minor neurological abnormalities, they complain of nausea/vomiting or imbalance/dizziness [101]. Furthermore, NIHSS is heavily weighted towards anterior circulation/hemispherial strokes and has low sensitivity to posterior strokes [102]. Headache can occur in 27% of all strokes, therefore its presence or absence is not specific to neither stroke nor mimics [78].

Stroke patients are more frequently burdened with conventional/vascular risk factors such as smoking, hypertension and atrial fibrillation. However, the lack of risk factors do not exclude the possibility of stroke as there are a number of putative mechanisms such as paroxysmal atrial fibrillation, hypercoagulable state or undiagnosed malignancy especially in non-geriatric patients [103]. Mimics only have more frequent history of migraine and cognitive impairment. Interestingly, history of previously diagnosed psychiatric disorders was more frequent among stroke patients. It may be attributable to the increased risk of stroke among those taking antidepressants or antipsychotic drugs [104,105].

Despite of the centralized stroke services with available MRI scanning and perfusion techniques, plain CT is the first line of imaging modality even in unclear situations to avoid significant delay. More than 1/4 of mimics are thrombolysed, which is a surprisingly high rate. Thrombolysed stroke mimics had very low overall intracranial bleeding and mortality rates comparing to ischemic stroke individuals and had more favourable outcome, which is not surprising as symptoms were not of cerebrovascular origin. Although it underlines the safety of thrombolysis in stroke mimics, it also draws attention to the need of patient evaluation by physicians experienced in the diagnosis of both stroke and mimics, especially in vertigo, headache, seizure and conversional disorders [2,106].

MRI diffusion-weighted imaging (DWI) is the most sensitive and specific imaging technique for the visualization of an acute infarct, with excellent sensitivity and specificity within minutes after the onset of symptoms [6,107]. MRI DWI seem to be helpful to distinguish between stroke and stroke mimics, but diffusion restriction can be seen after seizure and migraine attack also [6,74,75]. Finally, MRI DWI can be negative in a small (~7%), but significant percentage of stroke patients, especially in patients with neurologic deficits consistent with posterior circulation ischemia who have 5 times the odds of having a negative DWI scan compared to patients with anterior circulation ischemia [6,74,75].

CT and MR perfusions are promising imaging techniques in the detection of regional differences in blood flow, thereby they are able to differentiate the ischemic penumbra from the infarct core, which can be useful in patients with stroke of unknown time of onset (SUTO) or patients with extended time window who are usually opted out from treatment [6,108–111]. They are potentially useful for helping to determine candidates for systemic thrombolysis or revascularization and may help in the identifications of stroke mimics, but it merits further investigation [6,109–111].

Little is known about long term outcome of stroke mimics. A recent study showed increased risk of major acute cardiovascular events (MACE) in ischemic stroke mimics, especially among those with with previous stroke, coronary artery disease, diabetes, and being hypertensive on admission. MACE were also significantly higher in patients where imaging showed a previous stroke [112]. In functional stroke patients (functional motor symptoms) levels of physical disability and psychological comorbidity at follow-up were high, but can be prevented with early diagnosis as short duration of symptoms, early diagnosis and high satisfaction with care predicted positive outcome [87].

Finally, our article has some limitations. Although it compared a relatively large number of patients and studies, it did not fulfill the criteria of a conventional meta-analysis, which may significantly affect our results.

In conclusion, this is among the first most comprehensive reviews focusing on stroke mimics. Peripheral vertigo, toxic/metabolic changes, seizure, migraine and functional disorders are the most common etiologies. Stroke mimic patients seem to be younger with female predominance, with less severe symptoms compared to stroke patients. Mimics also have less vascular risk factors, but a more frequent history of confusion or migraine. One out of three mimics is thrombolyzed with a very good outcome. Apart from HINTS manoeuvre or Hoover sign there is no specific method in the identification of mimics. MRI DWI or perfusion imaging have a role in the setup of differential diagnosis, but merit further investigation.

6. Ethics approval and consent to participate

Not applicable.

7. Availability of data and materials

The dataset supporting the conclusions of this article is available on request to the corresponding author.

Funding

This research was funded by NKFI (OTKA)-135316 project.

Authors contributions

All authors equally contributed to the manuscript including study concept and design, collection of data, analysis and interpretation of data, writing of manuscript and critical revision of manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2021.09.025.

References

[1] Mikulík R, Caso V, Bornstein NM, Svobodová V, Pezzella FR, Grecu A, et al. Enhancing and accelerating stroke treatment in Eastern European region: Methods and achievement of the ESO EAST program. Eur Stroke J 2020;5 (2):204–12.

[2] Tsivgoulis G, Zand R, Katsanos AH, Goyal N, Uchino K, Chang J, et al. Safety of intravenous thrombolysis in stroke mimics: prospective 5-year study and comprehensive meta-analysis. Stroke 2015;46(5):1281–7.

[3] Ramadan A-R, Denny MC, Vahidy F, Yaman J-M, Wu T-C, Sarraj A, et al. Agreement Among Stroke Faculty and Fellows in Treating Ischemic Stroke Patients With Tissue-Type Plasminogen Activator and Thrombectomy. Stroke 2017;48(1):222–4.

[4] 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49:e46–e99.
