

Stroke mimics in a Brazilian stroke center: a retrospective cohort in a Brazilian stroke unit

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Abstract: This study assessed stroke patients in a Brazilian unit to describe the prevalence, clinical presentation, etiology, and treatment outcomes of cases initially diagnosed as stroke mimics (SM). SM refers to conditions that mimic stroke but are not caused by cerebrovascular events. Misdiagnosis can lead to unnecessary and potentially harmful treatments. The study examined patients admitted between October 2012 and September 2013. Among patients with symptoms onset within four hours, 7.1% (10 patients) were classified as SM. Six of these patients received intravenous thrombolysis, a treatment for acute ischemic stroke. The main clinical presentations among SM cases were motor symptoms (90%), dysarthria, and sensory symptoms (60%). The etiology of SM cases varied, with functional disorders being the most common (60%). The findings reveal a significant percentage of patients admitted to the stroke unit were ultimately diagnosed as SM, highlighting the need for improved diagnostic strategies to differentiate between stroke and SM. The study underscores the importance of developing well-defined guidelines to assess SM risk and utilize imaging methods for distinguishing between stroke and SM. Further research is necessary to address these issues and enhance stroke diagnosis accuracy.

Keywords: Stroke; Stroke mimics; Stroke chameleon.

1. Introduction

Stroke is one of the main causes of mortality and incapacity in the world [1]. It is estimated that, only in 2019, there was an incidence of 12.2 million new cases. From 1990 to 2019 there was an increase of about 70% in the incidence and of 43% in the deaths re-

sulting from stroke [2]. It is calculated that the annual global cost of stroke, currently, is superior to 721 billion, corresponding to 0.66% of the gross domestic product, due to the hospitalization and rehabilitation costs [3]. The decrease in mortality and morbidity in the years to come is a constant challenge [3,4].

Stroke is a cerebrovascular condition characterized by a deficiency in the blood supply that should reach the nervous tissue [5]. Depending on its mechanism, it can be classified into two types: ischemic and hemorrhagic stroke [1,3,5]. The ischemic stroke is characterized by a deficit in the brain's blood flow due to a vascular obstruction, and it is subdivided into five types in relation to the obstruction's origin, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST), them being: great blood vessel atherosclerosis, cardioembolism, occlusion of small blood vessels, other etiologies and undefined [4,5,6]. The hemorrhagic stroke occurs due to the extravasation of blood to the interior or to the periphery of central nervous system (CNS) structures [5,6].

In the context of ischemic stroke, besides the necessity of an early diagnosis in the thrombolysis time frame, a second problem is added: the diagnostic error. In this spectrum, there are two main possibilities: the stroke chameleons and the stroke mimics (SM). When it comes to stroke chameleons, stroke has an unusual clinical presentation [7,8]. Additionally, SM is characterized by a broad range of other non-ischemic causes that lead to an acute neurologic deficit, mistaken for ischemic stroke [9,10]. It is estimated that up to 25% of hospitalization ischemic stroke treatment units happen unnecessarily, due to the failure in diagnosing SM cases [11].

On this topic, both the high incidence of ischemic stroke and the necessity of an early revascularization treatment for a better clinical outcome can contribute to wrong diagnosis and management. Other possible aggravating factors for such errors are the lack of adequate training of the emergency team to recognize SM, as well as the relatively low specificity of the currently used stroke scales [12,13]. It is known that the inadvertent administration of thrombolytic to the SM patient causes hemorrhage and death 0.7 and 1.9% of the time, respectively [11]. The inadvertent administration of reperfusion therapy to a SM patient also leads to unnecessary costs, increased hospitalization time, diagnostic delay and, consequently, damages the assertive treatment of the subjacent cause to SM [11,14].

Thus, it is fundamental to develop strategies to enhance the diagnostic accuracy of SM aiming to minimize possible damage to the patients, as well as unnecessary costs to the health system. Since high-accuracy diagnostic criteria do not exist, a more detailed epidemiologic description from different places is essential to increase the suspicion rates in the emergency service. It is known that previous knowledge about the prevalence statistics and clinical data of a disease increases the chance of diagnosing it. This study aims to contribute with an epidemiologic description of the prevalence, main etiologies, clinical presentation, and thrombolysis outcomes in SM patients. In this context, it can be used as a subsidy for future actions of patient risk stratification, as well as diagnostic approaches and more adequate treatments.

2. Methodology

2.1 Study population

This study is a retrospective observational analysis of all patients admitted in the Stroke Unit of the Clinical Hospital Complex of the Federal University of Paraná (CHC-UFPR) in Brazil between October 2012 and September 2013 as acute strokes with less than four hours of symptoms onset.

2.2. Ethics Committee

Firstly, the proposal was approved by the Ethics Committee in Research of CHC-UFPR under the protocol CAAE 57378822.5.0000.5049.

To execute this research the practice preconized in Brazil 2012, through the Resolution 466/12, that concerns the research involving human beings, which obeys the ethical principle of autonomy, mainly when it comes to consenting and enlightening the research's participants, was taken into consideration. In correspondence with the resolution cited above, highlighting that, under no circumstances, the name of the people involved in this research will be publicized. The participants' data accepted the Informed Consent.

2.3 Definitions

The study was a retrospective observational single-center study. SM were defined as a patient with a stroke-like clinical picture but with another disease that was not a stroke (ischemic, hemorrhagic, or transient ischaemic attack) after a complete evaluation, including brain Magnetic resonance imaging (MRI).

2.4 Search strategy

Research of the current literature on SM was executed in the PubMed database. The search was done for complete articles, without language restriction, of literature published from September 2020. Besides, additional references were considered through the research in the references of the selected articles, as well as articles recommended by experts in the neurology field. The research strategy was the combination of keywords that refer to SM, using: ("ischemic stroke"[MeSH Terms] OR ischemic stroke [Text Word]) OR ("hemorrhagic stroke"[MeSH Terms] OR hemorrhagic stroke [Text Word]) AND ("stroke mimic"[Text Word] OR "stroke chameleon"[text word]).

2.5 Statistical analysis

Descriptive statistics were used to present the data. The results were expressed as a percentage. The analysis was performed with Jamovi software.

3. Results (Review)

3.1 Patients Included

During the period analyzed in the study (between October 2012 and September 2013), 253 patients were admitted to the stroke unit of the CHC-UFPR. 140 patients (55.3%) of the total number of patients admitted had less than four hours of symptoms onset. 10 patients (7.1%) of the total number of patients with less than four hours of symptoms onset were considered SM. The flowchart of the evaluated patients can be seen in detail in Figure 01.

3.2 Clinical Presentation

Six patients (60%) were female with a mean age of 43.1 ± 16.2 years old. The main comorbidities in patients with SM were hypertension and dyslipidemia, in four patients (40%), diabetes mellitus in two patients (20%), and previous seizures in one patient (10%). The main clinical presentations of symptoms of the 10 patients included in the study with SM were motor symptoms, dysarthria, sensitive symptoms, cortical symptom (negligence), and gaze paresis. Motor symptoms were presented in nine patients (90%); dysarthria and sensitive symptoms in six patients (60%); cortical symptoms (negligence) and gaze paresis in one patient (10%). The percentage data of the clinical presentation can be seen in Figure 02.

3.3 Rate of intravenous thrombolysis and degree of disability

Of all patients diagnosed with SM, six (60%) were submitted to intravenous thrombolysis without any complication. The National Institutes of Health Stroke Scale (NIHSS) median at hospital admission, 24 hours after admission, and seven days were

7.5, 2.5, and 0.5, respectively. At discharge, all 10 patients had a modified Rankin score (mRS) of less than three. Five patients (50%) were mRS zero (mRS = 0). In functional patients, only 20% were mRS zero.

3.4 Etiology of SM

The final diagnosis of the 10 patients with SM were functional disorders in six patients (60%), Todd paresis in one patient (10%), exogenous intoxication in one patient (10%), diabetic ketoacidosis in one patient (10%), and a clinically isolated syndrome in one patient as well (10%). The percentage data about the etiology of SM can be seen in Figure 03.

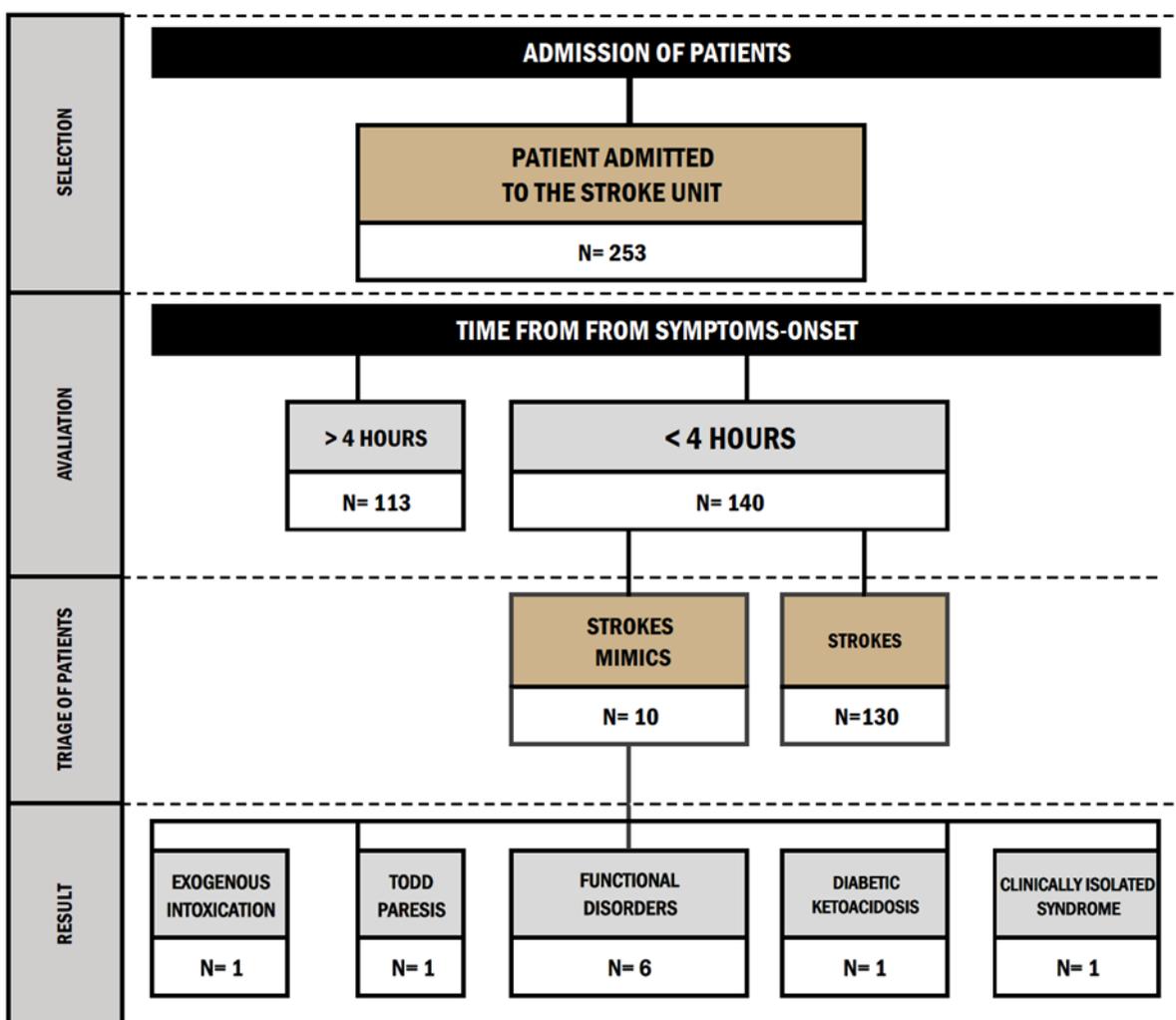


Figure 1: Flowchart of admitted patients in the stroke unit.

4. Discussion

The present study described the prevalence, clinical presentation, etiology, and treatment outcomes in the cases of SM primarily diagnosed as stroke. It was a retrospective study that evaluated patients admitted in the stroke unit of CHC-UFPR in Brazil. In conclusion, our results showed that an important percentage of patients admitted in a stroke unit are SM and that a significant part of the SM are submitted to unnecessary thrombolysis procedures. The clinical presentation and etiology of SM is variable, being discussed in greater detail subsequently.

In which concerns the prevalence, a great review involving the analysis of 61 studies on stroke and a total of 62.664 patients found that the general rate of SM was 24.8% [11].

In another study, it was evidenced through a retrospective analysis of 1063 patients with stroke suspicion in the emergency department that 12.3% were SM [15]. Therefore, our study identified an average percentage prevalence of SM in the emergency department below than what the current literature shows. Such results can be explained by the epidemiologic heterogeneity of each place in which the studies were conducted. Thus, it is important to recognize the prevalence of such conditions in the most diverse places, being the present study one of the first analyses done in Brazil on the prevalence of SM.

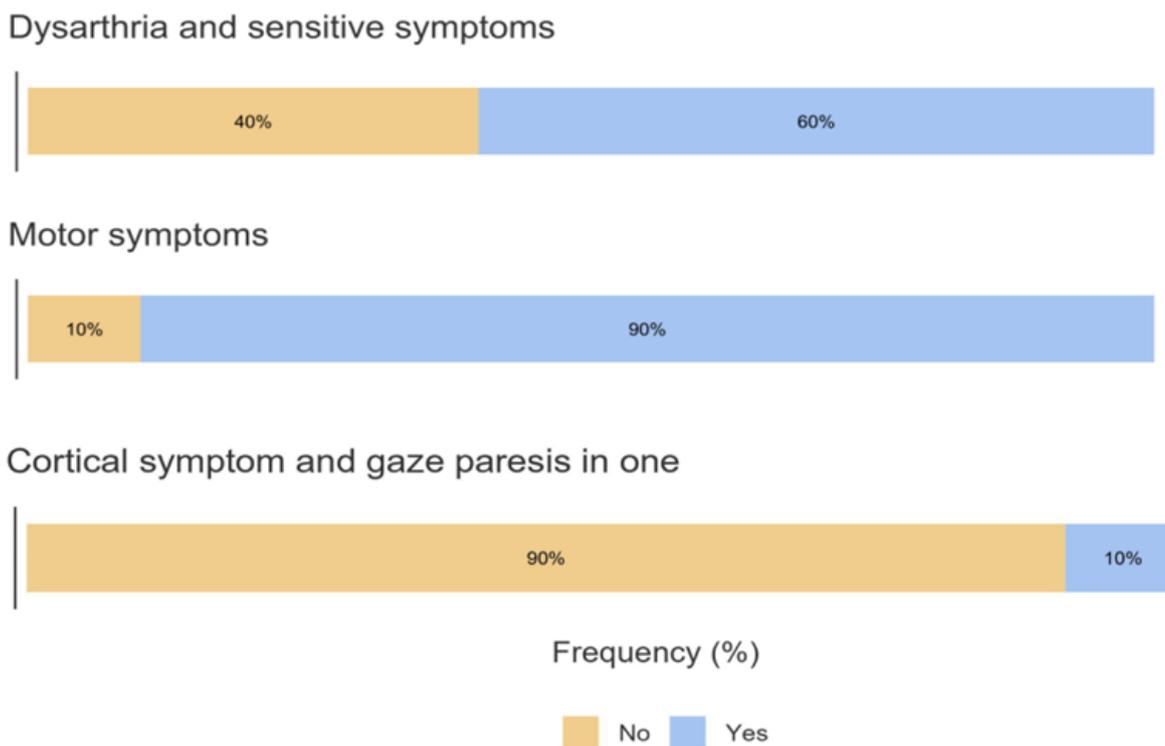


Figure 2: Frequency of clinical presentation in patients with stroke mimics.

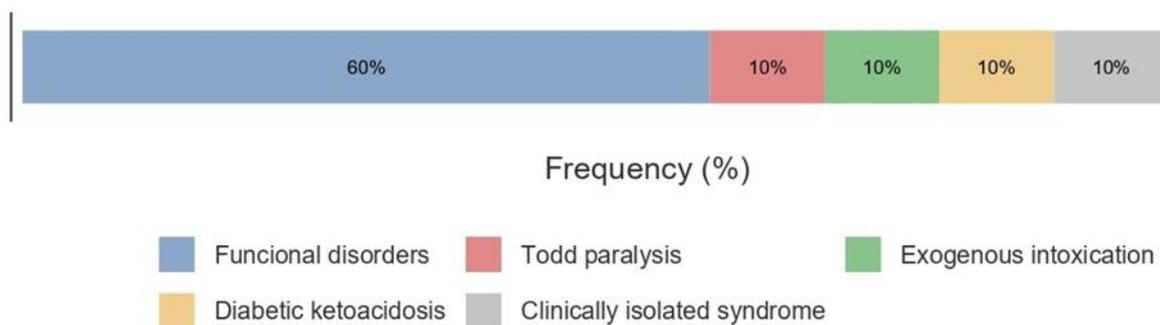


Figure 3: Etiology of stroke mimics.

In this context, due to the probable epidemiologic heterogeneity between different locations, recognizing the prevalence of SM cases becomes an important aspect for the preparation of emergency services. Primarily because of the inherent risks associated with the wrong diagnosis, such as inadvertent thrombolysis and unnecessary costs [11,14,16]. Secondly, because despite the patients diagnosed with a SM episode not hav-

ing a stroke in that moment, there are evidence that these patients have an increased risk of developing a cardiovascular event, such as myocardial infarction and stroke, in the years after the episode diagnosed as SM [18].

Our findings regarding etiology are in accordance with the literature, in which the most common causes of SM are functional disorders, seizures, migraine, peripheral vestibular dysfunction, toxic-metabolic conditions, tumors and CNS infections [9,11,15,17]. Amongst every possible etiology, it is highlighted in our study the high proportion of functional disorders. In literature, a significant part of SM is functional disorders [15,18], however not in such high proportion as 60%. In this context, to diagnose a functional disorder it is indispensable an evaluation taking into consideration a clinical and neurological well executed examination, along with imaging tests that lead to the exclusion diagnosis of non-functional causes [10].

In which concerns the clinical presentation, numerous studies point the sudden appearance of minimally specific clinical manifestations to the direction of the adequate SM treatment, such as sleepiness, mental confusion, agitation and fever. It is also observed, with a high prevalence amongst the observed patients, vertigo, dizziness, altered level of consciousness, paresthesia and numbness, monoplegia, speech disorders, member ataxia, headache, and visual disturbances [17]. Additionally, a higher incidence in young and female individuals has been reported [15]. Thus, it is noted that the specificity of the clinical findings interferes and delays the accurate diagnosis in the emergency department, turning it into a challenge before the heterogeneity of clinical presentations between SM and stroke. In the context of medical care, besides a thorough clinical evaluation, the current imaging method with the highest accuracy to differentiate between a stroke mimic and an acute ischemic stroke is an MRI with Diffusion weighted imaging (DWI) [9].

Regarding the diagnostic errors, a great interest in identifying and combating the common cognitive biases, such as anchoring and the framing effect, which favors the failures in diagnosing patients correctly, has existed for a long time [19]. These biases are very relevant in the scenario of stroke diagnostic errors since these patients commonly present typical stroke signs or symptoms or nonspecific ones [8]. However, the most recent educational methods to train students and healthcare professionals in strategies of cognitive bias were not considered effective [8]. Furthermore, a study directed to experienced doctors, which evaluated them using openings from clinical cases, determined a very low confidence degree amongst the examiners regarding the presence or the absence of individual cognitive biases [20].

Still in this context, a possible simple tool, but much ignored, proposed by some studies to avoid diagnostic errors that come from cognitive biases and its great damages to the patients, is the implementation of a brief pause of healthcare professionals to reflect about the plausibility of the possible work diagnosis, as well as preventively considering what can happen and how to proceed in cases of an incorrect diagnosis [8]. In stroke cases, simply taking a short pause during the patient's evaluation to reflect about whether the presented signs and symptoms are more typical or not of vascular etiology can lead to good results [8]. In this perspective, a pilot randomized controlled trial was conducted that determined that having doctors taking breaks during the diagnosis with a verification list of differential diagnosis did not reduce the average rate of diagnostic errors but reduced these mistakes considerably in the subgroup of emergency doctors [21]. In another study, with primary care providers, taking this pause during the diagnosis led to a different action in 13% of cases, but it did not significantly reduce the diagnostic errors [22].

Therefore, it is concluded that this diagnostic method has the potential to considerably reduce the diagnostic errors, which is associated with the fact of it being a low risk and easily adoptable approach to enhance the diagnostic precision, but more evidence and improvements are necessary. The reflection regarding stroke or transient ischemic attack can be the etiology of any of the frequent known characteristics amongst the stroke

chameleons and can reduce the risk of wrong diagnosis. However, it is worth highlighting that this diagnostic strategy is more adequate to subacute or chronic cases, since before a presentation of an acute cerebrovascular event, any delay in intervention can lead to great damages to the patient. Thus, this method would be more viable and efficient considering an ambulatorial environment, which brings a different focus than a great part of the literature, which focuses on analyzing only the emergency setting.

Still in the context of stroke diagnosis, although the more reliable tests are the MRI and the cranial tomography, laboratory tests, such as D-dimer values, are an important clinical addition in its diagnosis [23]. In a study with 2901 patients, published in February of 2022, it was evidenced that stroke patients present D-dimer values significantly higher in comparison to the patients with SM, making them a useful stroke predictor still in the six-hour period after the beginning of the event [23]. In another study with 22.590 patients, an analysis was done before the stroke happened, which found that higher levels of D-dimer increased the stroke total risk in 40% of the patients, it was also found that an increase of 50 ng/ml could increase this risk in 0.3% [24].

Regarding the thrombolysis rate, studies showed that the rate of SM patients which have undergone thrombolysis is highly variable, some studies bring a variation of 1.4% to 16.7% [25]. Most of these patients will not present complications due to the thrombolysis [11,25]. Our study, despite the high rate of thrombolysis in SM patients, did not evidence any complication, a fact that agrees with the current literature. Currently, there are drafts of risk stratification of the patients in the emergency services to increase the diagnosis probability and minimize the costs and the risks for the patient due to an unnecessary thrombolysis [25]. Besides, new technologies have been developed with the aim to try to differentiate a SM of an ischemic stroke, for example the purine concentration in blood as a hypoxia marker in ischemic stroke [26].

The main limitations of the present study include the fact that data from only one emergency department was utilized, as well as the decreased sample space. Besides, a descriptive statistical analysis was utilized, with no statistical power to infer possible risk factors and patient prognosis.

4. Conclusion

The present study showed that patients with SM make up a significant part of stroke diagnoses in emergency services. The diagnosis of SM is a challenge. In these cases, the preliminary diagnosis of stroke can lead the patient to be thrombolysed without indication, generating the risk of unnecessary complications for the patient and unnecessary health service expenses. Based on this, it is necessary to develop well-defined protocols that stratify the risk of SM and assess, based on this stratification, the risk-benefit of requesting imaging methods that can help distinguish between stroke and SM, such as MRI with DWI.

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