**Abstract**

**Background:** The prompt recognition of stroke symptoms is mandatory in the emergency department (ED) in line to assure the right therapy and clinical monitoring of patients with an acute neurological deficit. Intravenous thrombolysis is the first line therapy suggested in all the on course stroke guidelines, it may consent vessel recanalization and neurological deficit regression.

In ED, unfortunately, many conditions can mimic a focal neurological deficit in the acute stage. Stroke mimics can account for up to 25% of all acute stroke presentations. Mimes are more frequent in younger patients (often under 50 years of age), usually healthy (no particular medical history). The rate of false-positive diagnoses of ischemic stroke, "stroke mimic", ranges from 1.3–25% in patients not treated with thrombolysis. Among all mimics "functional neurological disorder” is increasing over world.

**Material and Method:** We describe the experience of our stroke unit in the recognition and management of acute neurological deficit due to functional neurological disorder. Moreover, we would like to remark the safety of thrombolysis in those patients with acute neurological deficit due to a mimic, in which a correct diagnosis is not always possible in the ED and in a well known short window therapy.

**Conclusion:** In the ED, it is quite difficult to discriminate real stroke from psychogenic stroke mimic but physicians have to decide in a short period which treatment start quickly. Thrombolysis is safe in stroke mimics. More data are required to draw up a right diagnostic protocol that may guide clinicians in the proper selection of patients that would benefit from thrombolysis.

**Keywords:** Neurological Disorders; Thrombolysis; Recanalization; Stroke mimic

**Introduction**

Stroke is a main cause of major long-term disability all over the world and is an enormous source of global disease burden. Since the landmark National Institute of Neurological Disorders and Stroke (NINDS) study in 1995, intravenous thrombolysis remains the only treatment approved by the U.S. [1]. As per the previous literature it was clear that earlier treatment related with prompt recanalization and improved mortality and clinical outcome [2–3]. Stroke is usually defined as a “sudden numbness or weakness of face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; or sudden trouble walking, dizziness, loss of balance or coordination”; on the other side Stroke Mimics (SM) are defined as a “nonvascular disease that presents with stroke-like symptoms, often indistinguishable from an actual stroke”.

In the emergency department (ED) a patient presenting with acute neurologic deficits, is quickly evaluated by the current physician and by the neurologist, after all, considering the short time window of 4.5 hours from symptom onset to administer tPA, a quick history and CT scan are collected. In that condition several other disorders that can mimic a stroke might be missed, and several mimic conditions like seizure, complicated migraine, or functional deficits, might be treated with IV tissue plasminogen activator (tPA).

The main reason to avoid tPA administration in mimics is that thrombolysis has no benefit and may carry an increased risk for hemorrhage. Anyway, data from literature have showed that stroke mimics treated with IVr-Pa have good clinical outcomes and low incidence of intracranial bleeding [4–8], suggesting that clinicians should not postpone thrombolysis because its potential benefit in confirmed ischemic stroke might be higher than the risk of complications in stroke mimics [9,10].

Stroke mimics comprise both non neurological condition like hypertension, diabetes mellitus, metabolic dysfunction, cardiac syncope due to arrhythmia, malignancy and atrial fibrillation; or neurological disorder as seizure (considered the leading cause of mimic), migraine (mostly aura with focal neurological symptoms like aphasia or hemi sensory loss), septic meningitis, heatstroke, spinal epidural mass, dementia [11–16].

Mimics are more frequent in younger patients. Vroomen PC, et al. found out that over 600 patients, under the age of 50 years, stroke mimics occurred in 21% of patients. Above the age of 50 years, stroke mimics were very rare (3%) [17,18].

Beside the risk of treating mimics instead of stroke patients there is a high possibility to miss real stroke. Using a prospective stroke registry, Richoz B, et al. found that often stroke symptoms were attributed to other neurologic diseases (81%); in particular, acute confusional state, epileptic seizures, and central nervous system (CNS) or systemic infections were incorrectly attributed chameleons; so that the 2.1% of stroke patients were missed [19]. Madsen TE, et al. reported in a large retrospective population based study of stroke patients that a total of 14% of patients were initially missed in the ED. The most common diagnostic label was altered mental status (described as confusion state or agitation and confabulation). Similar data were reported in another single-center study: physicians were often unable to elicit any focal symptoms among those with agitation and alteration of mental state [20–22].

In the last decade’s functional neurological disorders are increasing over time, accounting for 28–30% of all mimics; particularly conversion disorder are recognized over the 40% of psychogenic stroke [23–25].

We summarize our clinical experience in the management of stroke mimics and above all in the management of functional neurological disorder occurring in the ED of our department and then admitted to our Stroke Unit.

We believe that functional neurological disorder represent an emerging critical condition that needs prompt diagnosis and especially an accurate follow-up in order to avoid acute recurrences in the ED and misdiagnosis. In the same time our data report the safety and effectiveness of intravenous thrombolysis in SM.
Methods and Results

Every year among an approximate number of 500 patients admitted to our Stroke Unit (Cattinara Hospital in Trieste, IT) for a sudden onset of acute stroke, over 100 subjects are treated with intravenous thrombolysis, all these patients usually arrive to our emergency department as “ictus protocol”. In the last two years among almost a thousand of patients admitted for a sudden acute neurological deficit to the ED of Cattinara hospital, the majority were classified as stroke patients, according with literature, of those patients, the 20% were in the end discharged as SM. Between May 2015 and January 2017 almost 20% of patients were SM and among those nine patients were discharged with the diagnosis of functional neurological disorder.

Excluding all kind of brain hemorrhages (parenchymal hemorrhages and subarachnoid hematoma) as stroke mimics a total number of 41 patients were discharged with a different diagnosis than stroke.

In line with previous data, the majority of patients were epileptics (22 patients, 53.6%), the other mimics were represented by migraine, functional and metabolic disorders (19.5% 21.9% and 4.8% respectively) in one case a relapse of multiple sclerosis was seen (Figure 1). 10 of 41 subjects were treated with intravenous thrombolysis (24%), no one patients presented adverse event or bleeding.

In our sample, stroke mimics patients (general stroke mimics or functional neurological disorders patients) were usually younger and healthy with no significant medical history. Usually patients presented a lower NIHSS score at admission compared with those with acute stroke.

Nine patients were identified as functional stroke mimics, main age was 42.7 years old (minimum age 22 years old and maximum 63 years old), in our small sample we didn’t find sex difference and actually five patients were male and four were female (55.5% and 44.5% respectively) (Table 1).

Concerning symptoms presentation, two patients were admitted to the ED for a sudden onset of a language deficit (mostly described as aphasia) in the other cases patients presented with left or right hemiparesis and hemi sensory loss. In three cases also a partial deficit of the seventh cranial nerve was observed.

Median NIHSS score at admission was 4.5 (minimum NIHSS score was two and maximum was 10). No one patient presented impairment of conscience, only one patient was described as anxious at admission.

Medical history of psychiatric disorder was reported in 67% of subjects (mostly depression and anxious disorder, only in one case a bipolar disorder was detected), previous Stroke/TIA was described in over 44% of cases.

Regarding cerebrovascular risk factors, 44.4% of patients were affected by arterial hypertension, 44% of cases were suffering of diabetes mellitus and in 33.3% dyslipidemia was reported. Obesity was found in 44.4% of our sample, while heart disease (mostly previous heart attack) was reported in 11.1% of cases. Nobody was affected by atrial fibrillation. 67% of patients were current smokers, 11% of patients were alcohol abuser. In 22% of cases migraine disorder was described. No family history of epilepsy was reported, 1 patient presented a family history for cerebral vascular disorder.

At the time admission 44.4% of patients were taking antiplatelet drugs (mostly Clopidogrel 75 mg). No signs of acute metabolic or infectious diseases were reported in our sample.

CT scan that was normal in over 62% of the cases. In two patients previous vascular diffuse damage was seen (1%). Similarly, angiography CT of epicardic (TSA) and intracranial vessel was normal in all cases. In 4 subjects CT perfusion was performed not showing any abnormalities. Brain CT scan or MRI at 24–48 hours from admission didn’t show any focal vascular recent lesion.

Baseline neurological examination showed unusual details in most cases, for example the burden of the paresis was changeable during repetitive evaluation. Hoover’s sign was positive in 50% of cases (5 patients). Reflexes were normal throughout and plantar were down going bilaterally. Usually a real hemi sensory loss was undetectable. In only 22% of cases (2 of 9 patients) intravenous thrombolysis was administered, without any immediate and late complication.

During recovery all patients underwent EEG examination, no sign of epileptic disease was seen, and focal slow waves were observed in 22% of cases. Hematologic, biochemical and immunologic investigations were normal and electrocardiogram was unremarkable in all cases.

All patients were discharge at home with a NIHSS score of 0 and a Barthel score of 100. Median length of stay was 9 days (minimum of 1 and maximum of 23 days).

Discussion with a Focus on Functional Neurological Disorders

Stroke mimic are characterized by a stroke like clinical picture. The acute focal neurological deficits presentation may be indistinguishable from an ischemic stroke syndrome. Functional neurological disorder and conversion disorder are quite common, representing the 26.8% of cases in ED [4].

Among functional neurological symptoms non-epileptic attacks
and weakness have been largely reported; functional symptoms are often associated with distress and disability [26].

Functional neurological disorder recognizes often a pathological familiar background with history of psychiatric symptoms, physical disability, exposure to other disabled subjects and anxiety [27].

The prompt recognition of “organic disorders” versus “functional” is challenging.

The first challenge is to detect functional symptoms; recent studies have confirmed the importance of “positive” clinical bedside signs based on incoherence and discordance. Functional neuroimaging has allowed a better understanding of the pathophysiology, and highlighted abnormal cerebral activation patterns in conversion disorder in relation to motor, emotional, and limbic networks, different from feigners. This supports the theory evoked by Charcot of a “psychodynamic lesion,” which is also reflected by the new term introduced in the DSM-5: functional neurological disorder.

Nowadays, next to the classical neurological examination, physicians can count on several signs able to reveal the non-organic origin of the symptoms. The positive signs, first introduced by Freud in the 19th century, that worked in the shadow of his mentor, Jean M. Charcot, until 1893, are easily used by neurologist and have been showed to be reliable. In all maneuvers the main purpose is to deviate the patient’s attention during postural test or fine motor skills performance, eliciting complex movements non possible for a patient with real motor defect [28–31].

For motor weakness, among several signs, the collapsing weakness (the tendency for an arm or leg to ‘collapse’ when being tested. In patients with functional weakness typically find that the limb gets weaker the more they try) the Hoover’s sign (the affected leg may be weak when you try to push your feet down into the bed), and the dragging kind of walk (patients with functional leg weakness sometimes have a very characteristic way of walking which means that their affected leg “drags” along the ground. This is different to someone with a stroke or multiple sclerosis who swings their leg if they are able to stand up), are the most specific [32].

In case of sensory symptoms a feeling that a limb just doesn’t belong to them or ‘part of them’ is usually reported. Other symptoms include twitches, buzzing sensations, electric shock sensations. Often distribution pattern doesn’t fit with anatomical rules.

In functional gait disorder excessive slowness with a very slow walk with the feet having a tendency to stick to the ground, or the ‘Walking on ice’ pattern has been reported [33–36].

The principle that the absence of organic signs in paresis (a negative sign) does not exclude the presence of an organic disease confer to positive signs a special value.

All of those signs are easily tested even in ED especially in patients with functional weakness, affecting both superior and inferior arm. In literature they have been widely described, showing high sensitivity and specificity [37–40].

Beside the neurological examination, the anamnestic details are precious tools for neurologist/physicians. Has been reported that a previous history of Stroke/TIA increase the possibility of a functional disorder or a SM, similarly to general mimics, patients with functional disorder are younger, mainly women, they present with a less severe deficit, and with a positive familiar history for psychiatric disorders [38]. Moreover, in the majority of cases symptoms are precipitated by a physical event; they can rapidly progress or go to remissions and sudden recurrences.

Tobin WO, et al. proposed a protocol model to identified SM and included presence of initial lateralizing signs (strongest predictor of a stroke), presence of history of acute cerebrovascular event and diastolic blood pressure [41].

Functional neurological disorder may involve different system, usually the motor and sensory system are more involved (functional weakness, gait disorders, hemiparesis, hemi sensory loss, pain, tremors), also dizziness, vertigo, fatigue have been reported, finally psychiatric symptoms may be seen as dissociation, pain, low mood.

For a correct diagnosis the presence of positive signs and the variability of the examination are the key feature. A correct diagnosis is always a positive diagnosis; physicians should be brave enough to write down “functional” on their report, and to program a follow-up for the patients, giving them factsheets and website links for their education, keeping in mind that relapses are common.

Conclusion

Stroke mimics and functional neurological symptoms are an emerging subgroup admitted to ED. Diagnosis and treatment of all mimics need a multidisciplinary approach. Although functional neurological disorders are listed as a rare disease, researchers are finding that functional symptoms are often seen in neurological services making it a common disorder. Approximately 1/3 of outpatient neurology clinic attendances are patients reporting functional symptoms. While the exact prevalence is unknown, functional neurological disorder is the second most common reason for a neurological outpatient visit after headache/migraine. The mechanisms which cause functional neurological disorder continue to be poorly understood despite its prevalence within neurological clinics. The incidence of functional paralysis is probably similar to that of multiple sclerosis (around 5/100 000). Non-epileptic attacks make up around 10–20% of the patients referred to specialist epilepsy clinics with intractable seizures and up to 50% of patients admitted to hospital in apparent status epilepticus. Misdagnosis is seen in the 5% of cases.

A critical step in reaching a diagnosis of functional neurological disorder is careful bedside neurological examination, aimed at excluding organic signs and identifying ‘positive’ signs suggestive of a functional disorder.

In order to avoid false negative cases is mandatory to remember that numerous forms of stroke may present atypically, like movement disorders, confusional states, and lacunar strokes. Atypical presentations include: Acute hemiballismus, that can result from an infarct of the subthalamic nucleus; Dyskinesia, hypokinetic or hyperkinetic, following a lesions at motor cortical or subcortical regions; Confusion, agitation, and delirium that may present if a lesion in the limbic cortex or orbitofrontal regions occurs; finally Sensory deficits with paresthesias or loss of sensation that can occur with parietal and thalamic insults.

In the ED a quick history, neurologic examination and a CT scan to rule out hemorrhage, comprise the main components of the evaluation. In those selected patients advanced neuroimaging is mandatory (like perfusion CT in epileptic disorder mimicking a stroke) [42–44].

We believe that an accurate collection of patient’s personal data, an accurate neurological examination, considering the value of positive signs and having in mind the different atypically presentation of different form of stroke, can help clinicians also in a short time valuation; anyway, in the clinical practice in front of a possible functional neurological disorder, when a stroke might be missed, Thrombolysis should be considered, is not harmful and may indeed have a better functional outcome.
In our small sample of patients with functional disorder the diagnosis was often challenging, where positive signs were negative and in those patients arrived to the ED late, considering the short time window for acute treatment, an acute stroke couldn’t be rule out, so that, Thrombolysis was started and treatment was safe. More data are required to draft an appropriate functional neurological disorder management protocol.

References


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