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Psychogenic Stroke Mimics and Thrombolysis: Ready to Take the Risk?

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Abstract

Stroke is one of the leading cause of disability and death all over the world with a time dependent course and prognosis; during ages different new advances in acute treatment have changed the emergency approach of this cerebrovascular diseases. More rapidly the symptoms are recognized and more prompt thrombolysis treatment may consent vessel recanalization and neurological deficit regression. Early diagnosis is mandatory; unfortunately conditions that can mimic a focal neurological deficit are common in the acute stage. Stroke mimics can account for up to 5% of all acute stroke presentations. Mimics are more frequent in those under 50 years of age, without any particular medical history. The rate of false-positive diagnoses of ischemic stroke labeled "stroke mimic" ranges from 1.3% to 25% in patients not treated with thrombolysis, among all mimics "psychogenic stroke" are increasing in the last decades. In the emergency department is quite difficult to discriminate real stroke from psychogenic stroke mimic but physicians have to decide in a short period which treatment start quickly.

Our aim is to review the neurological signs in the rapid short examination in the emergency in order to define stroke mimic from real stroke and the most appropriate approach.

Keywords: Thrombolysis, Neurological disorder, Dementia, Vascular occlusion

Introduction

Stroke and thrombolysis

Stroke is the leading cause of disability, dementia and death among adults all over the world. Despite advances in preventive strategies and acute therapy for stroke, the burden of this pathology is still very high. Ischemic stroke results from vascular occlusion that reduces cerebral blood flow to the area of brain perfused by the occluded artery. In either thrombotic or embolic stroke, such occlusion is caused by obstruction of the artery by a thrombus. Thrombolysis, also known as thrombolytic therapy, is a treatment to dissolve dangerous clots in blood vessels, improve blood flow, and prevent damage to tissues and organs. Thrombolysis may involve the injection of clot-busting drugs through an intravenous line or through a long catheter that delivers drugs directly to the site of the blockage. It also may involve the use of a long catheter with a mechanical device attached to the tip that either removes the clot or physically breaks it up. Thrombolysis is often used as an emergency treatment to dissolve blood clots that form in arteries feeding the heart and brain which is the main cause of heart attacks and ischemic strokes and in the arteries of the lungs. Since the landmark National Institute of Neurological Disorders and Stroke (NINDS) study in 1995, intravenous tissue plasminogen activator (IVtPA) remains the only treatment approved by the USA. In 1996, the Food and Drug Administration (FDA) approved the use of intravenous rt-PA for the treatment of acute ischemic stroke after NINDS rt-PA Stroke Study was completed [1]. After this several other clinical trials were needed to find the safe and functional dose of intravenous rt-PA that could be administrated in a narrow window of time for stroke management. Indeed intravenous rt-PA given within 4.5 h after symptom onset in acute ischemia significantly increases the proportion of patients with a score of 0 or 1 at the modified Rankin scale (mRS) after 3 months.

However, one of the most important factors of outcome is the delay between stroke onset and treatment, because the benefit of rt-PA decreases over time. Earlier treatment and prompt recanalization is clearly associated with improved mortality and clinical outcome due to prevention of neuronal ischemia [2,3]. Different exclusion's criteria for thrombolysis are well known, among these the occurrence of different clinical conditions that can only mimic a stroke (stroke mimics).

Although there is worldwide consensus among disease experts and independent regulators regarding the utility of IV tissue plasminogen activator (tPA) for acute ischemic stroke, there is concern about administering IV rt-PA to patients who present with clinical features suggestive of stroke but have an alternative diagnosis. The main reason to avoid tPA administration in mimics is that thrombolysis has no benefit and may carry an increased risk for hemorrhage. Anyway across several clinical trials and different studies, stroke mimics treated with IVrt-PA have significantly good clinical outcomes and, by the way, low incidence of intracranial bleeding [4-9]. Actually, data showed that patients with stroke mimics have a good safety profile when treated with rt-PA; so, physicians should not postpone thrombolysis because its potential benefit in confirmed ischaemic stroke might be higher than the risk of complications in stroke mimics [10,11]. It is also well known that recanalization rates with IV tPA are low when a large-artery occlusion is present with rates ranging from 4% to 68% depending on the study and the location of the occlusion, regarding this data alternative strategies have been studied and are now available, including intra-arterial (IA) thrombolysis (chemical/mechanical) and combined IV and IA thrombolysis.

By the way, the moto "time is brain" often occurs in the emergency department where physicians are responsible to quickly understand to whom, real stroke or stroke mimics subjects, best acute treatment is deserved, considering what a "non-treatment" could then implicate for patients.

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Stroke mimic

Stroke mimic is the term used to describe nonvascular disease with a stroke like clinical picture. The presentation resembles or may even be indistinguishable from an ischemic stroke syndrome. Patients with mimics usually present acute focal neurological deficits, later found to have non-vascular etiologies like migraine, epilepsy, hemorrhage, different medical illnesses like hypotension, intoxication, hypoglycemia, mass lesion [12]. Actually hypertension, diabetes mellitus, metabolic dysfunction (hypo-hyperglycemia for example) are most frequently identified in the stroke-mimicking patients, whereas malignancy and atrial fibrillation are less common, the association of migraine with focal neurological symptoms has been well described mimicking a stroke, uncommon is the association of encephalopathy and syncope with stroke mimics. Other mimics condition may identified in septic meningitis, heatstroke, cardiac syncope due to arrhythmia, spinal epidural mass, dementia or symptoms related to previous stoke [13-16].

Seizure has been recognized as a leading cause of mimic (the focal paresis (Todd's paresis) can be quite short or persisting several hours mimicking a TIA or Stroke). Diagnosis of mimics may depends on several factors including symptoms presentation, epidemiological factors, onset time of focal neurological deficit, presence of anterior vs. posterior circulation vascular distribution, and imaging exams [17]. Rates of mimics are extremely different between studies ranging from 1-6% to 14-20%, a clear uniform definition of mimic is also lacking. Clinical evaluation and radiological finding may help in the definition of mimics.

Elsewhere was reported that over 800 consecutive patients admitted to a stroke unit of a Canadian hospital, an initial diagnosis of stroke was incorrect in 13% of patients (most common misdiagnosis resulted seizures) [18].

Similarly a retrospective analysis of 671 patients with stroke showed that of these subjects, 87.3% were correctly diagnosed with stroke and treated as cerebrovascular event, while in 12.7% of patients different diagnosis was made. In almost the 24% of "non-stroke" patients impairment of consciousness was the first presentation of diseases, almost 17% exhibited weakness, 13% of patients experimented seizures, same proportion of people showed syncope, in the 10% of cases main symptoms were dizziness/vertigo [19].

Psychogenic stroke mimic and clinical examination helpful signs

Psychogenic stroke mimic between all mimics, are a small rate that is increasing over time, data from literature report a variable percentage that reach the 28-30% of all mimics. Among these conversion disorder represent as one of the most common situations faced by neurologists in their everyday practice and can account for up to 40% of psychogenic stroke. Conversion disorder is listed in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) under a somatoformic disorder group. It may present in many different ways and at all ages (it's rare before the age of 10), neurological disturbance is common, higher prevalence in women. Often it may occur after a traumatic event. The diagnosis of conversion disorder is often complex and long-lasting [12,20-22].

In a research of Tsivgoulis et al. regarding the safety of thrombolysis in stroke mimics, misdiagnosis of ischemic stroke was documented in 56 of the 539 cases (10.4%), of these conversion disorder represented the 26.8%. Similar results were reported by Zinkstok et al [4,23].

Since the first clinical description, the term 'functional neurological symptoms' was referred to symptoms that were not explained by disease. They have been described also as psychogenic, non-organic, somatoform, dissociative or conversion symptoms. The most common functional neurological symptoms are non-epileptic attacks and weakness, especially in emergency situations, where they may be mistaken for epilepsy or stroke. Functional symptoms often persist, are associated with distress and disability [24]. Moreover, psychogenic stroke patients have usually particular familiar background, including history of psychiatric symptoms and care, relatives affected by similar pathology. Most of them are professional worker in healthy system [25].

Since when neurology first emerged as a clinical specialty, how to distinguish between "organic disorders" and functional ("hysteric") ones became a crucial question. Conversion disorder ("hysteria") became a neurological issue since the 19th century, at the beginning with Freud and Janet they were more considered as psychiatric condition but soon a neurobiology component of the disease has been researched [26]. Different clinical signs enable to reveal psychogenic disorder were proposed [27,28]. These specific signs in the neurological examination may help to detect the psychogenic symptoms: deviation of attention during postural test or fine motor skills performance, eliciting complex movements non possible for a patient with real motor defect, asymmetrical strength test have been all used for this scope (Hoover sign, abductor sign for the legs and for the fingers, the drift without pronation sign) [29,30].

Among others first Joseph Babinski spent much of his career to devising signs useful for distinguishing the two conditions (organic and functional disorder). It is well known, that the absence of organic signs in paresis (a negative sign) does not exclude the presence of an organic disease (e.g., intermediate phenotypes and, even different methodological issues). Consequently positive signs of functional weakness acquire a special value. Since decades neurologists tried to build up knowledge regarding a specific semiotics for positive signs of functional weakness to bring to reliable diagnoses [31].

In the end of the 19th century was described useful sign to differentiate organic paralysis from hysterical paralysis, this is the toe extension sign that can be seen only in cases of organic paralysis [32].

The Hoover sign, first described in 1908, is still the commonly described positive sign for detecting functional paresis at the lower limb (best carried out with the patient seated, weakness of hip extension returns to normal with contralateral hip flexion against resistance), it can help to distinguish organic from non-organic paresis of the leg. Hoover's neurological sign indicates functional weakness of leg extension by taking advantage of the basic principle of contralateral synergic movement (complementary opposition), used repeatedly for developing positive signs of functional weakness. What made Hover to come up with his sign could be explained with the "Ersatzphenomän", or "substitution phenomenon" of Bychowski, closely to the earlier "Ersatzbewegungen" ("substitution movements") formulated by Babinski who described the trunk–thigh test, also known as "the rising sign". Both concepts are related to the clinical observation of synkinetic oppositional movements during the execution of specific maneuvers in hemiplegic patients [33-35].

Similarly the dragging gait sign is frequently used (patients with acute functional weakness may drag their leg behind them, with the hip externally or internally rotated while subjects with organic hemiparesis can't). Common but less reliable signs are global pattern of weakness (left hemiparesis due to an upper motor neuron lesion bring weakness

with pyramidal in distribution, so with extensors weaker than flexors in the arm and flexors weaker than extensors in the leg; global weakness suggests functional weakness) and collapsing weakness (a limb seems to have normal power but collapses at a slight touch; pain or misunderstanding can cause false positives) [36,37].

During ages other different modified procedures have been proposed, for example the "Abductor sign" has been tested; in this case the patient was asked initially to press both legs, at the beginning both legs are abducted against resistance, and – regardless of the cause of weakness – the weak leg will be always adducted by the force imposed by the examiner. After this the patient is asked to concentrate on each leg separately, keeping the other leg in an adducted position along the midline. Weakness of abduction in the affected leg returns to normal during contralateral abduction against resistance in functional presentations [38].

Similarly positive signs for detecting functional upper limb paresis have been promoted like the abduction finger sign or drift without pronation sign. Actually, Tinazzi et al. (2011) described the abduction finger sign for distinguishing functional from organic paralysis of the upper limb. The test consisted of abduction finger movements of one hand against resistance with a maximal sustained contraction to detect synkinetic abduction finger movements of the contralateral hand. In their cohort of patients this test showed 100% sensitivity and specificity [39]. Similarly, the hand pronation phenomenon was at length illustrated, first from Strümpell (1853-1925) and then from Babinski in 1901, the sign is used to identify a small paresis [40]. Regarding the diagnosis also other anamnestic facts may help, it's well known that risk factors include previous physical disability, exposure to other disabled subjects and extreme psychological anxiety [41].

All these tests are typical for motor disorders and can be detectable in a clinical setting with a long calm neurological examination. We do not define any rapid examination to detect psychogenic symptoms in emergency room and related to the important decision to perform the thrombolysis or not. Among other psychogenic disorders, "psychogenic seizures" are common and may support a diagnosis of neurological deficit [42].

Psychogenic non epileptic seizures (PNES) are, as altered movement, sensation or experience, similar to epilepsy, but caused by a psychological process. Psychogenic non epileptic seizures are a common cause of refractory seizures. Video-electroencephalographic (EEG) monitoring has allowed PNES to be effectively distinguished from epileptic seizures [43].

Anyway, still today, the best treatment plan for PNES patients in not found. As in other conversion disorder, diagnosis has to be clearly communicated to the patient. By the way, even is the correct diagnosis is made and communicated the major of patients continue to have seizures, serious disability and bad self-reported quality of life. Vossler et al. showed that Ictal stuttering was present in 8.5% of 117 consecutive patients with PNES. Even in this case specific familiar condition is recognizable. Compared with patients affected by epilepsy, subjects with PNES and ictal stuttering have been showed to present a shorter duration of seizure disorder and a more prominent conversion profile [44].

Identification of Mimics in Practice

Tobin et al. in 2009 tried to describe a validated model for the acute identification of stroke mimics suggesting a need for early Neurological opinion; in their experience 22% of acute stroke syndrome presentations were non-stroke in generally presence of lateralizing signs strongly correlate with a diagnosis of stroke and hypotension (diastolic values of less the 55 mmHg). Moreover they found that a previous history of Stroke or TIA increase the chance of a stroke mimic (probably occurring in the setting of a metabolic derangement, infection, or hypnotic/sedating medications which would cause global cerebral dysfunction in a patient with an abnormal brain). Like it has been described in other papers even in this case the commonest causes of stroke mimic were seizure, encephalopathy, syncope and migraine [45].

The diagnosis of stroke mimic can be challenging. The Decisional protocol model suggested by Tobin et al. included the presence of initial lateralizing signs as the strongest predictor of a stroke (LAT, 0=No, 1=Yes), with a positive predictive value of 90%, and negative predictive value of 43%, presence of history of acute cerebrovascular event (CVE), i.e., stroke or TIA (0=No, 1=Yes), and diastolic blood pressure (DBP).

In 2010 an evaluation of mimics etiology and safety of thrombolysis in mimics was made by Chernyshev et al. In this work 512 patients treated with IV tissue plasminogen activator (tPA) within 3 h of symptom onset were identified. Of this group 21% of patients were found not to have an infarct on follow-up imaging and were diagnosed as mimics (most common mimics were seizure 38%, complicated migraine 37%, and conversion disorder 21%). Anyway, as already in other manuscripts, thrombolysis was seen to be safe in mimics, and indeed almost all mimics patients were functionally independent on discharge (mRS0–1) [46,47].

Different authors have tried to find specific red-flags that may distinguish, even in the emergency department, mimics from stroke. Actually, specific characteristics for distinguish mimics from stroke can be identified; data from a prospective paper published in 2013 showed that of 8,187 patients 30% had a stroke mimic, this patients with a mimic had usually typical characteristics. Mimics are usually quite younger, most of them are women, patients usually haven't any risk factors for stroke, and familiar psychiatric disorders could be identified. Moreover was found mimics present with a less severe deficit at baseline, and have a shorter onset-to-needle time [11].

The proportion of patients with a stroke mimic was marginally higher among African Americans than Caucasians. Factors associated with the greatest odds of having a stroke mimic in the logistic regression were lack of a history of hypertension atrial fibrillation, or hyperlipidemia [48,49].

It has also been demonstrated that quite often also the intervention of non-neurologist may create a bias in the correct identification of stroke vs. mimics. This observation makes the scenario of the optimal patient framing in the emergency department even more difficult [50,51].

But most important, some studies showed that the rate of false-positive diagnoses of ischemic stroke labeled "stroke mimic" ranges from 1.3% to 25% in patients not treated with thrombolysis. As we already have marked, in the setting of acute stroke, the decision to administer IV-rtPA is typically made after the physician obtains a brief pertinent history, performs a neurologic examination, and receives the results of urgent laboratory studies and cerebral TC scan, because "time is brain," the evaluation must be done quickly and physician has to make rapid treatment decision.

Elsewhere the frequency of false-positive diagnosis of ischemic stroke has been estimated at approximately 1–14% [17], again different

patient characteristics may help in finding the correct diagnosis. Vroomen 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%) [52,53].

Implementing Standard Neurological Examination a Short Case Report Presentation

In all day clinical practice integrates neurological examination with few of those reported signs may help in recognition of mimics even in an emergency contest. A 55-year-old Caucasian female, normally fit and well, presented to the emergency department because of a sudden onset of head discomfort (sensation of "full head") with dizziness, right hemiparesis and right hemi sensory loss.

In the emergency department brain computed tomography (CT) and CT angiography (CTA) were performed. No anomalies of parenchymal brain or vessels were detectable. CT perfusion didn't show any abnormalities. Hematologic, biochemical and immunologic investigations were normal and electrocardiogram was unremarkable. After this, patient was admitted to the stroke unit of our department. Her medical history included sporadic headache. She had no cardiovascular risk factors.

On neurological examination, level of consciousness, cognition speech and sensibility were normal. Patient was extremely worried, during examination twice she cried. However, some details at neurological examination were unusual, actually right paresis was detectable, with normal tone and the burden of the paresis was changeable during repetitive evaluation. Hoover's sign was doubt. Reflexes were normal throughout and plantar were down going bilaterally.

There was a subjective decrease in sensation throughout the right side of her body but real hemi sensory loss was undetectable. Cranial nerve examination was normal.

Anyway, even if physicians showed some doubts, arriving within the time window for treatment, intravenous thrombolysis was administered, without any immediate complication. Aspirin was also started, at 300 mg daily. Subsequent MRI brain and MR angiography (MRA) scans were performed and no lesions were detected.

Further investigation revealed depression disorder, other information included a previous divorce and exposure to psychiatric problems in her family. Diagnosis of psychogenic stroke mimic was made, thrombolysis didn't bring anyway any complications and patient was discharged at home.

Conclusion

Functional psychogenic stroke mimics are an important subgroup admitted to acute stroke services and have a distinct demographic and clinical profile. Their outcomes are poorly monitored. Moreover there seem to be little data on the optimal treatment of stroke mimic secondary to conversion disorder. Most approaches include a multidisciplinary approach.

As we already marked in the clinical practice is also known that when patients present to the emergency department with acute neurologic deficits, time is important to make a rapid evaluation if IV tPA is being considered. The short time window from symptom onset to administer tPA may not lead physicians to make a correct diagnosis. A quick history and neurologic examination, with the NIH Stroke Scale (NIHSS) and a CT scan to rule out hemorrhage, comprise the main components of the evaluation. The clinical presentation at onset might be helpful to decide which patients should undergo immediate advanced neuroimaging (MRI- CT Perfusion) to rule out stroke mimics and facilitate treatment decisions in order to reduce the risk of unnecessary therapy, in clinical practice and in emergency condition advanced neuroimaging is difficult to perform. The use of perfusion CT in epileptic disorder mimicking a stroke has been investigated by Masterson et al. radiological examination seems to be accurately in detecting hyperperfusion in status epilepticus presenting as stroke (usually supported by a hypoperfusion state). In such cases, perfusion CT imaging may avoid the administration of thrombolytic therapy to patients experiencing seizures and not stroke. Similar conclusion has been reported elsewhere giving to the analysis of perfusion maps in epilepticus state a sensitivity of 78% [54-58]. In conclusion, stroke mimics comprise a large variety of different, predominantly neurological and psychiatric disorders and come along with a different clinical presentation compared to patients with proven acute ischemic stroke. However until now no neurological signs in acute phase of neurological defect are validated to exclude functional disorders in addition to a normal neuroimaging exam.

Therefore the potential benefits of intravenous thrombolysis outweigh the potential harm of delayed thrombolysis. Thrombolytics restore cerebral blood flow in some patients with acute ischemic stroke and may lead to improvement or resolution of neurologic deficits. Thrombolytic therapy is of proven and substantial benefit for select patients with acute cerebral ischemia. The benefits are substantial when given within 3 h of stroke onset. Its use may, however, be limited by delay in hospital admission. The treatment carries an increased risk of intracerebral haemorrhage and treatment with tPA in clinical routine may result in greater risk and lesser benefit than under the optimal conditions of controlled trials. To minimise the risks of thrombolytic therapy, patients should be carefully selected and treated following a strict protocol. The evidence base for thrombolysis in stroke includes 21 completed randomized controlled clinical trials enrolling 7152 patients, using various agents, doses, time windows, and intravenous or intra-arterial modes of administration. Although haemorrhages are the obvious complications in thrombolysing stroke mimics, data from literature showed that intravenous thrombolysis in stroke mimic patients is associated with a low risk of rtPA-related bleeding complications; moreover thrombolysis is not harmful in stroke mimics and may indeed have a better functional outcome. On the other side studies show that the rate of false-positive diagnoses of ischemic stroke labeled "stroke mimic" is quite high in patients not treated with thrombolysis, so would you really take the risk?

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