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How can we distinguish postictal Todd's Paralysis from acute ischemic stroke in the prehospital and early hospital setting?

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SUMMARY

Introduction. Acute Ischemic Stroke (AIS) is a medical emergency with focal neurological deficits. Todd's paralysis (TP) is defined as a transient loss of motor ability and weakness that lasts hours to days and typically occurs after a focal seizure. Given the high prevalence of stroke and the rising availability of reperfusion therapies, timely detection of eligible patients is critical. Pre- and early-hospital differential diagnosis of various conditions with comparable clinical presentations is still difficult.

Aim. This review discusses Todd's post-epileptic paralysis, one of the most common stroke mimics (SM), in pre- and early-hospital settings.

Discussion and Conclusions. The review covers the most critical findings on the TP and its emergency care as a common stroke mimic. Because TP is an excluding diagnosis, the most severe and curable illnesses must be recognised. Since thrombolysis is safe in SM, delaying or withholding medication may be improper when the advantages of treating a stroke mimic outweigh the dangers of treating a stroke mimic.

Key words: Todd's paralysis • epilepsy • acute ischemic stroke • stroke mimics

INTRODUCTION

A stroke is a medical emergency and presents with focal neurological deficits. Immediate evaluation, confirmation of diagnosis, and treatment to re-establish blood flow, improve symptoms and prevent brain damage. Given the high prevalence of stroke and the increasing availability of modern advanced therapy, correct diagnosis within the required time frame for these procedures is crucial. Differential diagnosis of other conditions exhibiting a similar clinical presentation is still challenging in pre and early-hospital settings.

A false positive diagnosis of stroke is referred to as 'stroke mimics' (SM), and false negatives are referred to as 'stroke chameleons' due to the clinical appearance resembling another condition (Huff, 2002). Stroke mimics account for up to 25% of admissions for probable stroke (Moulin and Leys, 2019). The seven most frequently encountered differential diagnoses for suspected stroke are seizures, syncope, sepsis, migraine, space-occupying lesions, functional disorders, and metabolic diseases (Gibson and Whiteley, 2013).

The rate of stroke negatives ranges from 2 to 26%, and 30–43% of false-positive cases (Liberman and Prabhakaran, 2017).

Failure to recognise stroke may restrict patients from receiving time-sensitive treatments, such as intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) for acute ischemic stroke. On the other hand, overdiagnosis of stroke diagnoses individuals with the incorrect disease, subjecting them to unnecessary testing and treatment and accumulating expenditures for the healthcare system. On the other hand, overdiagnosing stroke leads to unnecessary treatment, delayed correct diagnoses, and increased expenditures for the healthcare system.

Todd's paralysis (TP) was first described in the nineteenth century as a post-seizure hemiplegia (Todd, 1854). It is defined as a transient loss of motor ability and weakness that lasts hours to days. Todd's paralysis typically affects one or more limbs and typically occurs after a focal seizure (Werhahn, 2010). Postictal paralysis belongs to a broader group of symptoms that may appear after paroxysmal seizures, which can be described as a "variant" of TP. Postictal aphasia, hemianopsia, combined eye gaze palsy, ideomotor apraxia, retrograde non-memory or mid-body neglect, among others, have been described (Helmchen et al., 1994; Salmon, 1968).

AIM

This review discusses Todd's post-epileptic paralysis, one of the most common acute ischemic stroke (AIS) mimics, in pre-and early-hospital settings.

MATERIALS AND METHODS

This review contains current publications identified through the use of the PubMed database. In July 2021, the following terms were used in the search: "Todd's paralysis", "Todd's paresis", "post-epileptic paralysis", "post-epileptic paresis", and "postictal state".

It included English-language papers. Additionally, the various references indicated in the original publications were included where appropriate.

DISCUSSION

Todd's paralysis

Frequency of occurrence

Epileptic seizures and TP are among the most common differential diagnoses of AIS and represent the largest group of patients who have not had a stroke and are treated with IVT (Hand et al., 2006; Winkler et al., 2009).

A recent meta-analysis sought to estimate emergency department (ED) diagnostic accuracy for identifying acute cerebrovascular events, seizures (16.7%), vertigo/dizziness (9.4%), and migraine (8.1%) were the most frequent final diagnoses among identified cases misdiagnosed as stroke (Tarnutzer et al., 2017). The rate of seizure patients receiving IVT was 14.2% among the group diagnosed with stroke mimics (SM) in the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register 2003–2017 (SITS-ISTR) (Keselman et al., 2019).

When focal neurological deficit begins with an epileptic seizure, the risk of a diagnosis other than AIS increases from 2.61% to 39% (Polymeris et al., 2019).

Todd's paresis occurred in roughly 6% of 229 patients with focal to bilateral tonic-clonic seizures. The motor deficiency could last several hours but was not expected to last more than 48 hours (Robert S. Fisher and Engel, 2010; Rolak et al., 1992). In a study of 328 patients with partial epilepsy who had video-EEG screening before surgery, 44 (13.4 per cent) experienced TP. The median weakness duration was approximately three minutes but ranged up to twenty-two minutes. However, video monitoring in 40 of the 72 seizures in this study was discontinued before the complete resolution of TP (Gallmetzer et al., 2004).

Pathogenesis of todd's paralysis

Although more than 170 years have passed since the first description of the phenomenon, the pathogenesis and possible consequences of TP are still unclear. In the original description, Todd postulated that TP is associated with a sharp increase in metabolic activity and peripheral neuronal insufficiency (Todds, 1855). In contrast, Gowers believed TP was caused by inhibition of the motor cortex. These two theories have dominated the discussion since (Widdess-Walsh and Devinsky, 2010).

Recent animal studies in which epileptic seizures were induced with TP in mice have shown that after an epileptic seizure, blood vessels become narrower, which reduces blood supply to the areas of the brain involved in the seizure and dramatically reduces oxygen levels in those same areas. Using cyclooxygenase-2 or L-type calcium channel blockers prevented oxygen shortage and the behavioural impairments that follow seizures. In particular, oxygen pressure and blood flow were reduced for up to 1 hour following a seizure (Farrell et al., 2016). This study is the first to establish a link between a seizure, hypoperfusion, and postictal weakness in an animal model. One possible mechanism may be that arachidonic acid is metabolised by cyclooxygenase (COX-2), leading to the synthesis of prostaglandins (PG) such as PGE2 (Lacroix et al., 2015).

Clinical studies that have utilised Computer Tomography (CT) perfusion are inconsistent and have reported local hyper-, hypo-, and normoperfusion (Austein et al., 2018; Van Cauwenberge et al., 2018; Gelfand et al., 2010; González-Cuevas et al., 2019; Li et al., 2019; Payabvash et al., 2015; Serven et al., 2021). This may be

due to the changing metabolic demand observed during the different phases of an epileptic seizure, with increased perfusion during seizure activity and normal or decreased perfusion during the post-seizure phase. A possible explanation for TP is that perfusion cannot meet the metabolic demands of a highly activated focus during an epileptic seizure.

Another possibility is that the activation of endogenous seizure-inhibiting systems causes the postictal syndrome. The synaptic release of mediators that reduce neuronal epileptic ictal discharges and impede regular activity would be critical in this active inhibition concept (Tortella and Long, 1985).

On the contrary, the mechanism of AIS is well understood as ensuing from impaired oxygenation of cerebral tissue, which is dependent on cerebral blood flow.

Clinical presentation of Todd's paralysis

Epileptic seizures are a common cause of admission to neurology departments. A previous history of involuntary facial and limb movements and loss of consciousness may suggest TP. Therefore, an essential element in the diagnosis of TP is the patient's past medical history. Often because of epilepsy or TP, the patient has already been in contact with the healthcare system, and 62% of patients with TP receive antiepileptic drugs on admission to the hospital (Sato et al., 2017).

TP can occur in patients of all age groups, following different types of seizures. However, TP most commonly occurs after focal onset epileptic seizures (Doudoux et al., 2020).

In a comparative analysis performed by Sato et al., patients with TP were older, more likely to use antiepileptic medicines, and had a higher incidence of trauma following a seizure when compared to patients without TP following seizures. Additionally, a higher rate of convulsive status epilepticus and tracheal intubation was noted in the emergency department. Furthermore, a longer convulsions duration, decreased level of awareness, increased systolic blood pressure and heart rate, and a higher admission rate (Sato et al., 2017).

In the analysis of 27 individuals, TP invariably occurred contralateral to the epileptogenic hemisphere (93 per cent) (Kellinghaus and Kotagal, 2004). Therefore, hemiparesis of the same side is usually observed in repeated cases of TP. In the remaining two cases, the seizure onset could not be lateralised.

Although initially observed as a hemiparesis, bilateral Todd's paralysis was also described (Bergen et al., 1992).

The tone of the muscles may be flaccid, regular, or spastic, and the reflexes may be diminished, regular, or augmented (Rolak et al., 1992). Extensor plantar responses (EPRs) were detected following 27% of epileptic seizures in 42% of individuals with epilepsy, and if unilateral – were present contralateral to the side of the seizure onset (Walczak and Rubinsky, 1994).

Although the most common symptom is a muscle weakness opposite to the focus, depending on the anatomic epileptic focus, clinical symptoms of TP might include aphasia, gaze palsy, neglect, numbness, and visual field impairments (Gallmetzer et al., 2004; Rolak et al., 1992; Werhahn, 2010).

Differentiating TP from AIS

History and clinical examination

The correct diagnosis depends highly on the patient's history, which should be taken from the patient and eyewitness. The anamnesis should begin with the precise time of symptom start, the patient's experience, memory, and awareness of the event. In many situations, the patient's awareness is diminished during the occurrence, making witness reports critical. It is crucial to analyse and document independent patient and witness testimonies. Additionally, the patient may have previously had myoclonic jerks, staring spells, or stereotypic events (such as auras), all of which would fit the criteria for an epilepsy diagnosis. A brief evaluation of the patient's past medical history, emphasising vascular risk factors, provides insight into the patient's likelihood of a stroke. It is critical to ascertain whether the patient, relative, or any other reliable informant is on insulin or oral hypoglycemic medications, has a history of epilepsy, drug overdose or addiction, or has had recent trauma. Additionally, contraindications to thrombolytic treatment should be considered.

Correct diagnosis of ischemic stroke is vital because acute treatment with thrombolysis and endovascular therapy (EVT) can significantly improve prognosis (Powers et al., 2019).

Because TP is a benign and reversible condition, a wait-and-see attitude can be adopted in typical cases. However, the information obtained from the history is often inadequate, or the presentation is atypical, so the following considerations for differential diagnosis should be considered – results from laboratory tests, neuroimaging, and EEG. In practice, distinguishing TP from AIS can be difficult.

Stroke mimic prediction scales

Scales for predicting stroke mimics based simply on history and examination findings may aid in identifying stroke mimics in the emergency department. In addition, the scales may assist in detecting stroke mimics during intravenous thrombolysis decision-making in the presence of an emergency physician, a neurologist, and computed tomography.

Among all the stroke diagnostic tools, the Recognition of Stroke in the Emergency Room (ROSIER) scale was introduced in 2005 to help differentiate between stroke and SM in the emergency department. In the ROSIER scale, a 7-item recognition instrument (ranging from – 2 to + 5), arm weakness, leg weakness, speech disturbance, facial weakness, and visual field defect (+1 for each item) predict stroke. In contrast, seizures or confusion/loss of consciousness (-1 for each item) indicate a nonstroke diagnosis. A score of + 1 or above was considered positive for stroke or transient ischemic attack. However, the application of the ROSIER scale in further studies reported lower specificity (0.66 (95% CI: 0.52–0.77)) (Han et al., 2020) as compared with the initial research (0.83 (95% CI: 77–89)) (Nor et al., 2005).

The FABS score was developed to aid in the differentiation of SM from AIS cases in the emergency scenario. FABS included six variables (+1 point for each - a stroke mimic is more likely the higher the score): absence of Facial droop, adverse history of atrial fibrillation, age, systolic blood pressure at presentation, history of seizures, and isolated sensory deficit without limb weakness (Goyal et al., 2016).

Khan et al. devised a 9-point scoring system (a stroke mimic is more likely the higher the score) considering the patient's age (<50 = +2, 50-70 = +1, >70 = 0), stroke risk factors – hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation (none = +3, 1 without AF = +2, 2 or 3 without AF = +1, AF = 0) and history of migraine (+2), epilepsy (+1), and psychiatric illness (+1) (Khan et al., 2018).

With the global expansion of remote consultations, an increasing percentage of SM patients are evaluated by the Telestroke network. The score (a stroke mimic is less likely the higher the score) was developed to identify ischemic SMs prospectively during the Telestroke evaluation (Ali et al., 2014). The TeleStroke Mimic Score (TM-Score) was calculated using variables related to SM status independently, including age (+0.2 per year), history of atrial fibrillation (+6), hypertension (+3), seizures (-6), facial weakness (+9), and a National Institutes of Health Stroke Scale >14 (+5). Seizures/epilepsy were the most frequently reported alternative diagnosis in the SM group (3.2%).

Though none of these ratings was designed explicitly to discriminate between actual cerebral ischemic stroke and postictal state, their validation cohorts included patients with a history of seizures. Three of the previously mentioned (FABS, Telestroke Mimic Score, and Khan Score) were verified externally in research conducted in Singapore. Among the scores assessed, the Telestroke Mimic Score demonstrated the strongest discrimination for stroke mimics (AUROC = 0.75, 95 per cent CI = 0.63–0.87). Telestroke Mimic Score showed the best sensitivity (91.3%) and the highest specificity (Khan score) (88.2%) (Tu et al., 2020).

Biomarkers

Numerous biomarkers and panels have been investigated to aid in the early detection of stroke and seizures. Still, it is essential to underline that none have shown sufficient sensitivity or specificity for routine clinical usage. Moreover, waiting for the lab results can be time-consuming.

NT-proBNP and D-dimer biomarkers may provide the most significant data to justify their clinical usage, particularly for distinguishing stroke mechanisms.

D-dimer levels are often raised in individuals who have suffered a stroke due to a cardioembolic event; however, they are usually lower than those associated with D-dimer and cancer hypercoagulability (Ohara et al., 2020).

BNP measurement in the case of the cryptogenic stroke helps determine the possibility of a cardioembolic cause, including paroxysmal atrial fibrillation; however, appropriate cutoff values for specific assays are unknown (Palà et al., 2021).

Transient elevations in serum ammonia are a typical result following a generalised seizure. According to various studies, hyperammonemia occurs in 50%, 61%, and up to 76% of patients with generalised tonic-clonic seizures (Hung et al., 2011).

In intensive care units, the lactate test is frequently utilised. It has been demonstrated to be a sensitive indicator of tissue hypoxia. Increased venous lactate levels have been associated with persistent muscle activity in hypoxic conditions following a seizure (Andersen et al., 2013). Following a seizure, an increase in leukocytes may be detected, owing to a phenomenon in which

white cells lose adherence to the vessel wall due to the significant catecholamine release (Vezzani et al., 2015).

For many years, creatine kinase as a marker of generalised seizure has been recommended in clinical practice; however, little research supports this strategy (Chesson et al., 1983).

Imaging

According to guidelines (Powers et al., 2019), computed tomography (CT) or magnetic resonance (MR) scan of the brain, supplemented by CT or MR angiography in case of suspected Large Vessel Occlusion, is essential in assessing AIS and evaluating acute treatment options.

For patients with ischemic stroke lasting 4.5–9 hours (known onset time) who have a CT or MRI core/perfusion mismatch and are not candidates for mechanical thrombectomy, the European Stroke Organization (ESO) guidelines suggest intravenous thrombolysis with alteplase (Berge et al., 2021). In addition, CT/MRI perfusion may, in some cases, contribute to findings confirming TP's diagnosis. One possible discriminator is that the area of hypoperfusion immediately following a seizure is frequently reasonably significant, comparable to that seen with large arterial occlusion. However, flow in the relevant arteries is normal (Austein et al., 2018). Although van Cauwenberge concluded that volume perfusion CT might distinguish ictal stroke mimics with hyperperfusion from acute ischemic stroke, but not postictal patients with ischemic stroke-like perfusion patterns (Van Cauwenberge et al., 2018).

Brain magnetic resonance imaging can be used to distinguish TP from AIS with greater certainty. The typical MRI features in TP include DWI hyperintensities consistent with epileptic-induced cytotoxic edema that lack arterial distribution, sometimes associated with pulvinar and hippocampal lesions (Adam et al., 2018). In addition, partial or complete resolution of diffusion and perfusion abnormalities was observed in the follow-up MRI examinations, depending on the length of the interval (Szabo et al., 2005). In contrast, changes in ischemic stroke are usually similar, often in a larger confluent area including both cortical and subcortical parts of the area supplied by the artery, with changes occurring over days to weeks as DWI intensity decreases and hyperintense changes due to fluid-enhanced inversion capture become chronic (Danière et al., 2014).

Brain MRI is more time-consuming and is not readily available around the clock in every location. In addition, it requires the patient to be able to cooperate with the examination and not have metal implants or claustrophobia. Recent meta-analyses, however, indicate that a small but significant fraction (6.8%; 95% confidence interval [CI], 4.9 per cent to 9.3 per cent) of AIS cases present as DWI-negative (Edlow et al., 2017).

Electroencephalography

Except for some types of seizures, the EEG alterations that occur following the cessation of the epileptic discharge are straightforward: decreased signal amplitude, focal or widespread slowing, and, in certain situations, suppression of EEG activity (So and Blume, 2010). Postictal EEG suppression is characterised as aberrant slow-wave activity or suppression with amplitudes more than ten volts occurring within thirty seconds of seizure termination and lasting longer than two seconds Fisher and Engel, 2010). It has been detected in 84% of seizures and 94% of epilepsy patients (Bateman et al., 2019).

Mecarelli's study found that EEGs performed within 24 hours of the onset of stroke symptoms revealed focal or diffuse slowing of background activity in 84 per cent of cases and epileptiform abnormalities in 16%, with periodic lateralised epileptiform discharges (PLEDs) accounting for 6% of the entire cohort of patients (Mecarelli et al., 2011).

A Structural Brain Injury Index was calculated using a binary discriminant classification system built independently and fed with required aspects of brain electrical activity (recorded from a reduced frontal montage using a hand-held device). Quantitative EEG (QEEG) features of absolute and relative power, mean frequency, inter- and intra-hemispheric coherence, and symmetry were calculated for the delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), beta (12.5–25 Hz), and gamma (30–45 Hz) frequency bands using the artefact-free EEG data. It had a 91.7% sensitivity to stroke and a 50.4% specificity (to stroke mimics) (Michelson et al., 2015).

As a result, the EEG is of little use in the differential diagnosis, as both the slowing and epileptiform activity can occur in acute vascular brain lesions and seizures but can be used to distinguish ongoing seizures from TP.

Missed strokes

A seizure at onset (SaO) is defined as any clinically apparent seizure, as witnessed by witnesses or medical practitioners, ranging from stroke onset through IVT (Abend et al., 2011). One study found that 10 of 209 patients (4.8%) initially diagnosed with epileptic seizures

had an ischemic stroke on closer examination (Boesebeck et al., 2010). The mechanism by which acute ischemic stroke causes SaO is unknown. Tissue hypoperfusion/hypoxia (reperfusion may also play a role) results in physiologic abnormalities that combine synergistically to decrease the seizure threshold and increase the excitability of brain circuits. Disruption of the blood-brain barrier, altered neurotransmitter activity, ion channel dysfunction, electrolyte concentration alterations, and metabolic dysregulation have all been seen in the ischemic penumbra of an acute ischemic stroke (Tanaka and Ihara, 2017). Convulsive motor activity may be the first sign of basilar artery occlusion. Convulsive-like motions are distinct from epileptic seizures in brainstem stroke, and the quick beginning of decerebrate posturing is frequently mistaken as a seizure (Saposnik and Caplan, 2001). The latest American Heart Association (AHA)/American Stroke Association (ASA) Guidelines (2018) removed SaO from the IVT contraindications list and made a moderate recommendation for IVT in patients with SaO "if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon"(Powers et al., 2019).

Consequences

In two scenarios, missing a stroke mimic in the pre-hospital or emergency department has serious repercussions. On the one side, failing to recognise the proper diagnosis will delay treating the disease appearing as a stroke mimic (e.g., appropriate treatment of focal seizures). On the other side, there is a risk connected with excessive long-term usage of stroke preventive medications.

The cerebral haemorrhage, significant systemic haemorrhage, and death rate are used to determine the safety of thrombolytic therapy. Intravenous thrombolysis appeared safe in SM patients since no significant complications were observed. All patients maintained their functional status at three months, according to data from the SITS International Stroke Thrombolysis Register 2003–2017 (Keselman et al., 2019). In one study of 539 patients undergoing thrombolysis, 56 were retrospectively determined to have had stroke mimic, of which diagnosis of epilepsy was determined in 19.6% of patients (Tsivgoulis et al., 2011).

Another study discovered that seizure-associated stroke mimics accounted for 85 per cent of all mimics treated for acute stroke (Winkler et al., 2009). In both investigations, no patient in the stroke mimics group experienced an adverse reaction to the IVT.

It is essential to emphasise that the majority of research indicates that reperfusion therapy does not raise the likelihood of early post-stroke seizures (PSS). In a prospective, multicenter study, no significant difference in the rate of early PSS was observed between 262 patients who got tPA and 254 patients who did not (Belcastro et al., 2020). A large systematic review and meta-analysis concluded that there was no increased risk of acute seizures in patients treated with intravenous thrombolysis (13 753 patients with stroke, 592 of whom had seizures) – the pooled incidence of PSS was 5.9 per cent (95 per cent confidence interval [CI], 4.2 per cent -8.2 per cent). Rates among patients treated with IVT were 6.1 per cent (95 per cent CI, 3.6 per cent -10.2 per cent) (Lekoubou et al., 2020).

CONCLUSIONS AND RECOMMENDATIONS

Focal neurological deficit of acute onset preceded by epileptic seizures presents a diagnostic challenge in the differential diagnosis. As TP is an exclusionary diagnosis, the most severe and treatable diagnoses must be identified using a rational screening strategy. The rising body of evidence establishing the safety of thrombolysis in SM implies that postponing or withholding therapy may be inappropriate when the benefits of thrombolysis in stroke outweigh the risks of treating a stroke mimic. Spontaneous recovery is expected if TP is overwhelmingly likely, and the prognosis is considered good.

There are a lot of possible strategies for lowering stroke mimics rates. To begin, it may be beneficial to facilitate using current scores in clinical practice for acutely distinguishing mimics from actual cerebral ischemia. Additionally, establishing epilepsy-specific scores in patients with a high probability of seizure and clinical decision support systems is a viable future direction. Advanced neuroimaging, such as perfusion MR, may also increase diagnosis accuracy. The development of recent cerebrovascular events biomarkers could help differentiate MRI-negative ischemic episodes from TP.

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