

Received: 2019.10.16

Accepted: 2019.12.24

Available online: 2020.01.24

Published: 2020.03.05

Frequency and Pathophysiology of Post-Seizure Todd's Paralysis

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support:

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Shanxi Provincial Health and Family Planning Commission Program (2017033); Doctoral Fund of the First Hospital of Shanxi Medical University (YB161706; BS03201631); Shanxi Applied Basic Research Program (201801D221426)

Todd's paralysis, a neurological abnormality characterized by temporary limb weakness or hemiplegia, typically occurs following a seizure, without enduring consequences. Since limb weakness or hemiplegia can also be a common symptom of an acute ischemic stroke, it is often difficult to diagnose Todd's paralysis in individuals experiencing an acute ischemic stroke if they do not have a pre-existing history of epilepsy. Given that there is a limited understanding of Todd's paralysis, this review discusses the history, prevalence, clinical manifestations, duration, etiology, and diagnosis of Todd's paralysis. A few factors that may help clinicians distinguish Todd's paralysis from other clinical indications are as follows: (1) Todd's paralysis is commonly observed after partial seizures or generalized tonic-clonic seizures. (2) The incidence of Todd's paralysis is greater if the epilepsy is associated with old age or stroke history. (3) The duration of Todd's paralysis can range from minutes to days, depending on the type of seizure or whether the patient has experienced cortical structural damage. (4) The etiology of Todd's paralysis is associated with cerebral perfusion abnormality after seizures. Further research is needed to explore factors that distinguish Todd's paralysis from other indications that may lead to limb weakness in order to improve the diagnosis of Todd's paralysis.

MeSH Keywords: **Epilepsy • Hemiplegia • Paralysis • Seizures**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/920751>

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Background

In 1827, Bravais first reported a case of paralysis following limb convulsions, known as hemiplegic epilepsy [1]. Following this, Todd described a case of hemiplegia following seizures in 1849, highlighting that the hemiplegia lasted for a period of time after the lateralized seizures sometimes affecting only one limb have stopped [2]. In cases where limb weakness or hemiplegia would last for several hours or days, this condition was termed Todd's paralysis (TP) [3]. The severity and clinical manifestation of the neurological deficit associated with TP is highly variable, from diffuse signs of cerebral paralysis such as stupor and coma to localized signs of neurological deficit such as hemiplegia, hemisensory disorder, and hemianopia [4]. Given that there is a limited understanding of TP, this review aims to discuss the prevalence, clinical manifestations, duration, etiology, and diagnosis of TP.

Prevalence

TP is commonly observed after partial seizures or generalized tonic-clonic seizures (GTCS) [5]. The incidence of TP following a seizure is 0.6–13.4% [6]. However, Gallmetzer [7] estimated that the incidence of TP was 13.4% in a sample of 328 patients with partial seizures, when excluding patients who had non-epileptic seizures, status epilepticus, or Lennox-Gastaut syndrome. By contrast, Rolak [8] estimated that the prevalence of TP was 6.1% in a sample of 229 patients with GTCS.

Convulsive status epilepticus (CSE), prolonged seizures, and high scores on the Glasgow Coma Scale (GCS) are risk factors for TP. The incidence of TP is greater when the epilepsy is associated with structural damage [8]. Moreover, if TP occurs in the context of stroke, incidence rates of TP increase to 19.7% [9]. The incidence of TP does not appear to be influenced by sex, but age does seem to play a role; TP patients are typically older and are often taking more anti-epileptic drugs.

Clinical Manifestations

The severity and clinical manifestation of the neurological deficit associated with TP is highly variable [10]. For example, Dai [11] reported on 3 patients with TP who were only affected on the right upper limb and the right lower limb. However, there have also been reports of TP affecting other body parts. A study of 14 patients with TP following GTCS reported that [8] TP affected the upper and lower limbs in 50% of cases, whereas TP only affected the face and the upper and lower limbs in 21.4% of cases. It was less common that TP only affects the upper limbs (14.2%) or only the lower limbs (7.1%) or the face and upper limbs (7.1%).

Duration

The duration of a TP episode varies, ranging from minutes to days, depending on the type of seizure, the associated structural damage, and other symptoms arising after the seizure. TP is most common following partial seizures and GTCS. A review of 328 TP patients [7] showed that 44 patients (13.4%) developed TP after a seizure. However, patients with GTCS had a longer duration of TP relative to partial seizures. In particular, patients with GTCS had a TP duration of 0.5–36 hours, with an average of 15 hours [8]. The mechanism may be related to a significant reduction in blood flow in the thalamus, mid-brain, and cerebellum, leading to severe hypo-perfusion [12] and inhibition of whole-brain activity following a seizure [13].

The duration of TP can be prolonged in patients with structural brain damage in the part of the brain affected by epilepsy, especially if the patient has a history of stroke [8]. This may be due to impaired cellular metabolism or alterations in biochemical functioning, leading to disruptions in synaptic transmission. In line with this, previous reports show that a stroke can damage the stability of neuronal cell membranes, leading to electrolyte disturbances [14]. Moreover, post-stroke epilepsy can also exacerbate alterations in synaptic transmission, such as glutamatergic excitotoxicity [15]. Studies have indicated that the duration of TP tends to be longer in patients with clonic activity on the same side of the brain as the seizure [6]. Unilateral clonic activity is one of the most common (56%) lateralization symptoms in seizures, and its occurrence may be related to activation of the primary motor cortex.

Etiology

Although the pathophysiological changes underlying TP are still unknown, many hypotheses about its pathogenesis have been proposed. Todd and Jackson [2] postulated that TP is associated with a sharp increase in metabolic activity and peripheral neuronal failure. By contrast, some scholars [5] suggested that TP is related to increased inhibitory activity in brain regions regulating movement.

Recent studies have suggested that TP is associated with ischemia and hypoxia caused by hypo-perfusion after seizures [16–18]. Farrell and colleagues demonstrated that the paralysis following a seizure is associated with hypo-perfusion in both preclinical and clinical models [19]. In particular, oxygen pressure and blood flow are reduced for up to 1 hour following a seizure. One possible mechanism may be that arachidonic acid is metabolized by cyclooxygenase (COX-2), leading to the synthesis of prostaglandins (PG) such as PGE₂. The prostaglandin EP₁ and EP₃ receptor subtypes induce vasoconstriction, leading to severe hypoxia, which can trigger TP. However,

elevated free calcium concentrations in vascular smooth muscle, such as increases in L-channel calcium levels, can also lead to vasoconstriction [20].

TP is typically characterized by slow, focal, or normal waves in the contralateral cerebral hemisphere relative to the side of the body that is affected, as determined by an electroencephalogram (EEG) [8,21]. Moreover, in cases where the epileptogenic focus is lateralized, TP always appears on the contralateral side [22], perhaps because the synaptic transmission within a particular hemisphere is more pronounced relative to synaptic transmission between the hemispheres [6].

Berge and colleagues [23] reported 2 GTCS case studies of patients with bilateral paralysis in the supplementary motor area (SMA), originating from the midline of the frontal lobe. This may be because the SMA has strong bilateral projections to the primary motor cortex (PMC). There are numerous reciprocal projections from the SMA to the cerebral cortex, PMC, anterior cingulate cortex, and various parts of the parietal somatosensory cortex. In this context, functional activation determined using the blood-oxygen-level-dependent response, thought to be an indirect measure of neuronal activity, is greater in the PMC and motor area following electrical stimulation [24].

The most common cortical abnormalities in TP can be measured using diffusion-weighted imaging (DWI). The strong signal shadow does not conform to the distribution of intracranial blood vessels, but it is along the local cerebral gyrus [25]. Brain computed tomography perfusion (CTP) can help diagnose a seizure when the initial presentation was that of a stroke [26,27]. Interestingly, the results reported in the existing literature are inconsistent. CTP can reliably measure postictal hypo-perfusion, which is maximal at the seizure onset zone [28]. However, a contradictory case report with TP demonstrates hyper-perfusion using CTP [29]. On the acute-stage CTP examination, seizure patients presenting with a unilateral motor deficit have contralateral hyper-perfusion in the corresponding eloquent brain regions.

Studies using susceptibility-weighted imaging (SWI), sensitive to deoxyhemoglobin, that aid the detection of perfusion, demonstrated hypo-perfusion in a case study of a patient with TP exhibiting left-limb paralysis. Koppi [30] published a case study on a patient with TP, depression, and hemiplegia, which persisted for 25 days without remission. The patient demonstrated poor perfusion between the left middle cerebral artery M1 segment and the left dorsolateral prefrontal cortex, suggesting a persistent cortical metabolic disturbance. Following the use of repeated transcranial stimulation (rTMS), the patient no longer experienced depression or hemiplegia. The rTMS treatment involved the use of a high frequency (10 Hz) treatment, followed by a low frequency (1 Hz) treatment.

Since TP can also occur after unilateral electroconvulsive therapy (ECT). Its pathogenesis may be similar to TP demonstrated following a spontaneous seizure. Compared with TP associated with epilepsy, the duration of TP that occurs in the context of ECT is shorter [31]. In particular, previous studies have shown that transient paralysis of the left face lasting 20 minutes has occurred in the context of electrical stimulation to the contralateral side of the brain [32]. However, when ECT was administered bilaterally, the patient did not experience any further episodes of TP.

Diagnosis of Todd's Paralysis

The misdiagnosis of TP as a limb weakness after acute ischemic stroke (AIS) may result in unnecessary intravenous thrombolysis, which is contraindicated for individuals with neurological deficits [33]. However, TP and AIS are more difficult to diagnose in the context of a prolonged hemiplegia in patients who do not have a history of epilepsy [34]. Of note, according to the latest guidelines, administration of tPA in patients with seizure at onset is reasonable if the deficits are thought to be related to stroke and not postictal phenomenon [35].

At present, there are no standardized tests aiding the diagnosis of TP. The diagnosis requires reviewing the patient's medical history and symptomatology, as well as structural and functional evidence using MRI and EEG [36]. Since TP is most commonly seen in the context of GTCS or partial seizures, this may aid the identification of TP. As previously mentioned, CTP could help to diagnose a seizure when the initial presentation was that of a stroke. When CTP abnormalities occur in atypical vascular distributions, and the CT angiography shows no corresponding large-vessel occlusions, Todd's paralysis should be considered prior to acute stroke [37].

Conclusions

A few factors that may help clinicians distinguish TP from other clinical indications are as follows: (1) TP is commonly observed after partial seizures or GTCS. (2) The incidence of TP is greater if the epilepsy is associated with old age or stroke history. (3) The duration of TP can range from minutes to days, depending on the type of seizure or whether the patient has experienced cortical structural damage. (4) The etiology of TP is associated with cerebral perfusion abnormality after seizures. Further research is needed to explore factors that distinguish TP from other indications that may lead to limb weakness in order to improve the identification of TP.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

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Conflicts of interest

None.