Original article

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Tonic status epilepticus in patients with idiopathic generalized epilepsy

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ABSTRACT – *Rationale.* Tonic status epilepticus (TSE) in patients with idiopathic generalized epilepsy (IGE) is not well recognized. The objective of this study is to report episodes of TSE in patients with IGE. *Methods.* We retrospectively reviewed the clinical and EEG evaluation of three IGE patients who presented TSE. *Results.* The three patients had mainly clinical features of IGE, but had developed, in addition, focal discharges, diffuse EEG abnormalities and some focal or diffuse neuropsychological dysfunction. The tonic attacks eventually responded to treatment, but were not completely controlled in any of the patients. *Discussion.* The continuum between IGE and secondary generalized epilepsy is demonstrated in these patients. Most of their clinical and EEG features are however, in keeping with an idiopathic generalized epileptic process with additional focal and diffuse components. Recognition of the significance of TSE in such patients has important therapeutic and prognostic implications.
[Published with video sequences]

Key words: idiopathic generalized epilepsy, tonic status epilepticus, tonic seizures, absences

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Descriptions of tonic status epilepticus (TSE) usually refer to patients who are severely impaired and who have a catastrophic epilepsy such as the Lennox-Gastaut syndrome or other encephalopathies, associated with widespread cerebral dysfunction. Aggravations of seizure control leading to SE are well recognized as a part of the natural history of these patients.

The borderline between secondary generalized (SGE) and idiopathic generalized epilepsy (IGE) is often blurred. The seizure types usually associated with IGE are absence, myoclonus and generalized tonic-clonic. The diagnosis of IGE is based mainly on features such as normal EEG background activity (Mattson 2003), early onset, an obvious or implied genetic origin, good response to antiepileptic drugs (AEDs) and normal intelligence. On the other hand, patients with SGE, by definition have abnormal EEG background activity, cognitive impairment, poor response to AEDs, and evidence of diffuse brain pathology.

Episodes of status epilepticus (SE) consisting of minor attacks may rarely occur in patients with a well-established diagnosis of IGE, but are usually associated with inadequate treatment, in the form of myoclonic or absence SE (D'Agostino *et al.* 1999, Wheless 2003). Because the occurrence of tonic seizures and tonic status

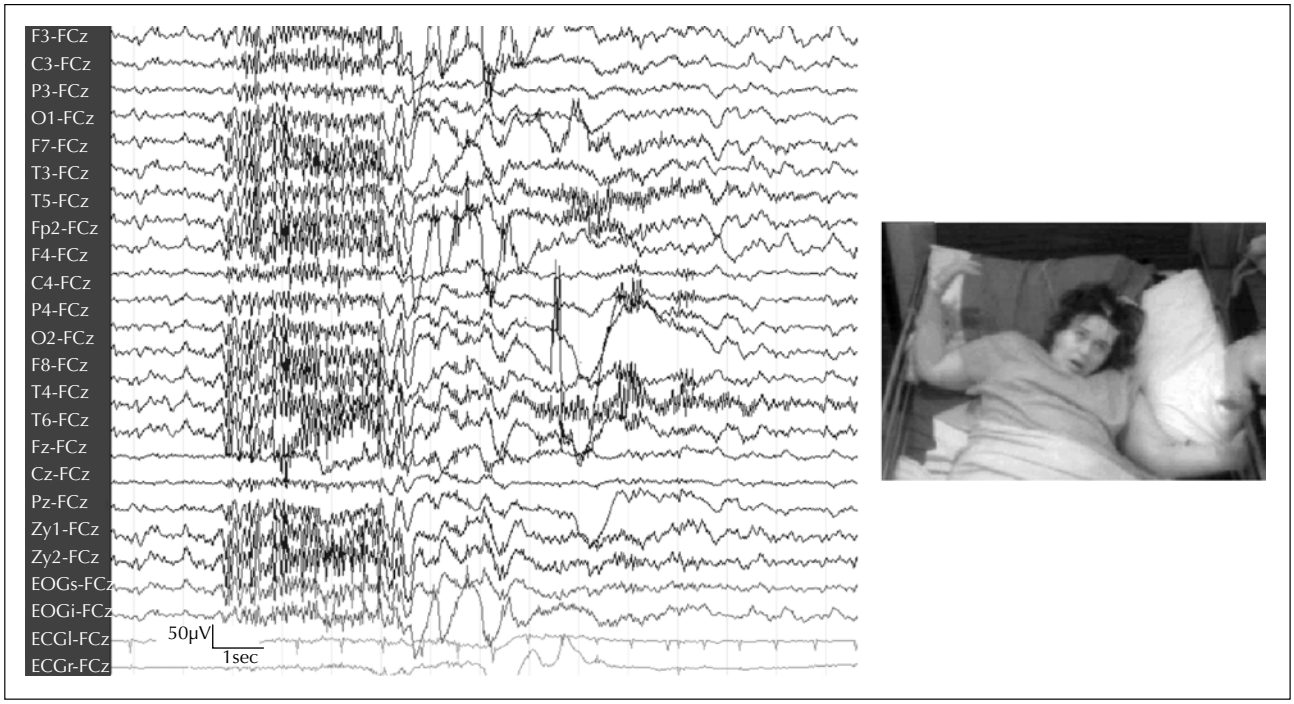

Figure 1. Ictal EEG recording from patient 1 showing generalized polyspikes and irregular GSSW pattern, during a tonic seizure characterized by a brief tonic flexion of neck, trunk and arms.

epilepticus (TSE) in patients with IGE is not widely recognized, we describe three patients with IGE who presented episodes of TSE.

Methods

We retrospectively studied the clinical and EEG characteristics of two patients with recurrent SE with tonic seizures at the Montreal Neurological Hospital and one from the Neurological Department of the Nice University Hospitals.

Results (case descriptions)

Patient 1

A 24 year old woman had typical childhood absences diagnosed at age five. Routine EEGs since that age showed frequent, brief bursts of irregular, 2.5-3Hz generalized spike and slow waves (GSSW) maximum over anterior regions, and sometimes with left centro-temporal predominance. She had no identifiable risk factors or family history of epilepsy. She graduated from high school and worked in her sister's store. Nocturnal symmetrical tonic seizures, lasting 10 to 20 seconds, appeared during adolescence, mostly related to her menstrual cycle. These increased in frequency and after the age of 15 she was hospitalized on several occasions for clusters of such attacks amounting to status epilepticus. Her interictal waking EEGs and MRI were normal.

At the age of 17, she had a prolonged hospitalization because of refractory TSE. On admission, her neurological examination had been normal, except for drowsiness, and she had good valproate and ethosuximide levels. She was intubated and treated with thiopental for 36 hours. After discontinuing the Thiopental she remained in a coma, with a burst suppression EEG pattern. Complications included lung atelectasis, sepsis-related to *Klebsiella* infection and a lower extremity, sensory motor neuropathy. She improved progressively after treatment with vigabatrin 3000 mg, 300 mg of phenytoin, and 2750 mg of valproate. She had residual cognitive and behavioral changes, but was seizure-free for one year. She then developed similar, recurrent, brief, tonic, nocturnal attacks, mainly in the perimenstrual period, activated by fatigue and excitement. Interictal EEGs showed frequent paroxysms of irregular, bifrontal spike and polyspike and wave discharges during sleep.

At the age of 24, she again developed TSE, with attacks every five minutes characterized by elevation and flexion of both arms, flexion of the neck and trunk, upward eye deviation, and unresponsiveness lasting up to four seconds (*figure 1A*). During monitoring, attacks occurred mainly during sleep, at an average of two per hour, and ictal EEGs showed generalized polyspike activity. She improved after treatment with propofol 25 micrograms/kg,

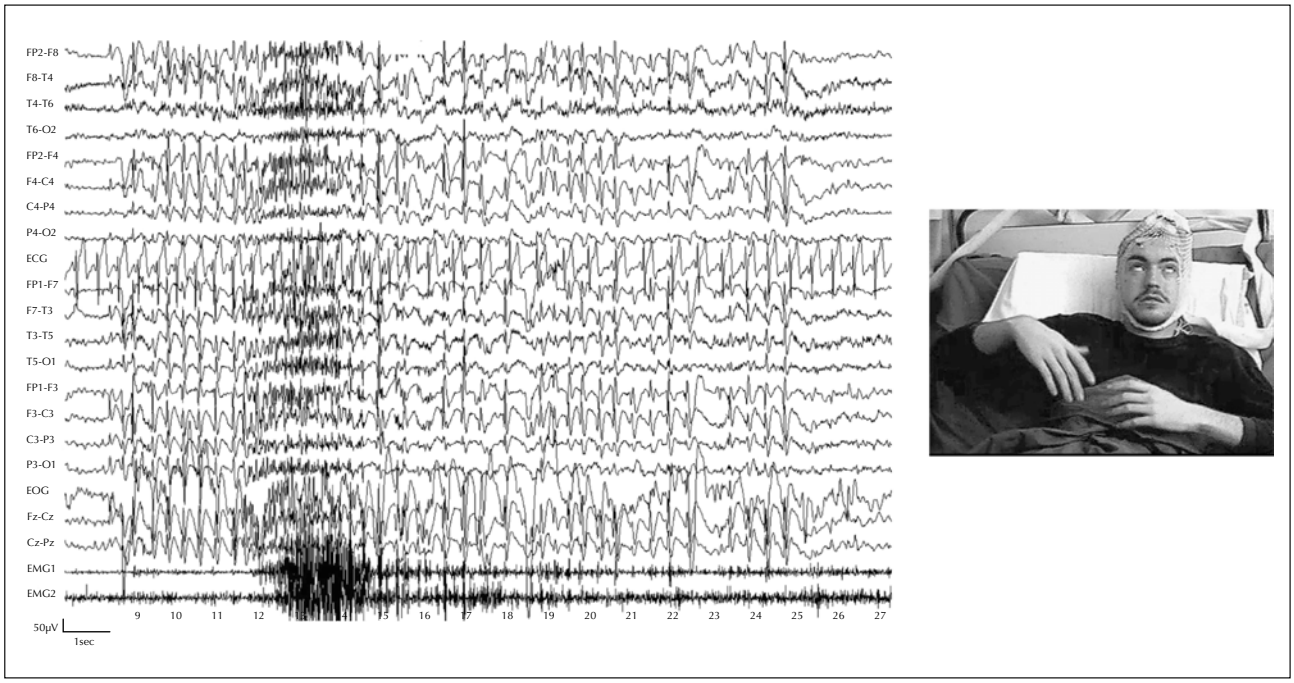

Figure 2. Ictal EEG recording during a tonic seizure from patient 2, showing rhythmic, 3Hz GSSW, followed by generalized polyspikes and then by irregular GSSW.

and was treated with valproate and levetiracetam two grams per day, with no additional, identifiable, cognitive impairment or focal deficit. She remained seizure-free for a year and then again began developing similar, infrequent, nocturnal, tonic attacks, but not amounting to SE.

Patient 2

A 21 year old man developed generalized tonic clonic and absence seizures at the age of eight years. Absences were atypical since they were associated with marked bilateral myoclonic jerking of the lower part of the face. Consciousness was partially preserved, but he was unable to respond. He had no cognitive deficits. There were periods of worsening of seizure control, mainly associated with carbamazepine use, but he was finally treated successfully with lamotrigine and valproate, and later with 400 mg of lamotrigine as daily monotherapy. His EEG showed irregular GSSW with some additional rhythmic discharges over the left frontal region. He then developed attacks while falling asleep, characteristically related to fatigue and occurring in series or clusters, and therefore was admitted for video-EEG monitoring. Many seizures were recorded, consisting of brief tonic asymmetric posturing of both arms, more evident on the right side, upward eye deviation, and contraction of perioral muscles with some downward deviation of the labial commissures (*figure 1B*). These were associated with generalized polyspikes with fragmentation and irregular GSSW. Typical perioral myoclonia with absence seizures were also recorded. He was treated with lamotrigine 400 mg and topiramate 200 mg, and became seizure-free.

Patient 3

A 22 year old man with a history of seizures since the age of five. Attacks occurred during sleep, but characteristically occurred in clusters during the first hour after awakening in the morning. He had tonic stiffening and slight flexion of the arms and neck associated with altered consciousness. He had a third degree cousin with epilepsy. Seizures were recorded during video-EEG monitoring. Episodes started with tonic flexion of the body and head, with upward deviation of both arms; some were followed by left hand automatisms and chewing movements. EEG showed 2 Hz GSSW with some additional interictal bitemporal spikes with left side predominance. No focal onset was found in the ictal EEG. MRI was normal and neuropsychological evaluation revealed frontocentrotemporal dysfunction. He was discharged receiving phenytoin 500 mg/day, lamotrigine 500 mg/day and clobazam 50 mg/day.

Discussion

Status with minor seizures, mainly absence or myoclonus is common in patients with IGE (D'Agostino *et al.* 1999, Wheless 2003). However, there are no descriptions of TSE in this group of patients. TSE is commonly associated with

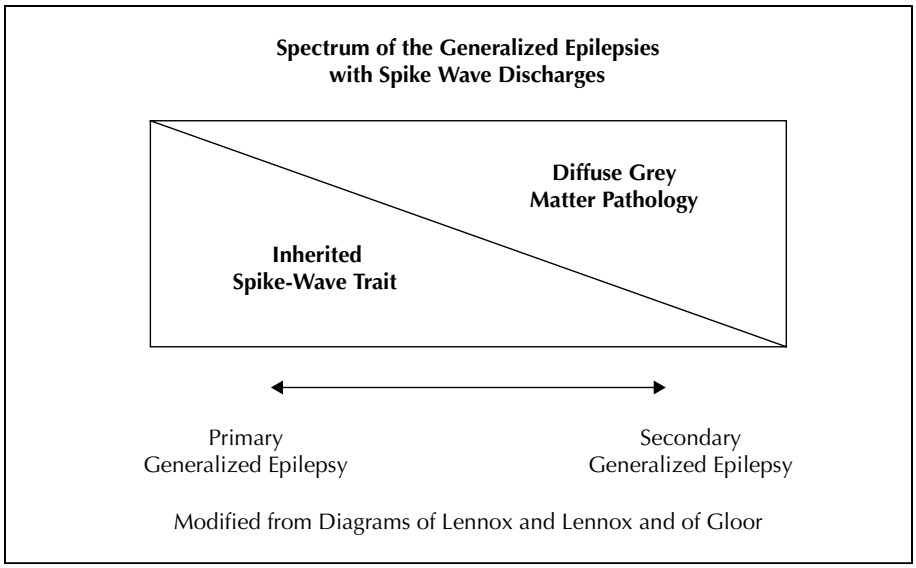

Figure 3. The biological continuum from idiopathic generalized epilepsy to secondary generalized epilepsy (after Gloor).

secondary generalized epilepsy as a frequent complication of catastrophic epilepsy. The biological continuum between SGE and IGE leads to difficulty in differentiating mild SGE from severe IGE, especially in patients with absences (Berkovic *et al*. 1987, Guye *et al*. 2001). Although most SGE patients show clear mental retardation, abnormal EEG background, and multiple refractory seizure types, some patients do not obviously fulfill all these criteria; many such individuals may actually have unusually severe and refractory IGE.

Tonic seizures in SGE patients are the most frequent seizure type, usually with an axial pattern involving the trunk and head, associated with polyspikes in the EEG (Markand 2003). In our patients, no particular pattern or sequence of the polyspike activity could be observed. There was clear predominance of arm involvement, which was different from the usual axial involvement in SGE patients. Previous studies have shown that the finding of polyspikes in the sleep EEG of IGE patients with absences is a predictor of poor seizure control (Guye *et al*. 2001).

Although our first patient now has some cognitive and behavioral changes, these manifested only after a complicated, prolonged admission for SE that might have led to additional, diffuse brain damage, in addition to the prolonged TSE. In our second patient, no clear risk factors could be identified, and he has no evidence of diffuse or subtle brain dysfunction. A syndromic diagnosis of perioral myoclonia with absences is proposed for this patient (Panayiotopoulos *et al*. 1995). Such individuals may have epilepsy that is more difficult to treat, although subtle face and neck myoclonia including perioral myoclonia can also occur in patients with childhood absences, and in patients that respond to AEDs (Capovilla *et al*. 2001).

Our third patient represents an example of the difficulty in distinguishing between generalized and focal epilepsy, but the peculiar time of the day-locked seizures, *e.g.* clustering during the first hour after awakening, in the absence of clear clinical or EEG focality (with automatisms occurring late during the events, and focal spikes in addition to the generalized discharges, not rare in IGE patients), is more compatible with a generalized epileptic process.

Despite all of these issues, the limited number of patients and the fact that patient 1 had severe systemic complications causing cognitive impairment, we suggest that TSE can occur in IGE patients. The mechanism of TSE in patients with IGE remains unknown but may be related to that more commonly found in SGE. These patients highlight the difficulty in establishing a syndromic diagnosis, and the fact that some of the seizure patterns occur in patients must be placed along a biological continuum *(figure 3)*. Identification of more patients with IGE, tonic seizures and TSE will enable us to better assess the nuances of such a continuum, as well as the significance of the tonic seizures in such individuals Dulac 1993, Nabbout et Dulac 2003. □

Legends for video sequence

Video 1. Tonic seizures in patient 1, showing upward eye deviation, tonic elevation of both arms and flexion of trunk and neck.

Video 2. Tonic seizures in patient 2. Note upward eye deviation, downward turning of the corners of the mouth, and after the tonic phase, myoclonus of the chin.

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