

Stimulus-sensitive burst-spiking in burst-suppression in children: implications for management of refractory status epilepticus

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ABSTRACT – Status epilepticus refractory to sequential trials of multiple medication is a rare but significant problem in children. We describe stimulus sensitivity arising during the treatment of convulsive status epilepticus in children (stimulus-sensitive burst-spiking in burst-suppression). We reviewed retrospectively clinical and EEG features in six children (three months to ten years), with status epilepticus requiring intensive care, in whom tactile, auditory and visual stimulation induced myoclonic jerks and bursts of EEG spikes. Sensitivity was not present at onset, but appeared after 24 hours as myoclonic jerks of the eyes, face and limbs, irrespective of the modality and site of stimulation. These were associated with burst-suppression in the EEG, the induced spiking forming the burst component. Various antiepileptic drugs, including GABAergic and NMDA blockers had no effect, but halogenated agents (used in two patients) abolished the sensitivity. Two children died, but the remainder returned to their previous clinical state. We conclude that stimulus sensitivity may appear in the context of refractory status epilepticus treated with high-dose barbiturates. Outcome may be more favorable than previously reported in adults, mostly in the context of post-anoxic or toxic coma. Evaluation of ventilated children in status epilepticus should include electroclinical assessment using sensory stimulation. If present, the drug regime should be reviewed and halogenated agents considered.

Key words: status epilepticus, stimulus sensitivity, child, barbiturate, isoflurane, halothane, post-anoxic myoclonus

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Refractory status epilepticus has been defined as seizures continuing for more than 60-90 minutes after initiation of therapy (Shorvon 1994). Patients who reach this stage are often unresponsive to sequential trials of multiple agents and usually require

anesthesia. Outcome is often poor, particularly in children (Sahin *et al.* 2001, Sahin *et al.* 2003, Baxter *et al.* 2003). Some authors have reported (Jäntti *et al.* 1994), or illustrated (without directly addressing) (Baxter *et al.* 2003), one uncommon phenomenon

in children with refractory status epilepticus. This consisted of bursts of spikes in response to sensory stimulation in an otherwise “suppressed” EEG. A similar phenomenon has been well-described in adults with post-anoxic coma (Van Cott *et al.* 1996, Morris *et al.* 1998) or carbamazepine overdose (De Rubeis *et al.* 2001), perhaps pointing to common pathophysiological mechanisms. Recently, Hirsch characterized various patterns of EEG discharges in intensive care patients in response to alerting stimuli such as auditory and tactile stimulation, suggesting that these might be linked to arousal mechanisms in critically ill patients (Hirsch *et al.* 2004).

We present six children with prominent evidence of stimulus sensitivity during status epilepticus and report on its phenomenology and response to pharmacological manipulation.

Materials and methods

Five consecutive children with refractory status epilepticus admitted to the pediatric intensive care unit of the Hôpital Universitaire des Enfants Reine-Fabiola (Brussels, Belgium) and one child with refractory status epilepticus admitted to the pediatric intensive care unit of Great

Ormond Street Hospital for Children (London, United Kingdom) were included in the study. While they were in status epilepticus, EEGs were taken using conventional electrode placements according to the International 10-20 system. In addition, the examiner touched the patients lightly on the arms and face (tactile stimulation), made hand claps (auditory stimuli) and flashed lights on and off in front of the patients face (visual stimulation) during the recordings. A retrospective review of the clinical notes and investigations was then carried out.

Results

Six children (clinical details in *table 1*) with prolonged convulsive status epilepticus refractory to medication showed clinical and EEG sensitivity to stimulation. This sensitivity appeared after more than 24 hours in response to tactile, auditory and/or visual stimuli. At this time, EEGs showed burst-suppression (not present initially) in all but one patient (Case 4) who showed brief periods of low EEG amplitude. Although none had myoclonic status epilepticus, motor responses to stimulation consisted mainly of myoclonic jerks of the eyelids and extremities. The same response was observed irrespective of the modality or site

Table 1. Characteristics of patients and stimulus-sensitive status epilepticus.

Case No.	1	2	3	4	5	6
Age	9 years	4 months	10 years	21 months	6 years	3 months
Gender	M	F	F	M	F	M
Previous epilepsy	No	No	Yes	No	Yes	No
Underlying condition	None	Tracheal stenosis	Cortical dysplasia	Tracheomalacia	Cortical dysplasia	None
Status epilepticus precipitant	Post-infectious encephalitis?	Cardio-respiratory arrest	Poor epilepsy control	Respiratory arrest	Poor epilepsy control	Upper airway infection
Duration of status epilepticus	8 weeks	6 days	24 h	3 days	2-3 days	2-3 days
EEG features	Generalized runs of fast activity and spike-waves	Generalized complexes including spikes and fast activity	Brief focal complexes of spikes	Generalized bursts of fast spiking	Brief focal complexes of spikes	Brief focal complexes of spike-waves
Other clinical neurophysiology	SSEP increased amplitude; fVEP initially normal, later absent; BAEP increased I-V latency	none	SSEP normal; fVEP absent, later normal; BAEP increased I-V latency	SSEP normal; fVEP absent, later normal; BAEP normal	none	none
Medication	DZP PHT PHB VPA CZP TP CLM MP LC VGB TPM KTM ISO+	LZP PHB PHT CLM TP	VPA LMT LEV LZP PHB TP LC ISO+ HAL+	LZP PHT PHB	VPA CLB CZP PHT PHB TP CLM PPF	DZP PHB PHT MDZ TP
Outcome	Died	Died	No sequelae	No sequelae	No sequelae	Hemiplegia

SSEP: somatosensory-evoked potentials, fVEP: flash visual-evoked potentials, BAEP: brainstem auditory-evoked potentials, DZP: diazepam, PHT: phenytoin, VPA: valproic acid, CZP: clonazepam, TP: thiopental, CLM: chlormethiazole, MP: methylprednisolone, LC: lidocaine, VGB: vigabatrin, TPM: topiramate, KTM: ketamine, ISO: isoflurane, LZP: lorazepam, LMT: lamotrigine, LEV: levetiracetam, PHB: phenobarbital, HAL: halothane, CLB: clobazam, PPF: propofol, MDZ midazolam; + indicates a clear positive response.

of stimulation. The clinical response was intermittent and only appeared in association with EEG spikes. The epileptiform EEG bursts were markedly stereotyped, and more readily seen against a low amplitude EEG background, constituting the bursts of activity during burst-suppression (*figures 1-3*). In three documented cases (Cases 1, 2 and 5), the phenomenon persisted when the burst-suppression pattern was clearly not related to medication but to the time course of the status epilepticus. There was some slowing in the rate of spiking before the end of many of the bursts (*figure 1B*), without any slow activity after the run of spikes (*figure 1C*). The electroclinical phenomenon lasted from hours to days, though it persisted for eight weeks in Case 1. Drugs that enhance GABA (barbiturates, benzodiazepines, vigabatrin), or that reduce NMDA activity (ketamine) as their main mode of action did not alter it. However, halogenated agents abolished it.

Three children survived without sequelae; Case 4 who is normal, and Cases 3 and 5 with pre-existing seizures who recovered their previous state, but subsequently required surgical excision of focal dysplasia. One infant (Case 6) was left with hemiplegia related to extensive cortical necrosis. Cases 1 and 2 died in the course of status epilepticus. Case 1 underwent a brain biopsy that showed extensive neuronal necrosis, confirmed at autopsy, although magnetic resonance imaging appeared normal after one week of status epilepticus. Clinical features, time course and effect of treatment are highlighted by two detailed examples.

Case examples

Case 1 – A previously healthy 9-year-old boy became drowsy and confused three days after the onset of a mild febrile illness. The following day he became comatose, and then developed convulsive, apparently generalized, status epilepticus. This did not respond to intravenous diazepam (two doses of 0.5 mg/kg), phenytoin (20 mg/kg), phenobarbital (20 mg/kg) or to infusions of valproic acid (2 mg/kg/hour) or clonazepam (10 µg/kg/h). Thiopental infusion led to hemodynamic problems requiring catecholamine therapy. Seizures disappeared after six days of thiopental (up to 1 mg/kg/h), although his EEG showed periods of virtual absence of activity alternating with runs of generalized discharges. By this time, he had multiple organ failure. Clinically, he was in coma, with no spontaneous movements, but tactile, auditory or visual (flash) stimulation provoked jerking of his face and of upper limbs. Stereotyped EEG sequences starting with generalized high amplitude fast activity (*figure 1A*) followed by slower rhythmic spike-wave complexes (*figure 1B*) were associated with the myoclonic jerks of the eyelids, jaw and upper limbs, which disappeared when electrocerebral inactivity returned (*figure 1C*). Flash, touch and noise were found to induce both jerks and EEG bursts. Repeated stimulation could trigger a similar sequence or a truncated one, with single or a few jerks associated with briefer

spiking over a flat background (*figure 2*). Thiopental withdrawal did not alter this electroclinical state, nor did subsequent chlormethiazole (10 mg/kg/h), corticosteroids (30 mg/kg methylprednisolone), vigabatrin (up to 120 mg/kg via nasogastric tube), topiramate (up to 30 mg/kg via nasogastric tube), lidocaine (up to 0.6 mg/kg/h) or ketamine (up to 7 mg/kg/h). In particular, EEG burst-suppression persisted. However, isoflurane induced a response with increased doses (from 2%), although clinical seizures recurred whenever the infusion was reduced. With effective doses of isoflurane, the phenomenon was abolished and the EEG activity changed, consisting of low amplitude, bi-occipital spikes without clinical correlates followed by total electrocerebral inactivity, however the patient developed tachyphylaxis. MRI (T1, T2, FLAIR sequences) performed after one week of status epilepticus was normal. A subsequent scan obtained one month later showed diffuse cortical edema and increased signal in the basal ganglia on T2-weighted sequences. A brain biopsy taken on the 42nd day of status epilepticus showed focal subcortical necrosis with macrophage proliferation and astrocytic reaction as well as neuronal loss in the cortex, associated with an increase in microglia. These changes were thought to be secondary to status epilepticus. The patient died two weeks later. Autopsy confirmed laminar necrosis, with cortical and subcortical hemorrhagic foci. No etiology was found. In particular, there was no evidence of a mitochondrial disorder, or of disease in other organs including the liver.

Case 3 – A 10-year-old girl with left frontal lobe epilepsy since the age of 7, presented with her 9th episode of secondarily generalized convulsive status epilepticus. There were no obvious precipitating factors. Seizure control had been difficult to achieve despite several combinations of multiple antiepileptic drugs. Current treatment consisted of valproic acid, lamotrigine and levetiracetam. The other episodes of status epilepticus were controlled with benzodiazepines and phenytoin ($n = 3$) or phenobarbital ($n = 3$) or all three drugs ($n = 2$). The current episode did not respond to two (1 mg/kg) boluses of lorazepam followed by phenobarbital (20 mg/kg). Thiopental and lidocaine were also ineffective in abolishing residual, mostly clonic seizures and EEG discharges, which occurred in multifocal, asynchronous runs of spike-wave complexes. Clonic seizures decreased in frequency while the patient remained deeply unconscious. By the 4th day of status epilepticus, myoclonic jerks could be easily evoked by touch, hand-clap or flash. They were correlated with multifocal EEG spikes, predominating in the right frontal region. The electroclinical response disappeared on repeat stimulation, the clinical component disappearing first. Central catheter replacement was performed under isoflurane anesthesia. During this procedure, EEG showed rare spontaneous right frontal discharges (*figure 3*) and there was no stimulus-sensitivity.

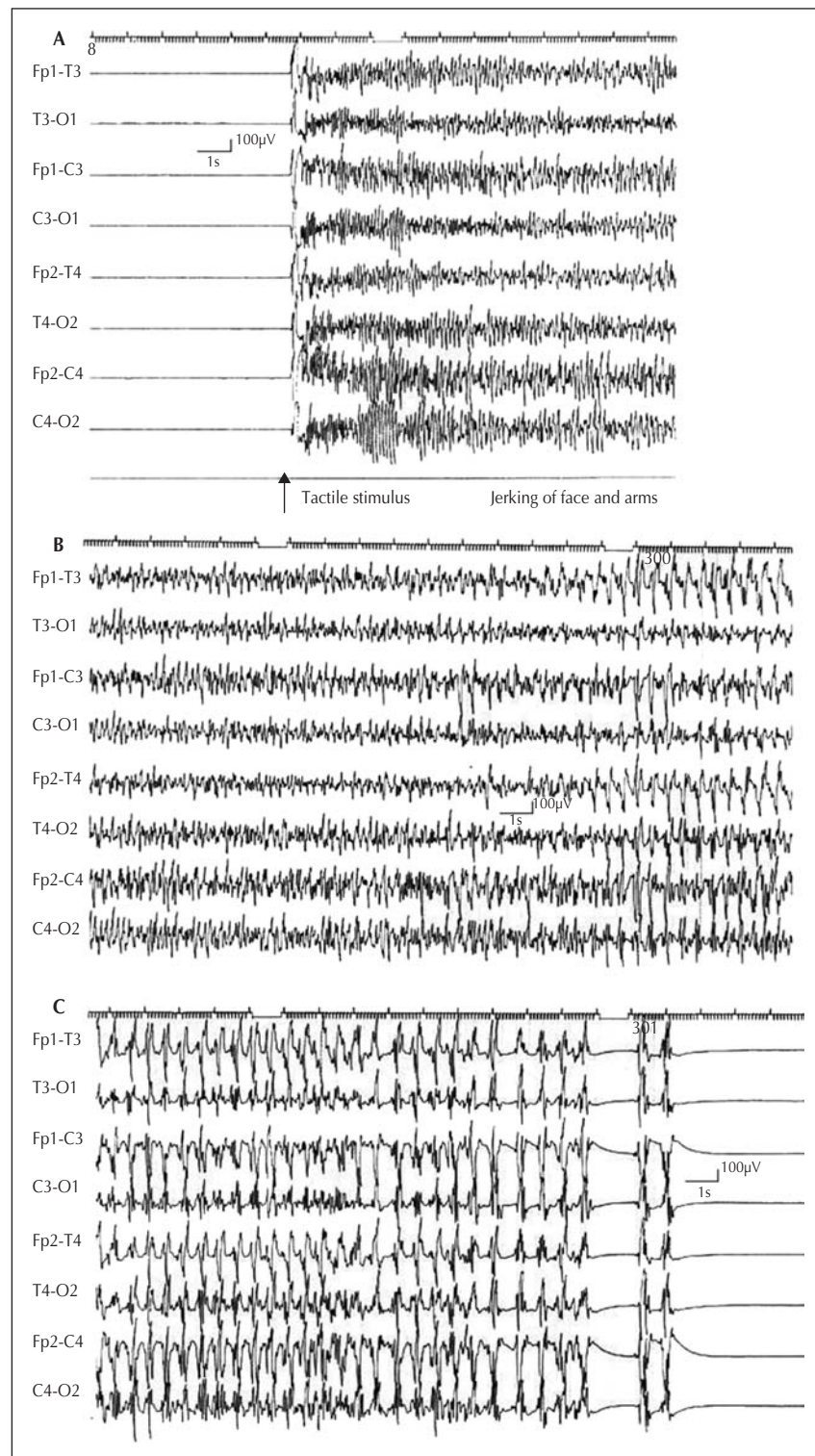


Figure 1. Case 1. Serial EEG excerpts from one episode of response to stimulation. **A)** Note the electrocerebral inactivity until tactile stimulation of the arm, which provokes a run of spikes and initially high amplitude fast activity, followed by slower rhythmic spiking. This is accompanied by myoclonic jerking of the face and arms. **B)** Note the gradual slowing of the bursts of spikes correlated with clinical myoclonic jerks. **C)** The spike bursts (and clinical jerks) cease with a return of electrocerebral inactivity.

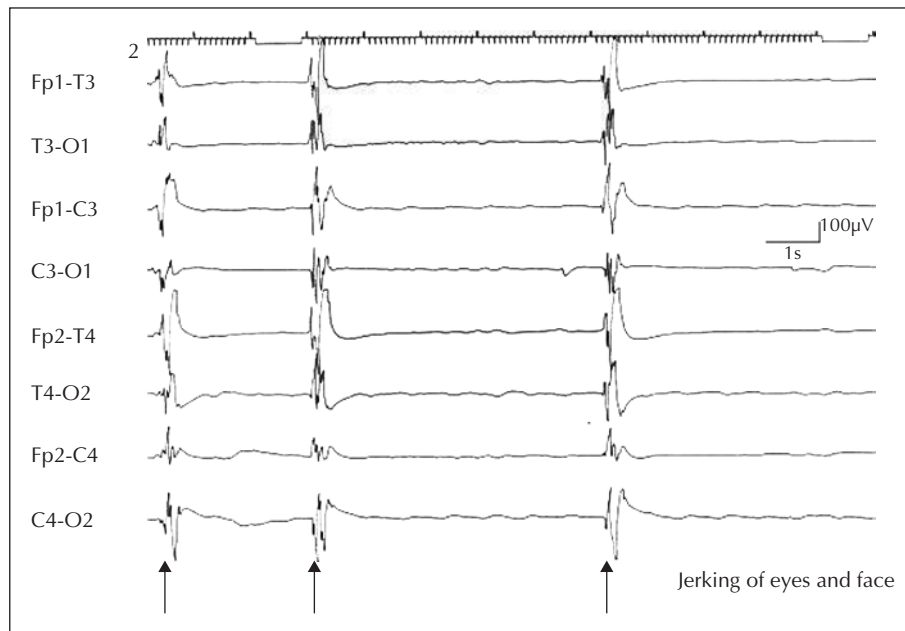


Figure 2. Case 1. The bursts of spikes provoked by stimulation (indicated by arrows), associated with myoclonic jerking, are very brief in these examples, although the spiking constitutes the bursts of the “burst-suppression”.

The status epilepticus was therefore treated with halothane, leading to its resolution.

She subsequently underwent anterior frontal lobectomy and has had no further episodes of status epilepticus over a 3-year follow-up. Pathological examination of the resected tissue confirmed dysplastic changes and showed a moderate loss of neurons as well as gliosis in the cortex and subcortical white matter.

Discussion

The children in this study developed stimulus sensitivity in the setting of refractory status epilepticus. The clinical manifestation of this sensitivity consisted of myoclonic jerks. Sensitivity was not restricted to a single sensory modality and did not depend on any specific location; it could, for example, be elicited by tactile stimulation of

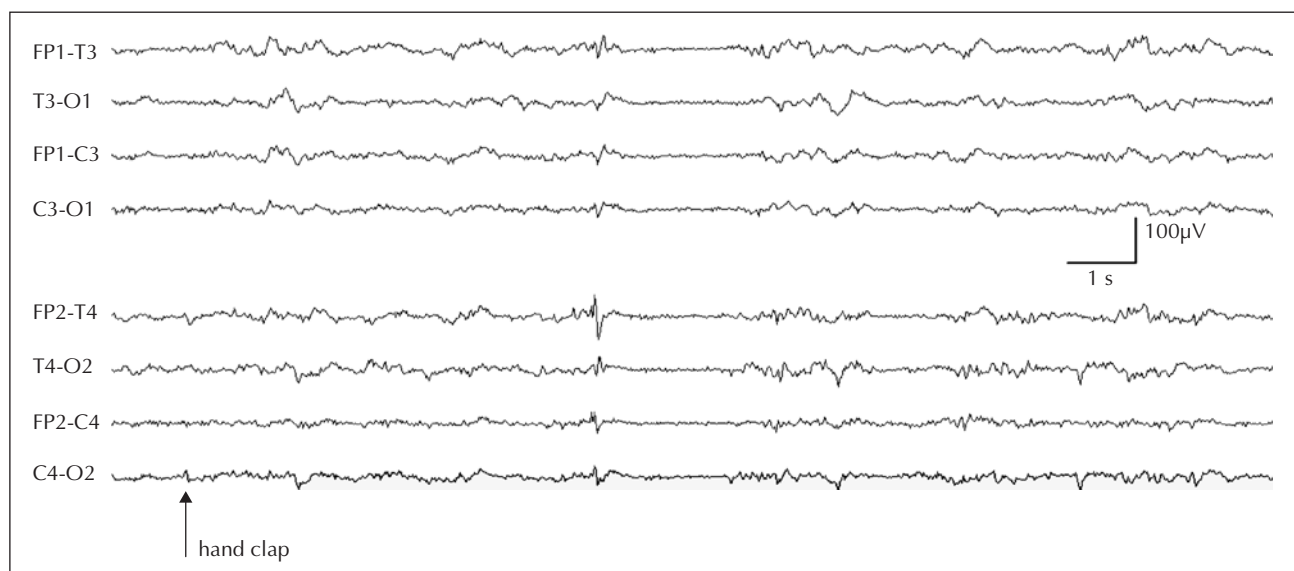


Figure 3. Case 3. EEG while the patient was on isoflurane. Occasional right frontal discharges with no clinical correlation, unrelated to sensory stimulation, and which did not induce any response.

any of the four limbs or the face or trunk, as commonly seen in post-anoxic myoclonus (Hallett *et al.* 2000) and other conditions without histological evidence of hypoxic neuronal damage (De Rubeis *et al.* 2001). While the functional mechanism underlying the phenomenon is uncertain, it does not seem to require extensive neuronal death. Four of the six children survived, including one who is entirely normal and two whose pre-existing seizure disorders have continued, indicating that this phenomenon does not necessarily imply a poor prognosis. However, it may be significant that the children who died had status epilepticus of longer duration, *i.e.* several weeks as opposed to up to three days in the other children.

All of our patients who could be assessed showed the typical EEG sequence of changes associated with convulsive status epilepticus (Treiman *et al.* 1990) and none showed EEG burst-suppression on initial assessment. However, this was present when stimulus sensitivity appeared after more than 24 hours spent in status epilepticus (with the exception of Case 4). Despite similarities with post-anoxic myoclonus, including time course, motor manifestations, sensitivity to multiple stimulus modalities and EEG burst-suppression, only two of our children (Cases 2 and 4) had suffered a definite hypoxic insult, including one (Case 4) who made a good recovery.

Burst-suppression is commonly regarded as a particular EEG pattern reflecting cortical disconnection (Spreafico *et al.* 1993, Steriade *et al.* 1994) seen in deep anesthesia or coma. Study of the morphology of the EEG bursts may give insights into the nature of the cerebral activity that generates them (Jäntti *et al.* 1994). Although the EEG waveforms could change from day to day in some of our cases, the complex but highly reproducible bursts of activity, whether spontaneous or evoked by stimulation, suggest a pathological network of interconnected neurons. The generalized distribution of the bursts and the lack of specificity of the stereotyped responses to varied stimulations suggest that such a network would have widespread connections either to, or within the cortex.

By contrast, EEG suppression indicates massive inhibition of the cortex, with persisting activity in 5% of cortical cells contrasting with 30–40% of the thalamic cells (Steriade *et al.* 1994). However, the existence of stimulus sensitivity, with motor and EEG changes in this state suggests preservation of at least some afferent and efferent connections to cortex. This is supported by the finding by Steriade *et al.* of sustained cortical activity following stimulation of the intralaminar centro-lateral thalamic nucleus during burst-suppression (Steriade *et al.* 1994). A propensity to stimulus sensitivity during burst-suppression would be facilitated by this thalamo-cortical interaction.

Alternatively, brain stem dysfunction resulting in “brain stem seizures” may be hypothesized, but brain stem circuitry is not sufficient to produce ictal myoclonic jerks (Kreindler *et al.* 1958). Thiopental-mediated depression of cortical activity may result in brain-stem disinhibition at

low doses, but at anesthetic doses, the effects of thiopental on the EEG are related to direct effects on cortical neurons (Lukatch and MacIver 1996).

Potentiation of GABA transmission commonly increases synaptic inhibition, leading to disconnection throughout thalamo-cortical systems. Most conventional treatment of status epilepticus is based upon pharmacological potentiation of GABAergic inhibition (Claassen *et al.* 2002). High doses of GABAergic medication (including thiopental in Cases 1, 2, 3 and 5) was of no benefit to any of our patients despite the absence of two commonly recognized factors leading to refractoriness to treatment, namely prolonged duration of status (Treiman *et al.* 1991) and late EEG stage prior to treatment (Treiman *et al.* 1992). Functional modification of GABA receptors (Kapur and Coulter 1995) as status epilepticus progresses, might explain resistance to benzodiazepines (Rice and DeLorenzo 1999) (as in Cases 1–6), phenobarbital (Borris *et al.* 2000) (as in Cases 1–6) and vigabatrin (Halonen *et al.* 2001) (as in Case 1). Despite the role of NMDA transmission as status epilepticus persists (Borris *et al.* 2000, Mewasingh *et al.* 2003), ketamine was ineffective in modifying the epileptic phenomena observed in response to stimulation in Case 1. This suggests that other mechanisms may be more relevant.

Jäntti's Case 2 (Jäntti *et al.* 1994) and our Cases 3 and 5 had chronic seizure disorders but no suggestion of stimulus sensitivity before the barbiturate treatment. This suggests that, paradoxically, high-dose treatment with GABAergic agents may promote the phenomenon in certain circumstances. Although the inhibitory action of GABA_A transmission is well established, increasing evidence of a depolarizing effect has recently been found in a variety of situations (Stein and Nicoll 2003, Gullledge and Stuart 2003, Cohen *et al.* 2002), including reduced *KCC2* gene expression (Hubner *et al.* 2001, Rivera *et al.* 2005). The latter has been associated with axonal damage (Nabekura *et al.* 2002) (documented in Case 1). Partial cortical deafferentation has been shown to promote epileptiform activity (Topolnik *et al.* 2003), though not solely as a result of pharmacological intervention.

Of the many antiepileptic drugs used in our patients, only halogenated agents appeared to suppress the phenomenon. Isoflurane was given in Cases 1 and 3, on the basis of its reported efficacy in refractory status epilepticus (Kofke *et al.* 1989, Mirsattari *et al.* 2004). However, its use was limited by tachyphylaxis (Ming *et al.* 2002) and it was replaced by halothane in Case 3, which proved effective. The mechanisms of action of halogenated agents are complex and not fully understood. Isoflurane and halothane are known to enhance GABA_A synaptic inhibition (Antkowiak 1999), and to block NMDA receptors (Ming *et al.* 2002, Kitamura *et al.* 2005). These mechanisms are shared by drugs that had no effect in any of the cases. However, halothane and isoflurane have also been shown to block gap junctions (Peracchia 1991). There has been mounting

evidence of a role for this non-synaptic transmission involved in neural synchrony in some epileptic processes (Traub *et al.* 2004). In particular, experimental work has shown that enhanced GABAergic activity with functional interneuronal connectivity via gap junctions is sufficient to trigger epileptiform activity in the absence of ionotropic glutamatergic transmission (Uusisaari *et al.* 2002). This might explain the emergence of the phenomenon we describe in the setting of intense GABA_A receptor activation.

There has been increasing awareness of the importance of recognizing heterogeneity in status epilepticus, underlining the need for more individually tailored approaches (Berg 2002). The stereotyped EEG and clinical manifestations suggest that this particular presentation is promoted by a neuronal network that involves the cerebral cortex, processes afferent information non-specifically, and gives rise to elemental motor responses. Stimulus sensitivity may appear in the context of refractory status epilepticus treated with high-dose barbiturates. Therefore, evaluation of children in refractory status epilepticus should include electroclinical assessment with multimodal sensory stimulation during EEG recording in the intensive care unit. Despite similarities with post-anoxic myoclonus, it is not exclusive to hypoxic-ischemic injury. Survival of four of our six patients suggests a possibly better outcome in children than in adults. This is also consistent with human and animal studies suggesting that the immature brain is more resistant to seizure and status epilepticus-induced damage than the adult brain (Haut *et al.* 2004). However, the phenomenon does not respond to conventional anti-epileptic drugs and might even be promoted by excessive GABA_A transmission. The failure to respond to increased GABAergic treatment and the effectiveness of isoflurane and halothane may point to the role of non-synaptic mechanisms such as gap junctions in maintaining epileptic activity. Further study of this phenomenon is required. In the meantime, we propose that once stimulus sensitivity is identified in the course of status epilepticus, GABAergic drug dosage should (at least) not be increased and the use of halogenated agents considered. □

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