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Status gelasticus associated with levetiracetam as add-on treatment

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ABSTRACT – We report the case of a five-year-old girl, presenting with difficult-to-treat, symptomatic focal epilepsy, who developed status gelasticus following the introduction of levetiracetam as add-on treatment to oxcarbazepine and diazepam. Gelastic seizures were documented by video-EEG and were responsive to i.v. administration of diazepam. A possible causative role of levetiracetam is suggested. Specific susceptibility to some AEDs is also discussed, as this patient, at the age of four years, had presented an episode of non-convulsive status epilepticus, following introduction of tiagabine, in association with vigabatrin and nitrazepam.
[Published with video sequences]

Key words: levetiracetam, children, status gelasticus, gelastic seizure, laughter

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Levetiracetam (LEV) is a new antiepileptic drug with a good pharmacokinetic profile. The drug is supposed to act by modulating the function of the synaptic vesicle protein SV2A in the brain (Lynch *et al.* 2004). Literature data underline a low incidence of adverse effects and drug interactions (Glauser *et al.* 2006; Coppola *et al.* 2004; Tan and Appleton, 2004). Nevertheless, a few cases of tonic-clonic and non-convulsive status precipitated by LEV have been reported in children and adults with refractory epilepsy, most often in mentally retarded patients, during the first two months of treatment and on relatively high doses (Nakken *et al.* 2003). Gelastic seizures, characterized by ictal stereotyped laughter in the absence of external precipitants, are quite uncommon and mostly associated with hypothalamic lesions (List and Bebin, 1956, Gascon and Lombroso, 1971; Striano *et al.* 2005; Iannetti *et al.* 1997); cryptogenic cases have been described as well (Arroyo *et al.* 1993; Striano *et al.* 1999).

We report on a five-year-old girl who developed "status gelasticus" (the term is used as suggested by Ng and Rekate, 2006), six days after the introduction of levetiracetam as add-on treatment for intractable focal seizures.

Case report

A five-year-old girl was admitted to our Department for intractable seizures. She was born at term, to

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unrelated, healthy parents after Caesarian section due to oligohydramnios. When she was eight months old, she presented with West syndrome. Cerebral palsy and a severe psychomotor delay were diagnosed. The patient presented with a double hemiplegia (the left side being more compromised than the right). Brain CT and MRI disclosed a marked loss of volume of the right hemisphere, probably due to intrauterine haemorrhage *(figure 1)*. The infantile spasms were treated successfully with ACTH, sodium valproate (VPA), nitrazepam (NZM) and vigabatrin (GVG). She then started having recurrent focal, sometimes secondarily generalized, seizures despite treatment with many antiepileptic drugs, variously associated, (carbamazepine, lamotrigine, phenobarbital, clonazepam, diazepam, oxcarbazepine, tiagabine, phenytoin). The seizures were mainly motor, never gelastic. Several EEGs showed the prevalence of a right occipital focus. When she was four years old, she presented with non-convulsive status epilepticus, attributed to concomitant tiagabine (TGB) administration (together with GVG and NZM), which was therefore, immediately stopped.

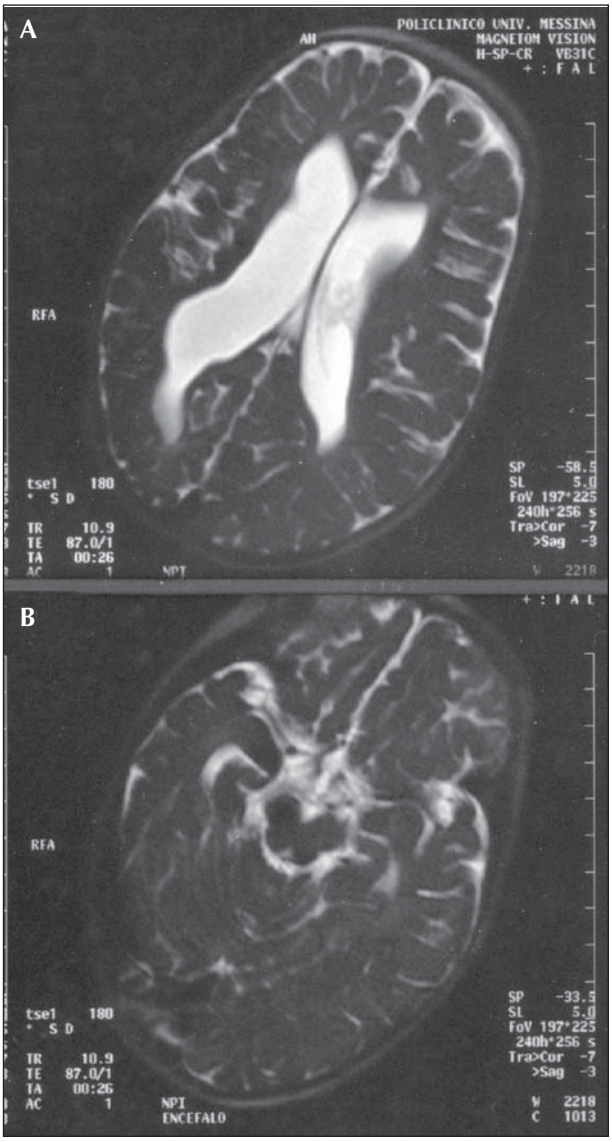

Figure 1. Brain MRI. **A**) Marked loss of volume in the right hemisphere. **B**) Absence of hypothalamic lesions.

Levetiracetam was added at the age of five years, at a dose of 125 mg/day (7.5 mg/kg/day) in association with oxcarbazepine (OXC) and diazepam (DZP); six days after, as soon as she reached the dose of 250 mg/d (15 mg/kg/d), she presented with status gelasticus. Seizures were characterized by paroxysmal, stereotyped and unprovoked laughter, lasting two-four seconds each, at intervals of about 15-20 seconds, during a total period of eight hours. During the episodes, the girl showed a brief loss of contact with her environment. Severe mental retardation and ictal loss of consciousness precluded the reporting of any possible emotional experience. No behavioural changes had been observed before the onset of status gelasticus.

Video-EEG was performed, demonstrating sub-continuous spike and wave-complexes, prominent over the right posterior regions, during the interictal phase *(figure 2)*. The onset of the ictal laughter was characterized by a sudden desynchronization of EEG activity, with disappearance of right posterior SW complexes, sometimes immediately followed by recruiting, rapid low-voltage rhythms in the same regions. Whenever the seizure ended, right posterior SW complexes appeared again *(see video sequence)*. Status gelasticus ended after iv administration of DZP. Levetiracetam administration was discontinued. During the following three years, the patient did not present a similar episode of status gelasticus or any gelastic seizures. The EEG still shows a right occipital focus, however less active than before.

Discussion

Gelastic seizures are quite rare as they account for less than 1% of all epilepsy seizures. The diagnostic criteria include stereotypy, lack of external precipitants, abnormal ictal or interictal EEG (Chen and Forster, 1973). They may appear alone or combined with other types of seizures. Most cases are symptomatic and attributed to hypothalamic hamartomas; some cryptogenic cases have also been described (List and Bebin, 1956; Gascon and Lombroso, 1971; Striano *et al.* 2005; Iannetti *et al.* 1997; Arroyo *et al.* 1993; Striano *et al.* 1999).

Laughter is considered to be the consequence of an automated motor program; many structural and functional anomalies may be involved in the pathogenesis of ictal laughter (thalamus, hippocampus, temporal lobes, primary and sensory motor areas). Recently, Schmitt *et al.* (2006) have assumed that the anterior portion of the right supplementary sensorimotor area (SSMA)/lateral premotor

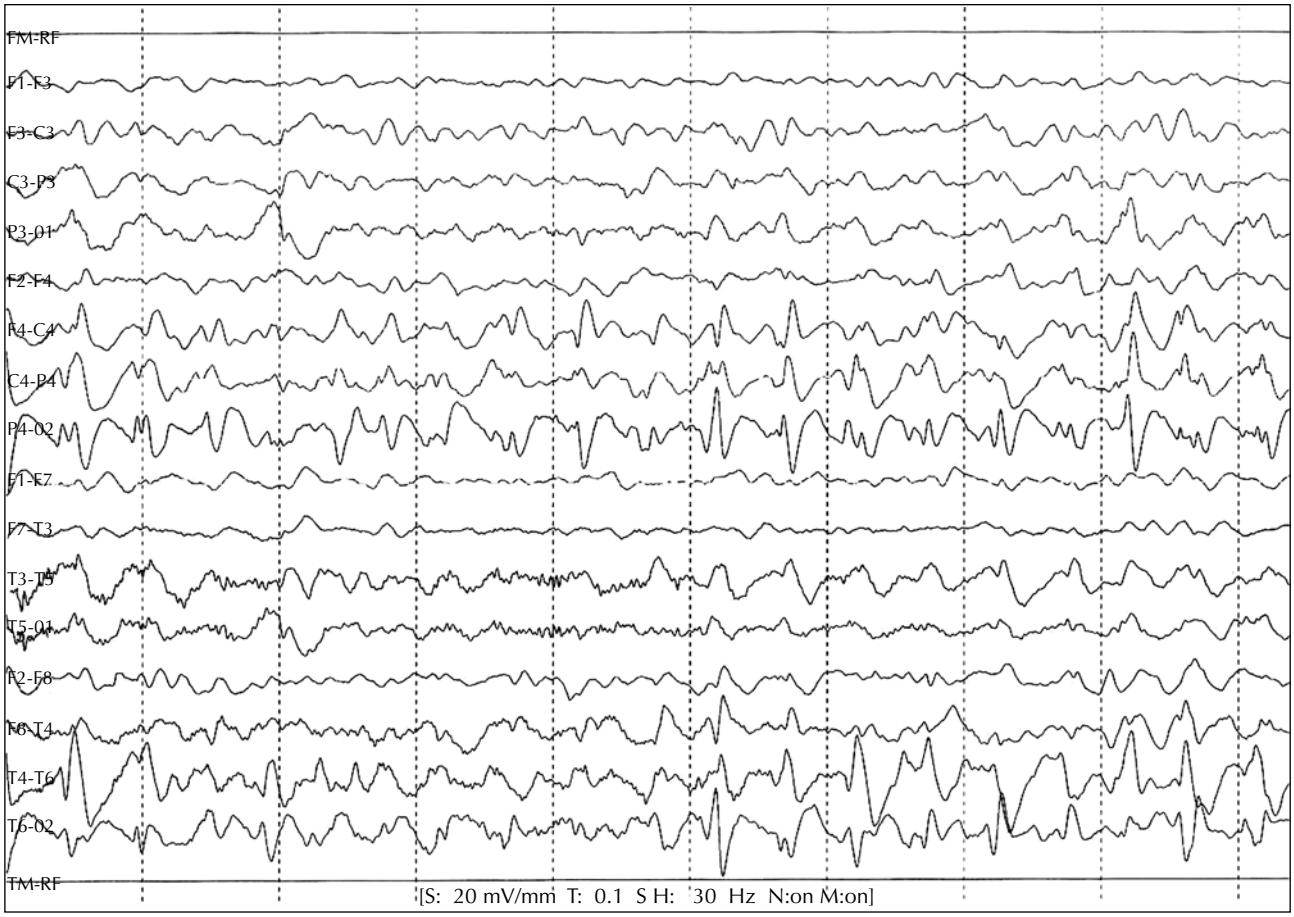

Figure 2. Interictal EEG: subcontinuous spike and wave-complexes, prominent on the right posterior regions.

cortex is involved in generating the motor pattern of laughter; a similar conclusion was reached by Sperli *et al.* (2006). Laughter's emotional content (mirth) has been assumed to be processed by basal temporal cortex (Papez, 1937; Dericioglu *et al.* 2005; Satow *et al.* 2003; Arroyo *et al.* 1993).

EEG recordings usually show frontal or temporal paroxysms, either in the ictal or interictal phase; however, gelastic seizures have rarely been associated with a different focus (Hashiya *et al.* 1991; Arroyo *et al.* 1993; Shin *et al.* 2006).

Our patient is affected by symptomatic focal epilepsy with recurrent, difficult-to-treat seizures, probably due to marked loss of volume in the right hemisphere following intrauterine haemorrhage. No hypothalamic lesions were detected by brain MRI.

The evidence of a right-sided occipital focus, although never described before, underscores the need to further elucidate the complexity of the cortical-subcortical gelastic network.

Our patient had never presented with gelastic seizures before being treated with levetiracetam. Furthermore, three years after levetiracem discontinuation, gelastic seizures have never recurred. The strict temporal relationship between levetiracetam treatment and the onset of status gelasticus suggests a possible causative role of LEV, although we cannot rule out the involvement of other factors.

To our knowledge, this is the first report of status gelasticus induced by levetiracetam treatment. Levetiracetam is a well-tolerated antiepileptic drug, efficacious for the treatment of focal, generalized tonic-clonic and myoclonic seizures (Glauser *et al.* 2006; Coppola *et al.* 2004; Tan and Appleton, 2004). LEV does not seem to act by way of any of the main mechanisms currently accepted for the antiseizure action of established AEDs. Lynch *et al.* (2004) identified SV2A as the binding site for LEV. The molecular action of SV2A is still unknown. Nakken *et al.* (2003) reported some cases of non-convulsive and generalised tonic-clonic status epilepticus as a paradoxical effect of levetiracetam and suggested a few risk factors such as presence of mental retardation and doses > 20 mg/kg/d, children being more susceptible than adults. Our patient had severe mental retardation, but the dose of LEV was not

Legend for video sequences

Video-EEG performed during the occurrence of status gelasticus (no voice): seizures were characterized by paroxysmal, stereotyped and unprovoked laughter, lasting two-four seconds each, at intervals of about 15-20 seconds. EEG demonstrated sub-continuous spike and wave-complexes, prominent on the right posterior regions, during the interictal phase. The onset of the ictal laughter was characterized by a sudden desynchronization of EEG activity, with disappearance of right posterior SW complexes, sometimes immediately followed by recruiting rapid low-voltage rhythms on the same regions. Whenever the seizure ended, right posterior SW complexes became evident again.

higher than 15 mg/kg/d. Our case report, although isolated, suggests the possible occurrence of status gelasticus following treatment with levetiracetam. Additional risk factors should be further investigated and specific susceptibility for some AEDs, taking into account induction of NCSE following introduction of tiagabine, envisaged. □

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