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ORIGINAL ARTICLE

Levetiracetam eff cacy in patients with Lennox-Gastaut syndrome. Presentation of a case

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Abstract
Introduction: The Lennox-Gastaut syndrome (LGS) is one of the most severe epileptic encephalopathies of childhood, characterized by electro-clinical triad of generalized peak-slow wave activity (PSW) in the electroencephalogram (EEG), multiple types of seizures and development delay. This paper intends to describe the syndrome in a patient with a history of hypoxic-ischaemic encephalopathy and Lennox-Gastaut syndrome, and a good response to treatment with levetiracetam (LEV).
Method: Descriptive study on the development of a 3 year old child with intrauterine asphyxia, multi-organ failure, metabolic acidosis, hypovolaemic shock, and seizures with cerebral oedema, who developed a W est syndrome, resistant to drug treatment. The semiology of seizures progressively changed to generalized episodes of hypertonia and myoclonus, with slow spike-wave electroencephalographic activity.
Results: With the diagnosis of Lennox-Gastaut syndrome the patient was treated with levetiracetam, showing a substantial improvement in the cognitive sphere, in the control of seizures, and electroencephalographic f ndings.
Conclusions: Lennox-Gastaut syndrome is one of the most severe epileptic syndromes in paediatric patients. Levetiracetam can help cognitive improvement, and contribute to seizure control in these patients.

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PALABRAS CLAVE
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Levetiracetam

Ef cacia del levetiracetam en pacientes con síndrome de Lennox-Gastaut. Presentación de un caso

Resumen
Introducción: El síndrome de Lennox-Gastaut (SLG) es una de las encefalopatías epilépticas más severas de la infancia, caracterizada por la tríada electroclínica de actividad generalizada de punta onda lenta (POL) en el electroencefalograma (EEG), múltiples tipos de crisis epilépticas y retraso mental. Con este trabajo pretendemos describir el cuadro sindrómico en un paciente con antecedente de encefalopatía hipóxico-isquémica y SLG, y su respuesta al tratamiento con levetiracetam (LEV).
Método: Estudio descriptivo evolutivo de un niño de 3 años con antecedentes obstétricos de asf xia intrauterina y repercusión multiorgánica, acidosis metabólica, shock hipovolémico y crisis convulsivas con edema cerebral que a los pocos meses de edad desarrolla un síndrome de West, resistente al tratamiento farmacológico. P rogresivamente, la semiología de las crisis cambia a episodios de hipertonía generalizada y mioclonías, con actividad electroencefalográf ca de punta-onda lenta.
Resultados: Con el diagnóstico de SLG se inicia tratamiento con LEV , observándose una mejoría sustancial en la esfera cognitiva, en el control de las crisis, y en los hallazgos electroencefalográf cos.
Conclusiones: El SLG es uno de los síndromes epilépticos más graves en los pacientes pediátricos, tanto por su semiología como por su farmacorresistencia. El levetiracetam puede producir una mejoría cognitiva, además de contribuir al control de las crisis en estos pacientes.

Introduction

Lennox-Gastaut syndrome (LGS) is an entity comprising the triad of the following electro-clinical f ndings: *a*) intercritical EEG with generalized PSW from 1.5 to 2.5 Hz while awake and generalized paroxysms of rapid rhythmic activity during sleep, *b*) different types of crisis, including tonic crises, atypical absences and drop attacks, and *c*) delay in mental development and/or behavioural alterations. However, there is still no consensus on how to name this illness if any of the three characteristics described above is not present.[1] The classif cation of epilepsies and epileptic syndromes proposed by the ILAE in 1989 included this syndrome as cryptogenic epilepsy or generalized symptomatic epilepsy, def ned as follows: "LGS appears in children from 1 to 8 years of age, but mainly appears in preschool children. The most frequent types of crisis are tonic axial crises, atonic crises and absence seizures, although it is frequently associated with myoclonic, tonic-clonic generalized or partial crises. The frequency of the crises is high and the epileptic status is frequent. The EEG generally has an abnormal baseline activity, PSW < 3 Hz, and multifocal abnormalities. During sleep, fast-cycling paroxysms (10 Hz) present. In general, these children present mental impairment. Their crises are dif f cult to control and the outlook is generally unfavourable. In 60% of cases, the syndrome occurs in children with a history of prior encephalopathy, but it may be primary in others".[2]

From the therapeutic standpoint, there is no uni f ed agreement about which drugs manage to achieve the greatest ratio of effectiveness/tolerability in this syndrome as, in general, none of them is able to control crises in isolation nor to stop the cognitive or behavioural impairment.

The association of valproic acid with lamotrigin and topiramate constitutes the treatment of choice.[3,4] Lamotrigin has been shown to be useful, particularly for controlling atonic crises with falls.[5] Felbamate has been effective in some cases, as it has been shown to diminish the number of crises by 50%,[6] but its use is currently limited because of its toxicity . Although the usefulness of carbamazepine and vigabatrin has been indicated, their use may entail risks, as they can exacerbate the absence seizures or trigger a non-convulsive epileptic state.[7]

Other therapeutic alternatives have been used, such as ACTH and corticosteroids, a cetogenic diet and immunotherapy.[8,9] Callosotomy has been shown to have transient effects on the control of falling.[10]

We describe here the case of a 3-year-old child with a history of hypoxic-ischaemic encephalopathy and LGS who presented a strikingly favourable evolution after treatment was started with levetiracetam.

Method

A longitudinal descriptive study has been carried out over 2 years on a 3-year-old male known to our Hospital from the age of 22 months, who came to the neuropaediatric clinic for assessment and monitoring of the progress of a perinatal

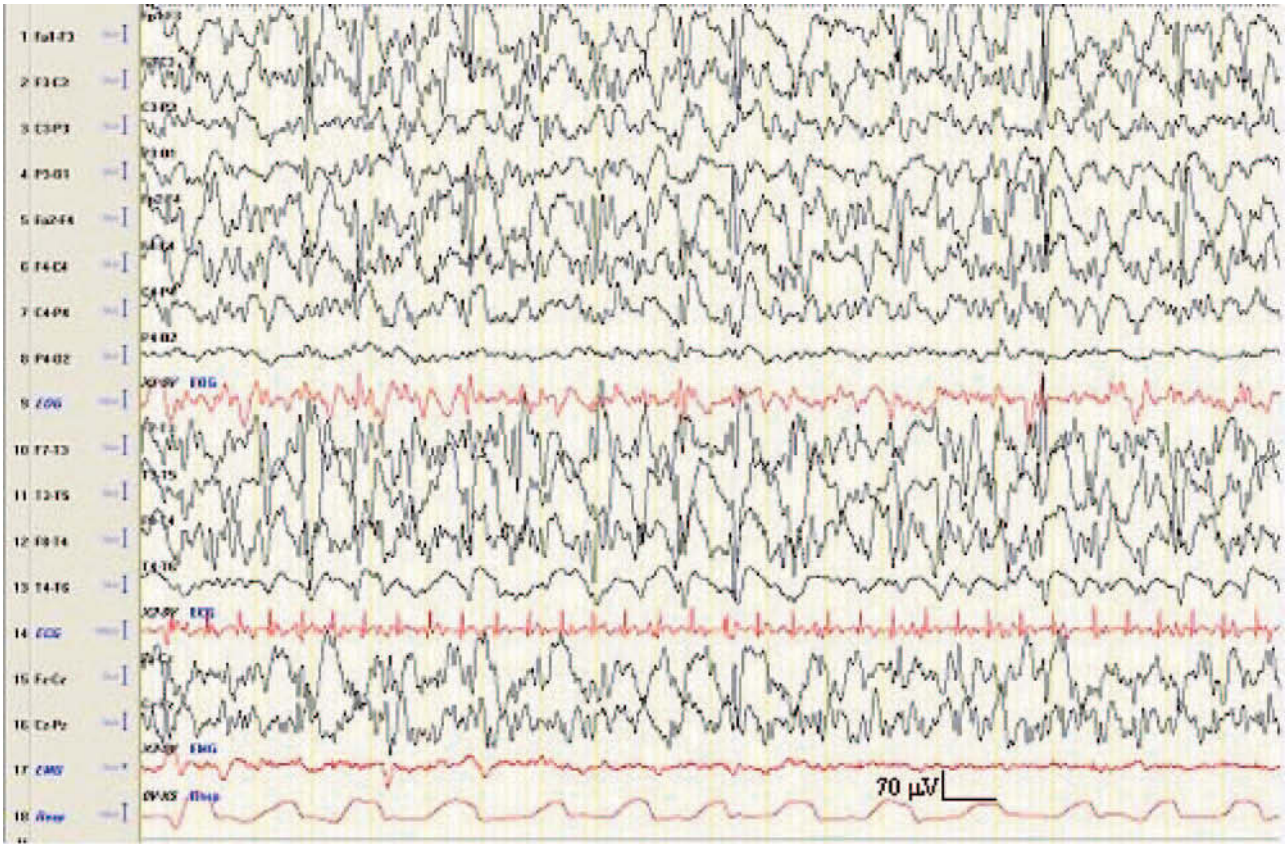

Figure 1 EEG polygraph showing disorganization of the brain' background activity together with the presence of multifocal/ diffuse paroxysms with acute waves and peak-slow wave, of greater amplitude in anterior regions. Time constant: 0.3 seconds. High frequency f lters: 35 Hz.

hypoxic-ischaemic encephalopathy . His personal history included a controlled pregnancy. Caesarean section at 39+2 weeks due to a suspicion of foetal distress. Score of 5 on the Apgar test (at 5 minutes of life), intrauterine pH was 6.97 and the pH of the umbilical cord was 6.05. he was admitted to the neonatal ICU for 23 days. During his admission, he presented convulsive tonic seizures affecting all four limbs from 28 h of life, and so was treated with phenytoin and phenobarbital. The cerebral MR scan identi f ed f ndings compatible with severe hypoxic-ischaemic encephalopathy, involving both hemispheres and the corticospinal tracts, accompanied by metabolic alterations in connection with diffuse ischaemia. He was discharged with diagnoses of intrauterine asphyxia with multi-organ repercussions: metabolic acidosis, hypoglycaemia, hypovolaemic shock with ischaemic cardiopathy , disseminated intravascular clotting, pulmonary hypertension with bleeding, hepatic lesion, digestive bleeding, kidney failure and convulsive seizures with cerebral oedema.

He was monitored at the neuropaediatric clinic of his hospital of origin, where he was prescribed treatment with vigabatrin, valproic acid and lamotrigin, and he was diagnosed as having a secondary West syndrome.

On arrival at our hospital, he was reported to suffer from sporadic crises (once a month) with hypertonia of the right side of the body , lasting for 1 m. He presented severe microcephalia and severe spastic paraplegia, with no connection with the observer and absence of voluntary movements.

A video-electroencephalographic study of spontaneous daytime wakefulness and sleep was conducted (with sleep deprivation) which revealed the existence of disorganization of the brain' s background bioelectrical activity , with a generalized slowdown of the same, with great amplitude, and on which abundant multifocal epileptiform anomalies were seen (acute wave, peak and peak-wave paroxysms), diffusely, although with more amplitude in fronto-central areas. Furthermore, from the clinical standpoint, the study showed some isolated spasmodic movements of the trunk and limbs appearing predominantly in f exion.

After a year without attending appointments, he came back to the clinic due to clinical worsening with the onset of daily crises of generalized hypertonia lasting for 15 s, as well as other bouts of gaze deviation and the buccal commissure, lasting for seconds. Myoclonic crises of the right hand side of the body were also observed. An EEG study of spontaneous daytime wakefulness and sleep was conducted (with sleep deprivation) and it revealed the existence of disorganization in the brain' s background bioelectrical activity, with a generalized slowdown of the same, as well as the existence of abundant multifocal epileptiform anomalies (acute wave, peak and peak-wave paroxysms at about 2 Hz), with diffuse presentation, persistent and greater amplitude in anterior areas (f g. 1).

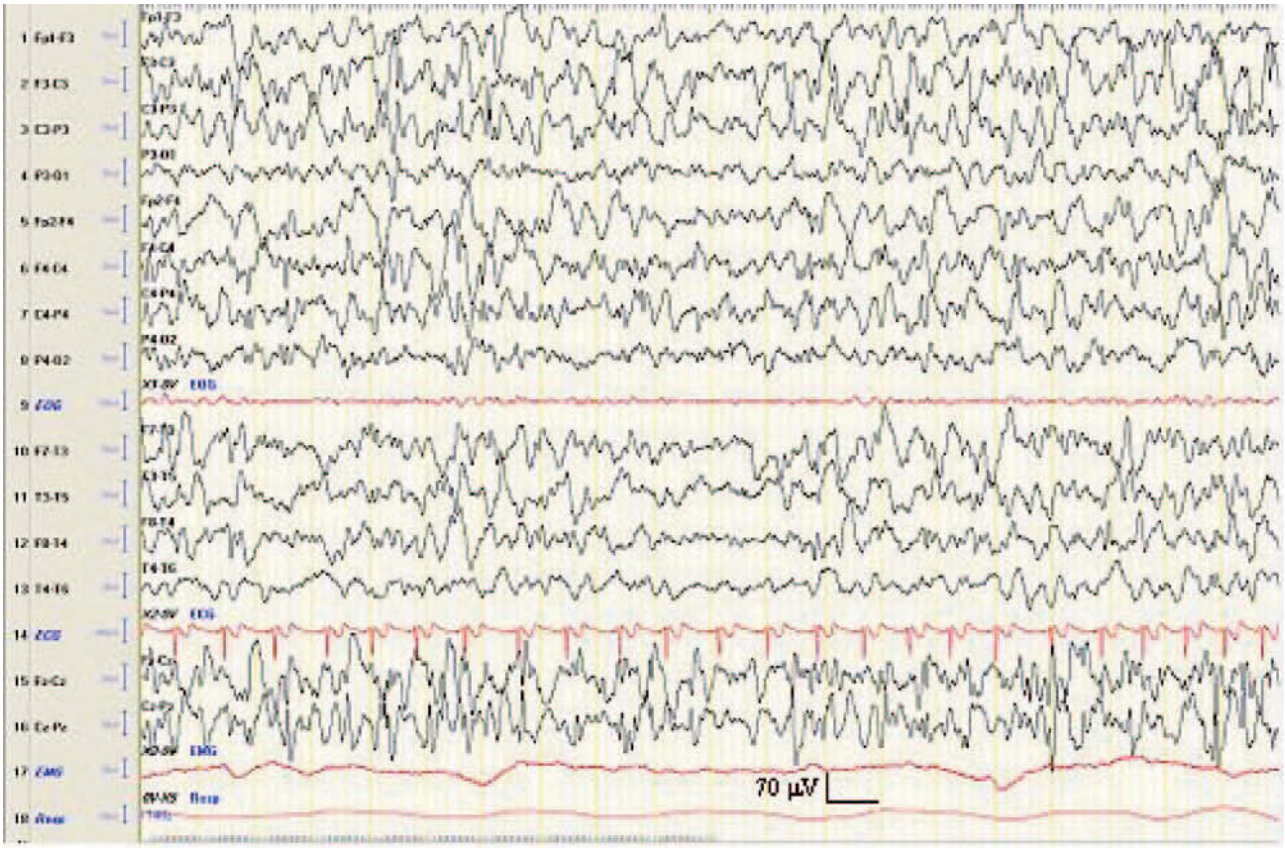

Figure 2 EEG polygraph after several months of treatment revealing an improvement in the brain' s background bioelectric activity, as well as a reduction in the amplitude and persistence of epileptiform anomalies. Time constant: 0.3 seconds. High frequency f lters: 35 Hz.

Results

The electro-clinical correlation leads us to think at this moment that it is an LGS that has evolved from a W est syndrome. Treatment was then started with levetiracetam at 35 mg/kg, bringing about an evident clinical improvement, with disappearance of the tonic and myoclonic crises, and reduction in the absences, as well as a clear improvement in social interaction.

The subsequent EEG tests performed showed an improvement in the background activity , with a gradual reduction in amplitude and persistence of the epileptiform anomalies (f g. 2).

Discussion

LGS is one of the most serious epileptic syndromes described in paediatric ages.[11] It is included in the classf cation of the ILAE in the epilepsy and generalized syndromes group with a symptomatic or cryptogenic cause. The estimated incidence is 0.1 per 100,000 inhabitants, but its prevalence is high (5-10%) due to the high level of resistance to the different anti-epileptic treatments (it represents from 1 to 4% of all epilepsies).[12,13]

From the pathophysiological standpoint, the most widely-accepted theory is that LGS is the result of a complex interrelation of a multifocal or diffuse cortical and sub-cortical involvement occurring at a precise time during the brain's maturing period.[1]

LGS mainly involves the frontal lobes, re f ected in the cognitive impairment pattern including, for example, fast data processing and anticipation; furthermore, PSW activity predominates in the frontal lobes. The age of onset of LGS also corresponds to the maturing of the anterior parts of the brain, as well as to the myelinization of the anterior part of the *corpus callosum*, which occurs in the second year of life to allow the synchronization of both frontal lobes.

From the aetiological standpoint, the most frequent form is symptomatic (30-75%), with a history of perinatal asphyxia, sequelae of meningoencephalitis, tuberous sclerosis, cortical dysplasias, cranioencephalic trauma and, less frequently , associated with tumours or metabolic disorders.[14]

The most relevant clinical manifestations to establish the diagnosis are:[15]

1. Tonic crises: these are the most frequent (17-92%), particularly during slow sleep.
2. Atonic crises (26-56%): these are the cause most frequently responsible for falls, and may be very short-lasting.
3. Atypical absences (20-65%): with diminished levels of consciousness and with less brusque starting and ending points than in typical absences.

Other types of crises that may be associated are generalized tonic-clonic seizures, partial seizures and spasms.

As for progress and prognosis, it must be borne in mind that this is one of the most acute treatment-resistant forms of epilepsy in infancy, frequently progressing towards mental impairment. The worst prognosis corresponds to the group of symptomatic LGS, especially when a West syndrome has been suffered (27-54% of cases evolve towards LGS). Negative electro-clinical markers are: high frequency of crises, repetitive epileptic states and a constantly slowed-down bioelectrical background activity in the brain.[16]

The pharmacological treatment of LGS is complicated and normally requires the use of polytherapy, with disappointing results in most cases. Different combinations of anti-epileptic drugs have been used and there is little scientific evidence for each of them. The ones most often studied are valproic acid, felbamate, lamotrigin, topiramate and, more recently, rufinamide. There are no controlled studies on levetiracetam supporting its use, but there are some studies that have mentioned a possible beneficial effect in these patients.[17-19]

In the bibliography consulted, there are strikingly few papers correlating the clinical improvement (when present) with favourable electroencephalographic progress.

In a paper carried out at the Children's Hospital at the University of Arkansas, 6 patients with LGS were studied and levetiracetam was added to their treatment, with a reduction in the number of clinical crises and epileptiform electroencephalographic activity. All the patients experienced an improvement in the control of their crises, with a particular reduction in myoclonic crises. It is important to point out the improvement in degree of alertness in 3 of these patients, which coincides with the observations found in our case. The most frequent adverse effect was irritability, especially at the start of treatment. The starting dose was 10 mg/kg of bodyweight per day, with a mean dose of 48 mg/kg/day.[19] In our patient, the beneficial effect was observed even before this dose was reached.

However, there are other papers in which the results are more controversial. In 2004, Huber et al.[20] analyzed the efficacy of LEV on 46 patients with refractory epilepsy and learning disorders of which 7 cases presented LGS. Of these cases, 85% (6 in total) did not adequately respond to treatment, with these negative efficacy data being significant (p = 0.028) versus refractory epilepsies of other aetiologies. Furthermore, a positive psychotropic effect was observed with this drug, but only in patients not affected by LGS.

In that same year, Weber et al.[21] assessed the efficacy of LEV on 10 patients with generalized epilepsy. Among those patients, the authors included 4 cases of LGS. The results were highly disparate: they found 2 cases (50%) of relative improvement in the number of crises (35 and 40%, respectively), 1 case of worsening (a 25% increase in the number of crises) and the last patient withdrawn, once more because of cognitive adverse effects. In this study, the authors have not reflected the positive evolution of cognitive involvement, suggesting however, the possible negative effect at the behavioural level.

In 2006, Labate et al.[22] published an observational study of 35 patients with different types of generalized epilepsy in which myoclonic crises predominated, including 2 patients with LGS. In this paper, the treatment results were not very homogeneous. In one case, it was necessary to suspend treatment due to a worsening in the number of crises and the other case (the child of least age) experienced an improvement of between 50-99% in the number of crises.

Nonetheless, in all the studies consulted, as in our case, myoclonic crises were those that responded best to treatment with LEV.

In the light of the results obtained and after comparing the different studies published on the subject in question, we can point out that LGS is one of the most severe epileptic syndromes among paediatric patients, frequently requiring the use of polytherapy. Levetiracetam may bring about a cognitive improvement in addition to contributing to the control of crises in these patients, fundamentally myoclonic seizures. The electroencephalographic findings and the electro-clinical correlation are extremely valuable tools for predicting the evolution of the condition and the possible response to treatment.

Finally, we wish to stress the need for further studies on the subject in order to help clarify the therapeutic bases of this syndrome.

Conflict of interest

The authors declare that they have no conflict of interest.

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