

CLINICAL CASE

Use of flunarizine in a case of Landau-Kleffner syndrome

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ABSTRACT

Background. Landau-Kleffner syndrome is characterized by acquired aphasia and electroencephalographic abnormalities during wakefulness and sleep. These abnormalities can be solved with anticonvulsive medications, but speech and behavioral problems cannot be treated using this therapy. Instead, there are reports that indicate that treatment with high-dose corticosteroids during early stages of the disease improves the speech difficulties. Use of calcium antagonists has also been proposed as possible treatment.

Case report. We report the case of a 5-year-old patient with normal development until the age of 2 years. At that time, the parents observed loss of spontaneous acquired speech. During neurological evaluation, the child showed abundant echolalia and indifference to external stimuli. Electroencephalogram showed sharp waves and generalized slow spike-wave complexes of 3-4 Hz during sleep. We began treatment with prednisone and valproic acid for 1 month; flunarizine was added. After 4 months of treatment the patient showed speech improvement.

Conclusions. Our case has the characteristic clinical and electroencephalographic findings of Landau-Kleffner syndrome. We observed significant symptom improvement when flunarizine was added to the treatment. This evidence offers support for the use of a calcium antagonist as possible therapy, which may help setting the way for future controlled studies in order to finally establish its utility with this illness.

Key words: Landau-Kleffner syndrome, acquired aphasia, calcium-antagonist, flunarizine, electroencephalogram, spike wave complexes.

INTRODUCTION

Landau-Kleffner syndrome (LKS), also known as acquired epileptic aphasia, was described for the first time in 1957 by Landau and Kleffner in six children with a history of normal language acquisition, but who later developed acquired aphasia with convulsive disorder.¹ The disease is observed with greater frequency in males than in females, between 3 and 5 years of age, and with prior normal psychomotor and language development.^{2,3} Language disorder is the first clinical manifestation and, in most cases, receptive language is the first to show abnormalities.⁴ It is at this stage of the disease that suspicion arises about the patient's deafness, and studies are carried out to assess hearing which in most cases is normal. Subsequently, there are also changes in expressive language such as omissions

and paraphasias that progress to a lack of language. It is often accompanied by behavioral disorders such as hyperactivity (which is the most common), indifference to the environment and, in many cases, autistic behavior is observed.^{5,6}

Electroencephalogram (EEG) abnormalities are part of the syndrome, although seizures occur in only 70-80% of cases.^{7,8} EEG may show normal activity, although it is common to see outbreaks of spikes, sharp waves or slow spike-wave complexes in temporal and parieto-occipital regions unilaterally or bilaterally. Some authors suggest that continuous slow spike-wave complexes of 1.5-5 Hz in at least 85% of the recordings in non-REM sleep may be characteristic of LKS.^{3,9-11}

In recent years, findings of magnetoencephalography (MEG) in patients with LKS have been described. The MEG suggests that bilateral epileptic activity is generated in the auditory and perisylvian cortex associated with language in >80% of patients.^{12, 13} Pateau reported that 20% of cases have unilateral perisylvian activity, which is subsequently projected to contralateral regions.¹⁴

The clinical course of the disorder is variable. Typically, seizures are controlled and EEG abnormalities tend to disappear with time, but the duration of aphasia is unpredictable and is not dependent on the presence of seizures or age of onset.^{15,16}

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In most cases it is not possible to establish the etiology. However, there are causal theories about the condition, among them an autoimmune origin. Nevsimalova et al. demonstrated the production of antibodies against central myelin.¹⁷ Other causes put forward are infections, arteritis, temporal tumors, cysticercosis, demyelinating disease, neuronal migration disorders and one case associated with complex I mitochondrial respiratory deficiency.¹⁸⁻²³

Anticonvulsant therapy has shown efficacy in controlling seizures, but its effectiveness in the management of language and behavior problems is scanty. Even drugs such as phenobarbital, carbamazepine and phenytoin may worsen seizures, whereas the first choice drugs are valproic acid (VPA), levetiracetam, lamotrigine, ethosuximide and clobazam.²⁴⁻²⁷ The treatment with the best results has been the use of steroids, including prednisone, methylprednisolone, and adrenocorticotrophic hormone (ACTH). Use of steroids has been substantiated by several authors who demonstrated their effectiveness. When used in early stages and at high doses, it is possible to see improvement in language, normalization of EEG changes and also seizure control.²⁸⁻³⁴ Use of intravenous immunoglobulin in LKS is also included among the therapeutic options; however, the evidence is insufficient to consider this treatment modality superior to the use of corticosteroids and/or anticonvulsives.^{35,36} Other forms of treatment are the ketogenic diet and vagal stimulator, but there are insufficient studies to determine their effectiveness.^{37,38} In general, there is no consensus on the drug treatment because there have been no controlled studies that establish the dose and duration of drug treatment or whether these drugs can be used alone or in combination. Surgical treatment using multiple subpial transections in the epileptogenic cortex has been used in patients where therapy with corticosteroids and anticonvulsants has failed and seizure activity is unilateral.

This case reported a significant improvement in seizures, behavioral disorders and language.^{37,39-41} The clinical findings and response to drug therapy in a patient with LKS are described.

Case Report

We present the case of a 5-year-old female who was the product of the second pregnancy, with a normal neonatal period. The parents were young, nonconsanguineous, and without family history of epilepsy. Psychomotor and language development were normal until 2 years of age when

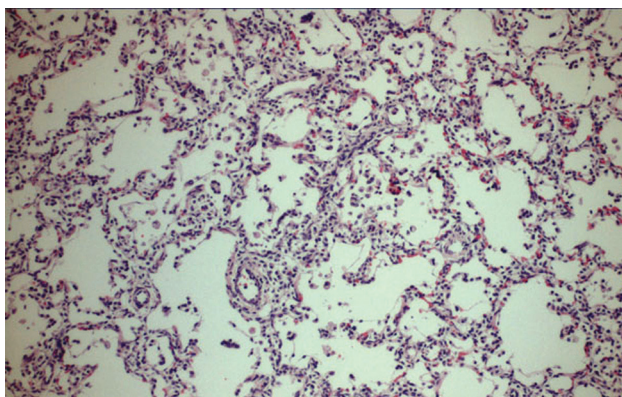
the parents noticed a lack of response to simple commands and indifference to external stimuli. The patient showed progressive loss of spontaneous speech with echolalia and at 3 years of age began speech therapy for a year without improvement. Hearing loss was ruled out by conducting brain-stem evoked potentials, and the patient was referred for neurological evaluation. During the interview, abnormal movements, ritualistic behaviors, stereotypes, or loss of eye contact were ruled out. The patient was found to have abundant echolalia, obeyed simple commands slowly, had proper visual contact but was indifferent to external stimuli, and abnormal movements were not appreciated. The patient did not meet DSM-IV criteria for diagnosis of autism during the neurological assessment. EEG was performed at rest, awake, and during non-REM sleep, in which intermittent bursts of sharp waves and slow spike-wave complexes of 3-4 Hz generalized during sleep were seen (Figure 1A). During the awakened state, no paroxysmal activity was observed (Figure 1B). Simple and contrast computed tomography (CT) of the brain were normal.

Treatment with valproic acid (VPA) at 20 mg/kg/day and prednisone (1 mg/kg/day) was initiated, and speech therapy was continued. A month later the patient improved spontaneous speech, speaking from five to ten words, although echolalia persisted. Responsiveness to external stimuli and response to simple questions was also enhanced. Prednisone was administered for 1 month and gradually discontinued. VPA and speech therapy were continued. After 4 months of treatment initiation, physiological sleep EEG was performed with isolated bilateral frontocentral sharp waves observed with normal sleep rhythms for age (Figure 2). Despite the persistence of echolalia, the spontaneous speech increased, and the patient was able to form sentences of three to four words and had a partial improvement in receptive language. VPA was continued at 25 mg/kg/day and it was decided to begin flunarizine (FNR) at doses of 2.5 mg/day. After the initiation of FNR, improvement was observed in the amount of vocabulary, pronunciation of more than 100 words and the ability to initiate a spontaneous conversation; echolalia persisted in lower amount. The parents mentioned that the patient began to exhibit aggressive behavior and FNR was suspended. At the following office visit, the parents and therapist mentioned a significant decrease in spontaneous language; therefore, the drug was reinstated at a dose of 1.5 mg/day.

At 20 months of treatment a control EEG was performed with induced sleep with chloral hydrate in which no paroxysmal activity was observed (Figure 3). At 24 months with VPA, FNR and speech therapy, no behavioral changes or other adverse events were reported. The amount of spontaneous speech increased considerably and, until the most recent evaluation, the patient was free of seizures.

Neuropsychological evaluation was performed at 24 months with drug treatment. Evaluation revealed a verbal IQ of 70, non-verbal of 88, mild deficit in visual memory, verbal memory, spatial skills, visuomotor and construction skills. The expressive language was mildly affected but the receptive language showed severe deficit.

1. A



1. B



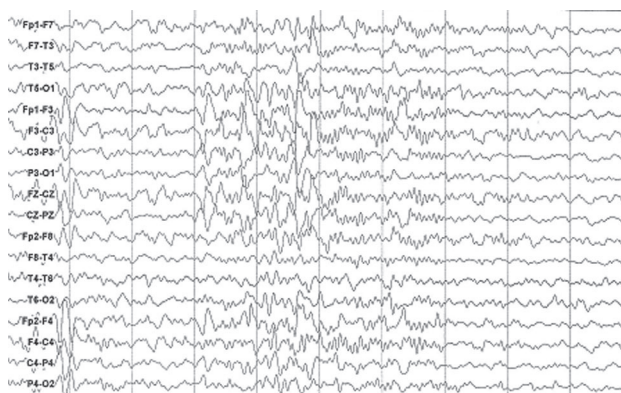
Figure 1. (A) EEG during physiological sleep with widespread bursts of slow spike wave complex of 3-4 Hz. **(B)** Awake state EEG with normal background rhythm for age and no evidence of paroxysmal activity.

DISCUSSION

Loss of previously acquired language is a diagnostic challenge in which different entities must be ruled out such as autism, anxiety disorders and neurodegenerative diseases. A careful evaluation should be done. A complete medical history with emphasis on neurodevelopment and the type of diagnostic elements to be applied to each case should be evaluated in an individualized manner.

The interview and physical examination assists in choosing the cases that will benefit from studies such as brain magnetic resonance image (MRI), EEG and/or expanded metabolic screening because up to now there is no diagnostic algorithm described for this condition. The performance of EEG provides valuable information even

2. A



2. B

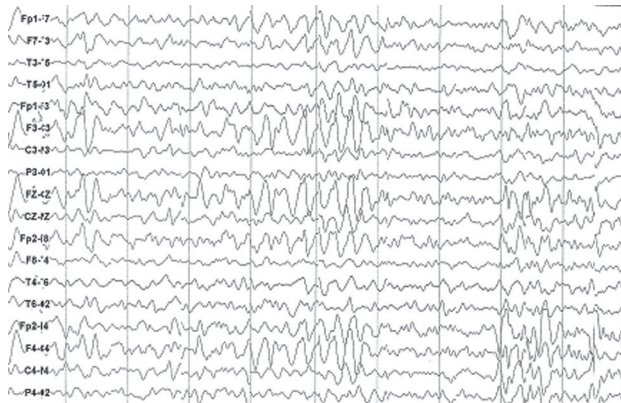


Figure 2. (A) EEG at 4 months after initiation of drug treatment in physiological sleep where there are vertex sharp waves, sleep spindles and K complexes, characteristic of phases II-III non-REM sleep. **(B)** Same tracing where there are isolated sharp waves seen in the bilateral frontocentral regions.

in cases without neurological symptoms and is particularly useful for distinguishing between aphasic disorders affecting language development.

LKS is a rare condition whose diagnosis is primarily done according to clinical data. It is characterized by acquired aphasia and EEG abnormalities during wakefulness and during sleep with or without clinical seizures. In this case, EEG abnormalities in sleep consisting of slow spike wave complexes of 3-4 Hz were instrumental in establishing the diagnosis. This abnormality is considered by many authors as a major feature of the syndrome that should be observed in 85% of recordings in non-REM sleep.^{3,9-11} Although it was not possible to perform a complete EEG study during sleep, clinical manifestations and EEG abnormalities are sufficient to support this diagnosis.

It is important to distinguish LKS from an epileptic disorder with continuous slow spike waves during sleep (EPOCS), which is an epileptic syndrome characterized by the association of various types of partial and/or generalized seizures during sleep and atypical absences during awakeness.^{42,43} Other symptoms of this condition are neuropsychological and behavioral problems, decreased IQ and language abnormalities,⁴⁴ transient motor disorders such as ataxia, dyspraxia or dystonia,^{45,46} and characteristic EEG abnormalities with continuous spike wave activity during non-REM sleep in >85% of the recordings. For some authors, both conditions could be considered as different clinical presentations of the same entity as determined by the location of the epileptic region,¹⁰ but other authors

claim that the neuropsychological manifestations and EEG findings are different for each disorder.⁴⁷

This patient showed a partial response to conventional treatment with steroids and anticonvulsants for the language disorder; therefore, it was decided to add FNR. This drug is frequently used as prophylaxis for migraine in children and has also proven useful in refractory epilepsy as concomitant treatment with antiepileptics. However, to our knowledge, there is no precedent for its usefulness in patients with LKS.⁴⁸⁻⁵¹ In previous studies, Pascual-Castroviejo et al. reported improvement in speech, behavior and EEG changes in seven patients with LKS treated with a calcium channel blocker (nicardipine) at doses of 1 to 2 mg/kg/day for periods ranging from 2 months to 9 years. In these cases the use of nicardipine was based on the finding of cerebral arteritis by angiography.^{52,53}

The prognosis of the syndrome is benign because seizures can be easily treated although the same cannot be said on language recovery and behavior that, in most cases, are incomplete. In our case the improvement in receptive and expressive language with FNR treatment was evident in further neurological examinations as well as in the evaluations made by different specialists and also noticed by the parents. It is evident that our patient had problems with language as well as in other cognitive areas. In the study by Eslava-Cobos and Mejía, it was reported that in addition to the language alterations, in LKS there are alterations in behavior and other higher cognitive functions.⁵⁴

In order to make definitive conclusions on the clinical usefulness of FNR in this syndrome, well-designed and controlled studies with measures of success based on neuropsychological assessments before and during treatment should be conducted to establish its efficiency, effectiveness, dosage, duration of treatment.

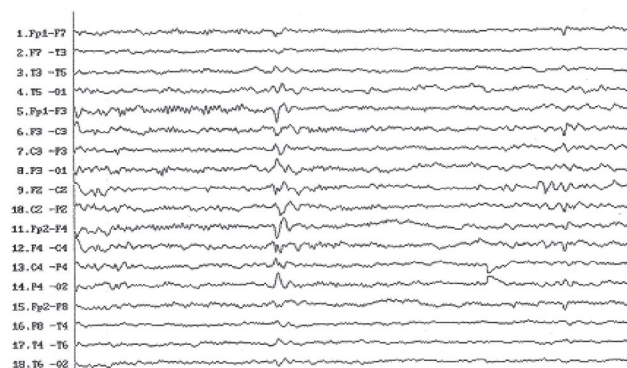


Figure 3. EEG during induced sleep at 20 months after initiation of treatment. Generalized fast activity is seen secondary to chloral hydrate, vertex sharp waves and sleep spindles of 12 Hz, characteristic of phases II-III non-REM sleep. No paroxysmal activity was observed.

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