

CASE REPORTS

One silence, different clinical pictures Landau Kleffner Syndrome: Differential diagnosis

Um silêncio, vários quadros clínicos

Síndrome de Landau Kleffner: Diagnóstico diferencial

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ABSTRACT

Landau Kleffner syndrome (LKS) is a rare epileptic encephalopathy characterized by acquired receptive and expressive aphasia and epileptic seizures in a previously normal child. The diagnosis can be challenging and commonly mistaken with other clinical pictures, namely emotional conditions, mainly when identifiable triggers are present in the patient's history.

The authors present the case of a four-year-old Portuguese girl who moved to China with her parents and sister and started presenting regression of expressive and comprehensive language and behavioral problems around the same time that they changed country. The aim of this study is to document a case of LKS and briefly review the subject, highlighting the complexity of the differential diagnosis.

Keywords: aphasia; auditory verbal agnosia; differential diagnosis; epileptic encephalopathy; Landau Kleffner syndrome

RESUMO

A síndrome de Landau Kleffner (SLK) é uma encefalopatia epilética rara caracterizada por afasia recetiva e expressiva e crises epiléticas, que se manifesta em crianças com desenvolvimento previamente normal. O diagnóstico pode ser desafiante, pois a condição pode ser confundida com outros quadros clínicos, nomeadamente problemas emocionais, sobretudo quando existem fatores precipitantes na história do doente.

Os autores apresentam o caso de uma menina portuguesa de quatro anos de idade que se mudou para a China com os pais e irmã e desenvolveu um quadro de regressão da linguagem expressiva e compreensiva e problemas comportamentais coincidentes com a altura em que se deu a mudança. O objetivo deste estudo é documentar um caso de SLK, fazendo uma breve revisão sobre o assunto e destacando a complexidade do diagnóstico diferencial.

Palavras-chaves: agnosia verbal auditiva; afasia; diagnóstico diferencial; encefalopatia epilética; síndrome de Landau Kleffner

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INTRODUCTION

Landau-Kleffner syndrome (LKS) is a rare epileptic encephalopathy that causes aphasia *de novo* in children with previous normal development. The clinical presentation includes loss of comprehensive language (auditory verbal agnosia) and verbal expression (aphasia), associated with electroencephalographic changes during sleep, often in the temporal and parietal areas.⁽¹⁻³⁾

The condition was first described in 1957 by Landau and Kleffner, who identified the disease in six children. Since then, only a few hundred cases have been reported. An epidemiological study in Japan found an incidence of LKS in individuals aged 5-14 years of 1:1.000.000. The disease seems to affect more boys than girls and occur more frequently in children aged three to eight years.⁽²⁻⁶⁾

The exact LKS etiology remains unknown, but genetic factors seem to make an important contribution. The syndrome correlates with mutations in the *GRIN2A* gene (16p13.2), which encodes for the GluN2A protein (also known as NR2A), consisting of a N-methyl-D-aspartate (NMDA) receptor subunit. This protein is identified in high concentrations in brain areas responsible for language and speech, where the NMDA receptor is involved in multiple memory and learning functions. Some studies also suggest the involvement of immune factors, stressing out the high number of autoantibodies against brain-derived neurotrophic factor in children with LKS compared to healthy controls. Clinical response to treatment with corticosteroids in some children with LKS also suggests the involvement of the immune system and inflammatory dysregulation.^(1-4,7,8)

The main characteristics of LKS are aphasia, electroencephalographic alterations, epileptic seizures, and behavioral changes. The disease onset may be abrupt or progressive, with complete or partial inability to recognize, process, and interpret verbal and/or non-verbal sounds (auditory verbal agnosia) and subsequent speech deterioration. Typical signs include difficulties with articulation, fluency, and word retrieval. Babbling, neologisms, verbal perseveration, and mutism may also be present.⁽²⁻⁴⁾

Two-thirds of patients manifest different types of seizures: absence seizures, focal seizures, or generalized tonic-clonic seizures. Patients without seizures may have severe language impairment, suggesting that language difficulties are elicited by epileptic activity and not by seizures. Cognitive deficits and behavioral changes, as well as attention deficit, hyperactivity, and impulsivity, have also been described. Anxiety, depressive symptoms, and emotional dysregulation, as well as sleep disturbance and hypersensitivity to sound, are commonly found.^(1,2,4,5)

LKS diagnosis is based on clinical and electroencephalographic findings. Performing an electroencephalogram (EEG) during sleep is mandatory to establish the diagnosis. This exam usually shows uni or bilateral activity, more pronounced over the temporal regions around the Sylvian fissure but also central or parietal. During non-REM sleep, epileptiform activity may develop into a continuous spike-wave pattern, with a frequency of 1.5 to 2.5 spikes per second. During REM

sleep, epileptic activity decreases or completely ceases.^(2,5)

No specific findings are observed in brain magnetic resonance imaging (MRI). However, volumetric changes have been reported, namely decreased volume of language areas, making this exam potentially useful to exclude vascular lesions or tumor masses.⁽²⁾

LKS treatment is far from standardized, and many therapeutic modalities have been attempted with variable success. The general goal is to reduce electroencephalographic disturbances and the consequent need for language, behavioral, and cognitive rehabilitation. Thus, treatment should be multidisciplinary and consider a pharmacological approach but also speech and language therapy. Augmentative and alternative communication devices and even sign language training may be useful for some children. Pharmacological treatment may include the administration of steroids, intravenous immunoglobulins (IV Igs), and antiepileptic drugs (AEDs). Considering AEDs, the use of valproate, clobazam or other benzodiazepines, and levetiracetam, ethosuximide, and sulthiame are the main choices. Carbamazepine, oxcarbazepine, phenytoin, and vigabatrin should be avoided due to the high risk of clinical worsening. Steroids (e.g., oral prednisone 1 mg/kg/day for six months or oral prednisolone 2 mg/kg/day for at least three months before gradual tapering) can improve language, cognitive, and behavioral difficulties, epileptic seizures when present, and EEG abnormalities. Studies have shown variable results with IV Igs (400 mg/kg/day over five consecutive days, and subsequently monthly). This treatment can be considered in cases of patients refractory to AEDs or steroids or when language deficits recur after discontinuing steroids. Some studies also suggest that ketogenic diet may be a valuable treatment option in selected patients. Multiple subpial transection, a surgical and thus invasive intervention, has been considered for LKS treatment in the past, but recent studies recognize that it has no benefits compared to pharmacological treatment.^(1-3,5,9)

Pharmacological seizure control is relatively easy, and spontaneous resolution may occur before adolescence. The prognosis of patients with language disorders is variable. The "active" phase of the syndrome may manifest over years through fluctuations in language skills, but clinical improvement is typically observed before adolescence. However, moderate-to-severe language impairment may persist in some children.⁽²⁾

Since LKS has a very low incidence and unspecific symptomatology, the differential diagnosis is challenging. When the clinical history is suggestive, typical childhood emotional problems may arise as primary diagnosis, making it even more difficult to recognize SLK. In this study, the authors aim to describe a clinical case of this rare syndrome and discuss its differential diagnosis.

CASE REPORT

A four-year-old girl was referred to the Neuropediatrics consultation due to gradual regression of expressive and comprehensive

language skills during the last 12 months. She also manifested *de novo* behavioral problems, with heteroaggressivity in the context of frustration. The parents reported the beginning of symptoms when they went abroad to live in China for a year. The child was attending preschool, where she spoke Chinese and English.

The teacher alerted the parents to the need to consult an otorhinolaryngologist due to difficulties experienced by the girl in understanding what she was told, believing that it could be due to hearing loss. The girl was thus submitted to an auditory screening, which revealed no significant alterations. Approximately three months after the teacher alert, the parents noticed that the girl had gradual vocabulary loss and difficulties in understanding spoken language, initially believing that these could be due to emotional issues or to the normal adaptative process and new language acquisition.

The pregnancy, delivery, and neonatal period had been uneventful, and until the beginning of symptoms, the girl had normal development, with no relevant personal or family medical history. Expression and comprehension problems intensified over time and started to be associated with behavioral changes, including increased intolerance to frustration, irritability, and problems in the relationship with peers, namely aggressive behaviors.

At the time of the first appointment, the girl expressed herself through gestures, pointing to what she wanted, and seemed to understand gestures and visual cues but not when people spoke to her. Daytime sleep and awake EEG and brain MRI had already been performed, with the EEG showing a slightly irregular basal rhythm, with slow (theta) activity in the right temporal and central-parietal areas indicating regional dysfunction and epileptiform discharges mainly in the right temporal area (Figure 1). Some periods with continuous bilateral spike and wave complexes were identified during sleepiness (Figure 2).

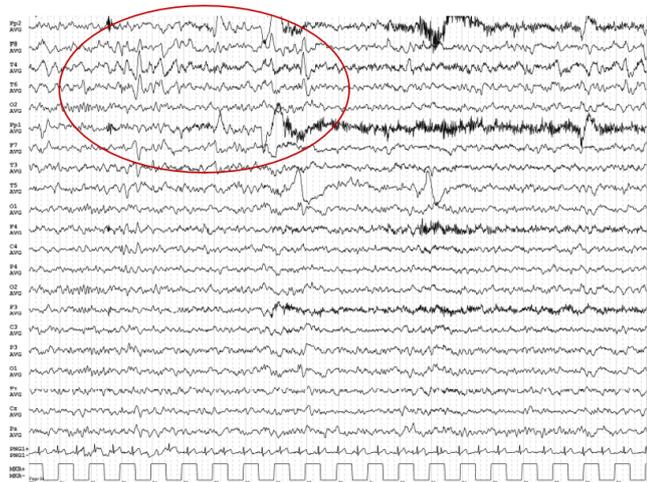


Figure 1 - Awake EEG recording showing focal epileptiform activity with sharp waves on the right temporal areas, with slight diffusion to the left temporal area.

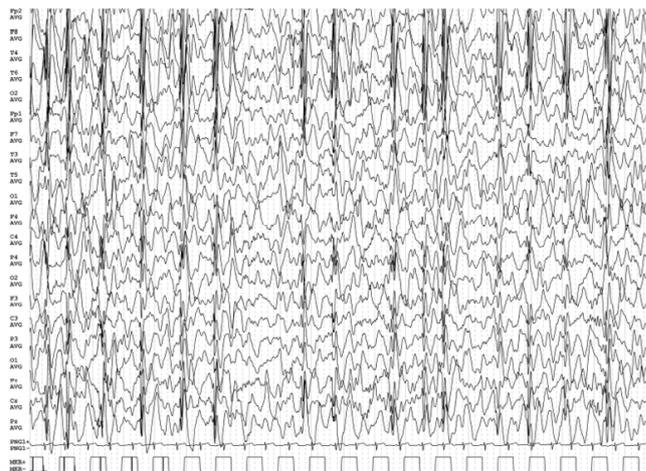


Figure 2 - EEG during sleep showing generalized/bi-hemispheric spikes and spikes and waves with right predominance including almost the entire recording page (continuous spike-and-wave).

Genetic study was conducted through next-generation sequencing (NGS) epilepsy panel, showing no changes in several genes, including *GRIN2A*.

Based on clinical and electroencephalographic findings, LKS diagnosis was suggested, and treatment with prednisolone (2 mg/kg/day) was started.

Due to electroencephalographic normalization (normal EEG at four months of treatment) and clinical improvement, with vocabulary acquisition and understanding of spoken language according to parents, weaning from pharmacological therapy was started about four months later, in a total steroid treatment duration of approximately 16 months.

The patient's clinical condition has improved since then, with the girl asking her parents to go back to China and saying that she likes living there.

DISCUSSION

The present study describes a case of typical LKS progression, in which a child with previous normal development starts presenting difficulties in interpreting and processing auditory stimuli between the ages of three and eight years, later experiencing difficulties in verbal expression. These clinical symptoms, together with electroencephalographic findings (slow activity in the right temporal and central parietal areas and continuous spike-wave pattern in sleepiness and sleep sections), suggested the diagnosis of epileptic encephalopathy with language impairment, such as LKS.⁽¹⁻⁵⁾

No clinical seizures were observed, which may have contributed to a later diagnosis. According to the literature, this occurs in about one-third of cases.⁽²⁾

Regarding the differential diagnosis, an emotional disorder, such as selective mutism (SM), could have been considered, as symptoms occurred after the family moved to a very different country. In SM, the child shows persistent inability to speak only in specific social situations, being able to speak with others. Children with SM usually do not talk at school or in strange environments, but they talk with family members at home. This disorder is currently considered an anxiety disorder and is associated with marked social anxiety. It occurs in children with evident shyness and insecurity. In this case, language difficulties were not restricted to a certain context, and there was no parental description of previous behavioral traits, like shyness, inhibition, shame, or situation avoidance.^(10,11)

Behavioral problems, such as irritability and aggressiveness, presented some months after the first symptoms and may be related to the girl's perception of her own difficulties in communicating with family or peers.

Autism spectrum disorder (ASD) is a common differential diagnosis in this setting that has to be excluded. ASD is characterized by qualitative anomalies in communication and social interaction, restricted and repetitive behaviors, interests, and activities, and sensory processing difficulties. In some cases, this disorder is associated with developmental regression and may thus resemble LKS. However, in ASD this regression seems to occur earlier. In the present case, the diagnosis of ASD was excluded since the girl maintained communicative intentionality, expressed herself by gestures, and showed no limitations in facial expression. There was no reference to repetitive play or restricted interests.^(2,3,10,12)

LKS may have a continuous spike-wave electroencephalographic pattern during sleep, similarly to other continuous spike and wave during slow-wave sleep (CSWS)-related syndromes. However, in CSWS the electroencephalographic anomalies present a more frontal location and are associated with broader cognitive impairment. Unlike CSWS, LKS is rarely associated with structural brain lesions.^(2,13)

Neuroimaging is important to exclude conditions that can be associated with childhood aphasia, such as tumoral, infectious, or dysplastic lesions.⁽³⁾

In this case, the patient's teacher urged parents to consult an otorhinolaryngologist due to auditory verbal agnosia confused with deafness. In LKS, peripheral hearing is normal, but children cannot interpret what they hear.⁽³⁾

Aphasia in LKS must be distinguished from difficulties in language acquisition in the context of language development delay, in which there is no regression but rather a delayed development of language comprehension or expression skills.^(2,10)

CONCLUSIONS

LKS is a rare epileptic encephalopathy that causes regression of language skills and has psychiatric conditions, among others, as differential diagnoses. High clinical suspicion and recognition of

clinical features and findings on complementary diagnostic tests are crucial for early diagnosis and intervention.

LIST OF ABBREVIATIONS

AED	- Antiepileptic drug
ASD	- Autism spectrum disorder
CSWS	- Continuous spikes and waves during slow wave sleep
EEG	- Electroencephalogram
ICD-11	- International Classification of Diseases, 11 th Edition
IV Ig	- Intravenous immunoglobulin
LKS	- Landau-Kleffner Syndrome
MRI	- Magnetic resonance imaging
NMDA	- N-methyl-D-aspartate
NR2A	- protein GluN2A
SM	- Selective mutism
TSM	- Multiple subpial transection

AUTHORSHIP

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