Landau-Kleffner syndrome: A systematic review and two illustrative cases

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Resumen

Introducción: Este estudio analiza los tratamientos disponibles para el Síndrome de Landau Kleffner (LKS) y evalúa sus potenciales beneficios, comparando la literatura con dos casos de pacientes diagnosticados de LKS tratados quirúrgicamente mediante la técnica adaptada de la transección subpial múltiple (MST). **Método:** Se realizó una revisión del PUBMED. Los artículos seleccionados fueron los que tenían "DOI" o en caso de no tener "DOI", el artículo contenido en la información resumida del paciente. Se seleccionaron y organizaron 113 artículos para el análisis estadístico. **Resultados:** Los pacientes masculinos son los más afectados. La probabilidad de tener una regresión total es más probable en el tratamiento quirúrgico. El MST está indicado en los casos reportados debido a la necesidad de resección quirúrgica de las áreas afectadas para asegurar el mantenimiento de funciones cerebrales elocuentes. **Conclusiones:** La MST presenta resultados de mejoría significativa en la epilepsia y afasia de los pacientes, mostrándose como una técnica importante en el tratamiento del LKS.

Palabras clave: Neurocirugía, Landau Kleffner, epilepsia, afasia adquirida.

Abstract

Objective: This study aims to analyze the treatments available for Landau Kleffner Syndrome (LKS) and evaluate the potential benefits for the patient, comparing the cases described in the literature with two cases of adult patients diagnosed with LKS treated surgically by the technique adapted from the multiple subpial transection (MST). **Methods:** A broad review was conducted on the PUBMED databases. The selected articles were those that either had “DOI” or information about the patient in the summary. Those articles that did not have a DOI and had not made the abstract of the article available were excluded. Two literature searches were carried out and a total of 113 articles were selected and organized for statistical analysis. **Results:** Male patients are affected 1.4 times more than female patients. The first symptom appeared at 4.67 years old. The probability of having a total regression is more likely in surgical treatment. As also seen in the literature, LKS cases in adults have a more favorable prognosis after adequate treatment, both in terms of improving aphasia and in reducing the occurrence of crises. The MST is indicated in the cases reported due to the need for surgical resection of the affected areas to ensure the maintenance of eloquent brain functions. **Conclusion:** MST presents significant improvement results in epilepsy and aphasia of patients, showing to be an important technique in the treatment of LKS, although it is not a frequent indication.

Key words: Neurosurgery, Landau Kleffner, epilepsy, acquired aphasia.

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Introduction

Landau-Kleffner syndrome (LKS) or acquired epileptic aphasia was described for the first time in 1975 by Landau and Kleffner[1]. LKS is a rare childhood epileptic syndrome in which epileptiform electroencephalographic abnormalities are more marked during sleep and are associated with acquired aphasia[2,3].

Its etiology is still unclear, but research suggests an autoimmune or infection-related origin[4]. LKS mainly affects male patients, more frequently between 3 and 7 years of age and with a previous history of normal language psychomotor development for their respective age[1,5,6]. Among childhood epilepsy cases, LKS presents in 0.2% of cases[7].

About the clinical presentation, epileptic seizures are a clinical finding found in 75% - 83% of the cases, but not a prerequisite for LKS[3,4]. In addition, LKS is often accompanied by behavioral disorders such as hyperactivity and autism-like behavior[3,6,8,9]. The first manifestation of language disorders is represented by auditory verbal agnosia or an apparent "word deafness"[2,10], when the patient might become completely mute and not respond to non-verbal stimuli[11,12].

Most cases do not have spontaneous recovery, and conservative treatment, mainly done with anticonvulsants and glucocorticoids, have partial improvement in the condition, with persistence of large deficits in the patients' language[5,13].

In 1989, a new surgical technique was implemented by Morrell in the treatment of patients with refractory epilepsy when the epileptogenic zone involves eloquent areas, called multiple subpial transection (MST). This technique is also important and used for LKS patients and presents positive results in the remission of epilepsy and also in language recovery[14]. The MST technique was adapted by Ntsambi-Eba et al, in 2013, proving a higher efficacy and low morbidity than the original technique[15]. This improved MST performance radiating transections from a single cortical entry point[15,16].

This study aims to analyze the treatments available for Landau Kleffner Syndrome and evaluate the potential benefits for the patient, comparing the cases described in the literature with two clinical cases of adult patients diagnosed with LKS and treated surgically by the technique adapted from the MST.

Materials and Methods

1. **Research strategy and article selection**

A broad review was conducted on the PUBMED databases in the literature until May, 2020. The selected articles were those that either had "DOI" or information about the patient such as gender, age of onset symptoms, clinical manifestations, presence of abnormalities in the EEG and aphasia, treatment and evolution of the patient after treatment in the summary. Those articles that did not have a DOI or had not made the abstract of the article available were excluded. There was no selection due to the language of the article.

The search was initially done with the "Cases Reports" filter with the keywords "landau kleffner syndrome", as shown in the search strategy below:

Search: landau kleffner syndrome,Case Reports,"(((""landau-kleffner syndrome""[MeSH Terms] OR (""landau kleffner""[All Fields] AND ""syndrome""[All Fields])) OR ""landau kleffner syndrome""[All Fields]) OR ((""landau""[All Fields] AND ""kleffner""[All Fields]) AND ""syndrome""[All Fields])) OR ""landau kleffner syndrome""[All Fields]",161,22:47:06

161 articles were found on this search. 38 articles were excluded because they either did not have DOI or they did not have enough information about the patients necessary for this analysis. The 123 selected articles underwent a second analysis regarding the full text. 5 studies did not report cases diagnosed with KLS and for this reason, were excluded. 10 articles reported other surgical treatments and were excluded. Thus, 108 articles from this research entered our analysis. (Figure 1A).

A second research was carried out in order to obtain the cases described in the literature with the treatment of MST. The following research strategy was used at PUBMED databases, without filters:

Search: multiple subpial transection landau kleffner,,,"(""multiple""[All Fields] OR ""multiples""[All Fields]) AND (""subpial""[All Fields] OR ""subpially""[All Fields]) AND (((((""transected""[All Fields] OR ""transecting""[All Fields]) OR ""transection""[All Fields]) OR ""transectioned""[All Fields]) OR ""transectioning""[All Fields]) OR ""transections""[All Fields]) AND (""landau""[All Fields] OR ""landau s""[All Fields]) AND ""kleffner""[All Fields]",22,22:57:07

On this research, 22 results were obtained. On this research, we followed the same selection criteria as the first survey. One article was excluded for not having "DOI". The remaining 21 articles underwent an analysis of their full text. 10 articles were excluded because they did not describe the individual information of each patient, necessary for the analysis made in this study. Another 6 articles were excluded because they had already been found from the first search. Thus, 5 articles were selected.

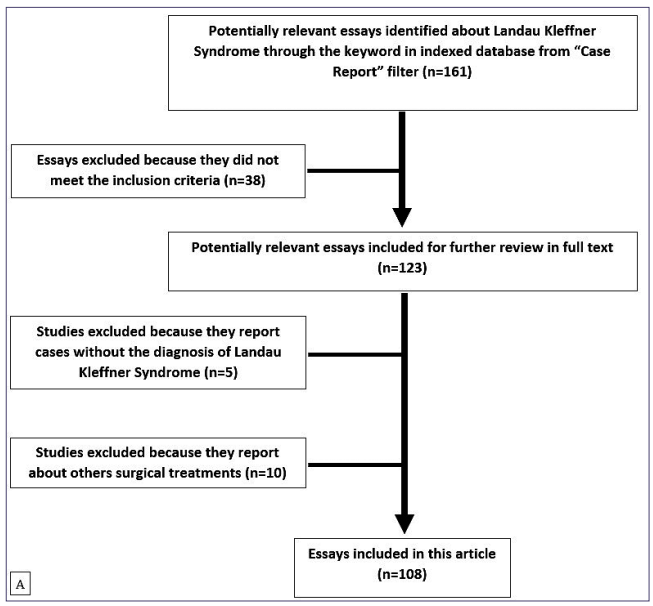

Figure 1 a.

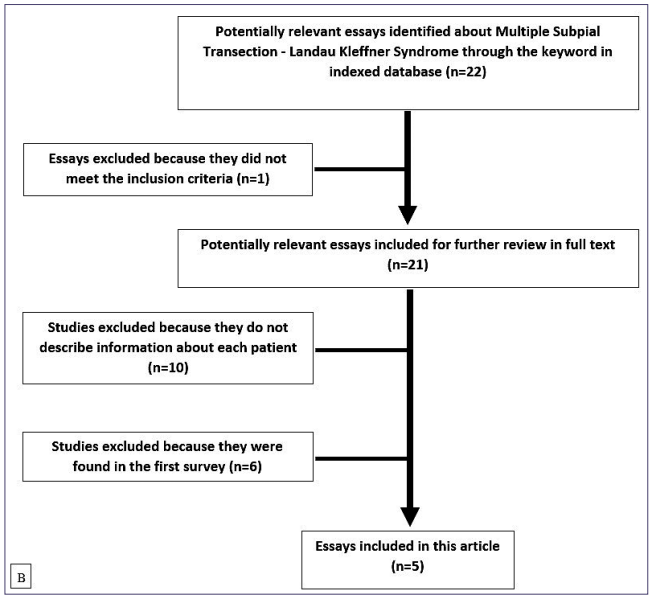

Figure 1 b.

2. **Data analysis**

The data obtained in the articles were arranged in a comparative table between patients undergoing conservative therapies (drug therapy or psychotherapy) or surgical therapy. These two groups were analyzed and the results were discussed.

Illustrative Cases

Patient 1: Female patient, 57 years old, operated on a basilar aneurysm 13 years ago, with Behcet's disease. Due to vasculitis resulting from Behcet's disease, she developed an epileptic focus in Wernicke's area, presenting aphasia and seizures, obtaining a previous classification of Engel IV. The patient underwent the MST procedure and evolved postoperatively with Engel II and language improvement.

Patient 2: Female patient, 35 years old, who had seizures associated with aphasia. The patient was classified in the preoperative as Engel IV. On MRI examination (Figures 2A, 2B) it was demonstrated the presence of an insula lesion extending to the region of the opercular gyrus. In the EEG it was indicated the presence of spike-wave complexes discharges in the Wernicke area and in the insula. The patient was then submitted to the awake MST 6 months after the manifestation of her first epileptic seizure. During the procedure, as the region with the lesion was stimulated, the patient presented aphasia. Local resection was performed. In the biopsy of the resected material, a ganglioglioma was diagnosed. In the postoperative period, the patient presented an improvement in the frequency of seizures, with Engel II classification and improved language.

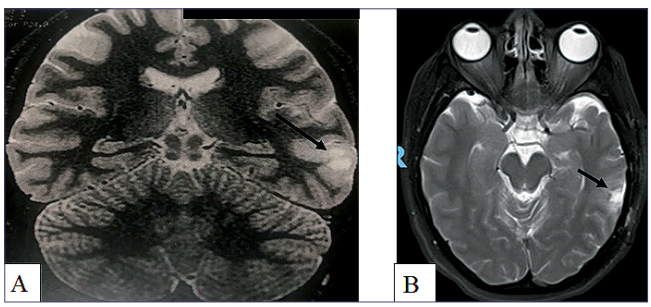

Figure 2 a y b.

Discussion

Landau-Kleffner syndrome also called acquired epileptic aphasia syndrome, was first described in 1957 by Dr. William M. Landau and Dr. Frank R. Kleffner, in six children with a history of normal language acquisition who developed language aphasia, that persists from two weeks to several years, associated with seizure disorders and severe abnormalities of the EEG[1].

LKS is a functional childhood disorder characterized by acquired aphasia associated with an EEG showing epileptiform discharges, usually over one or both temporal regions and an absence of neurological pathologies that can explain the symptoms[17,18]. In children who do not have a demonstrable age-appropriate language or in too young children, whose language never developed, auditory/verbal agnosia is the symptom developed by them in LKS[2,18].

LKS has been recognized by the International League Against Epilepsy (ILAE) since 1989 as a distinct epileptic syndrome of childhood and is currently within the range of childhood epileptic encephalopathies in which the epileptiform abnormalities may contribute to progressive dysfunction[19,20].

The prevalence and incidence of the syndrome are difficult to estimate[12,21,22]. In Japan, an epidemiologic study demonstrated that the incidence of children with LKS was about 1 in a million[23]. The cases described in the literature show that males are more affected by LKS than females, with a ratio of about 2:1[24]. In addition, the average age varies between studies, but remains mostly between 18 months and 14 years, with a higher incidence between 3 and 7 years old[3,5,24-26].

The etiology of the syndrome is unknown and may occur for several reasons, but the involvement of frontal and/or temporal lobes is declared, with involvement of the Wernicke and/or Broca's area[27,28]. There are also theories that autoimmune mechanisms and some infections, such as those caused by the herpes simplex virus and *Toxoplasma gondii* parasite, may be involved in its origin[29,30]. However, most cases have normal MRI[31]. A small proportion of patients have focal lesions, such as neurocysticercosis[32], vasculitis[33], tumors[34], demyelinating diseases[35,36], or cortical atrophy[37], that contribute to the creation of epileptogenic foci that are associated with characteristics of LKS.

The first manifestation of the language disturbance is an apparent "word deafness," auditory verbal agnosia or aphasia[2] which is present in all patients and is the first manifestation in 50% of cases[3]. Parents of children report that they no longer respond to commands and calls[10]. This clinical presentation can evolve into total unresponsiveness and impaired expres-

sive communication, and total mutism[2,10,38]. The children start to express themselves with signs and gestures[2], and in the cases with a little recovery of the speech or in a young child, it's important to introduce sign language in order to help them to communicate[39,40]. Older children, especially those who have already learned or were in an advanced process of learning reading and writing skills, have a better prognosis in recovering language and these skills[6].

The children with LKS will commonly begin to display hyperactivity, attention deficit and indifference to the environment[41], evolving with social isolation and behavioral disorders such as irritation, aggressivity and autism-like behavior[3,6,8,9,42,43]. Aphasia or language disturbs persists in most cases and can cause profound damage to the individual's social, educational and professional development.

In addition to language presentation, there is impairment of cognitive abilities, with occasional focal epileptic seizures[10], they are often nocturnal simple partial motor, occur in 75-83% of patients and are rarely severe[6,44]. They usually respond to drug treatment with anticonvulsants and rarely persist after adolescence[11]. The incidence of seizures, frequency or type of seizures have no influence on prognosis[3,10].

Alterations of electroencephalography (EEG) appear in all patients, classically with bilateral independent temporal or temporoparietal spikes and spike-wake discharges activated mainly during sleep[11,13,45]. In deep sleep recordings, sub-continuous wave-spike discharges of 1.5- to 5-Hz can be observed during slow-wave sleep and disappear or fragment during REM sleep[11,13,45]. Background activity is often normal or borderline[45,46]. Essentially all patients have bilateral spike-and-wave over 85% of non-REM sleep[44].

There is independence between EEG abnormalities and aphasia describe in literature[47-49]. This theory stems from the fact that EEG abnormalities are suppressed with the use of benzodiazepines and anticonvulsants, however, there is no improvement or aphasia response to the use of these drugs. Likewise, fluctuations or changes in the EEG do not cause changes during aphasia, which persist into adulthood, unlike the abnormalities of the EEG that usually disappear in adolescence[44,49-52].

A surgical treatment option for Landau-Kleffner Syndrome is the multiple subpial transection technique, first discussed by Morrell in 1989 for the treatment of epileptic seizures[9]. This technique is an important improvement for treating LKS because it can be applied in eloquent areas. It involves intracortical horizontal fiber sections, preserving the vertical fibers (Figure 3A). This prevents the propagation of abnormal electrical activity, preserving critical cortical functions[14] and without impairing significantly the major functional capacity of the tissue[53,54].

In his study of 14 patients with a previous diagnosis of LKS submitted to the MST technique, Morrell documented the previous states and outcomes of these children. Initially, all were mute or with important linguistic impairment, had only single-word utterances and with educational lag. After the MST procedure, 7 children returned to traditional schools and returned to follow activities indicated for the age group without impairment, and 4 children had a substantial improvement in their condition, although they still need therapy for speech development. Only 3 children had no improvement in relation to their preoperative condition[11].

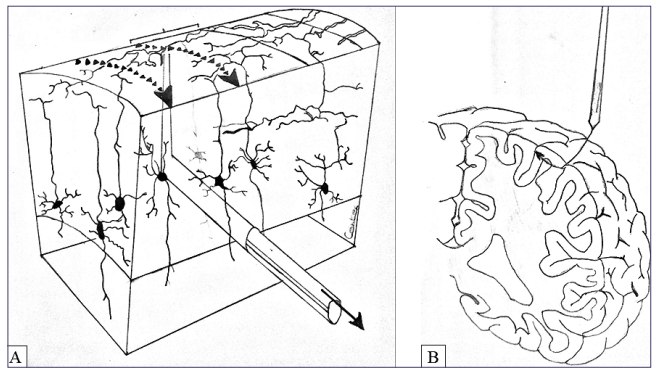

Figure 3 a y b.

Regarding the operative technique described by Morrell, the instrument used in surgery consists of an angled metal wire. Its length, after the 90° angle in the most extreme part, is 4 mm (Figure 3B). This length is defined so transection of the gray mass can be performed saving the fibers that leave the cortex, including the U fibers. It is by means of electrocorticography that the area that will suffer the transection is defined. Transections are performed as necessary and may include several turns, reaching the entire area with electrical abnormalities[55]. Results of the MST in LKS showed behavior and seizure frequency improved dramatically after surgery, with better improvement than pharmacological treatment[11,55].

Surgical treatment for epileptic syndromes and its updating is of great importance, as studies show that the number of patients with epilepsy refractory to pharmacological treatment is increasing[56,57].

Since 2003, in Belgium, Ntsambi-Eba et al using the modified subpial multiple transection technique, where transections occur from a single cortical entry point[16]. This reduces the number of bleeding between the entry points into the cortex and the potential for subsequent intra-arachnoid and extra-arachnoid bleeding, making the surgery safer for the patient[15].

The modified MST technique was first described by Vaz et al, in 2003. It is based on not descending into the grooves, but on executing cross-sections similar to "rays" so that a subarachnoid cortical entry is the initial site for generation up to five cross-sections that are between 10 to 15 mm. These cross-sections are made with the hook facing downwards and in this way, it is possible to visually follow its curvature through the pia mater. With this change in technique, there are results with less arachnoid-subpial perforations and thus it seems to limit the risks of subarachnoid hemorrhage[16]. The result of the study that describes in more detail this technique indicated that all patients show improvement in terms of severity and frequency of crises, associated with cognitive and behavioral improvement. In addition, no patient had sequelae related to the surgical technique[16].

In subsequent studies, with analysis on the outcome of patients undergoing MST, the safety and efficacy of the technique was confirmed[53,58-60]. The work conducted by Aguiar et al[58], analyzed 20 patients submitted to MST between 2007 and 2019 and showed that no patient had clinically significant

deficits due to MST, and that there was complete control of seizures in 60% of cases. Complete control of seizures has been obtained in 12 (60%) of the 20 cases evaluated[58].

MST surgery is mostly indicated for patients with high frequency of epileptic seizures associated with aphasia and refractory to conservative treatment, presenting low or no response to the drugs usually used. The use of anticonvulsants to control seizures is often indicated, but their effectiveness in treating language and behavioral problems is scarce[61]. Other forms of treatment include surgical resection of the primary cause of LKS (such as tumors) or of the epileptic focus, psychotherapy, ketogenic diet, immunoglobulins, steroids e vagal stimulation[62-67].

About 500 cases are described in the literature of patients diagnosed with KLS. A total of 243 cases of LKS in the literature have been reported with data on age, sex, presence of epileptic seizures and other symptoms in the clinical presentation, indicated treatment and occurrence of improvement or not of the symptoms and have been included to this. It was considered a total improvement in all the cases, when had a decrease of 50% or more in the frequency of epileptic seizures when it was present, concomitantly with an improvement of 50% or more in aphasia, which is consistent with the return of the child's language and autonomy in activities that require conversation. The data are distributed in Table 1, which describes information on patients who received conservative treatment, and information on patients undergoing surgical treatment.

In all cases, regardless of the treatment instituted, the gender of the patients was described in 243 cases. Among the 243 cases, 37.04% (n = 90) were female, while 51.85% (n = 126) were male. This data shows that male patients are affected 1.4 times more than female patients in Landau Kleffner Syndrome.

Regarding the age of appearance of the first symptom (aphasia or epileptic seizure), the average age obtained was 4.67 years old, with a standard deviation of ± 4,85 years old.

The presence or absence of seizures was described in 229 cases. Seizures appeared before aphasia in 79 cases, corresponding to 32.51% of the 243 cases. In 105 patients (43.21%), seizures were initiated after aphasia, and in 18,52% of the cases (45 patients) there were no seizures. Seizure appears in 80.35% of the indicated cases. The probability after aphasia is 32.91% more than the probability before aphasia.

In relation to the 47 cases treated by the MST technique, seizures appear in 87.88% of the indicated cases. The probability of an epileptic seizure after aphasia is 132.19% bigger than the probability of an epileptic seizure before aphasia. In cases submitted to conservative treatment, seizures were present in 79.01% of cases, with a higher prevalence in cases after aphasia.

170 out of 243 patients (69.96%) presented another symptom besides aphasia and seizures. Among the most common symptoms, we can highlight behavioral changes (such as social isolation or autism-like symptoms) and mood changes, especially aggressiveness and irritability.

In cases submitted to surgical treatment, the presence of symptoms other than aphasia was present in 91.43% (n = 43) of the reported cases. In cases treated with conservative therapy, 64.8% of patients had other symptoms.

Pharmaceutical treatment or psychotherapy was indicated in 76.95% of the cases (187 cases out of 243 cases), and surgical treatment was done in 19.34% of the cases (47 cases). There was a regression of symptoms, with no use of any therapy in 3,29% (8 cases). Surgical treatment is performed 0.25 times in relation to non-invasive treatment.

About the regression of symptoms, of the 243 cases, note that the partial regression (58.02% of the cases, n = 141) is 38,21% more frequent than the total regression of symptoms (41.98% of the cases, which corresponds to n = 102).

In cases submitted to surgical treatment, the total regression of symptoms was present in 1.76 times the partial regression of symptoms. While in surgery, partial regression of symptoms occurs 1.72 times more than the total regression of symptoms. In surgical treatment, the percentage of total symptom regression is 1.74 the percentage of total symptom regression in conventional treatment (66.1% / 33.33%). Therefore, the probability of having a total regression is more likely in surgical treatment.

The two reported cases of LKS show some differences from the data surveyed in the literature. Initially, it can be noted that the age of presentation of the syndrome is different in the cases reported, due to the fact that they are the consequence of an underlying disease presented by patients (in the first case, Behcet's disease, in the second case, ganglioglioma), and not as a consequence of infections or idiopathic causes in childhood, as is usually described in the literature. Although there are epidemiological differences, the results described in the literature and in the cases reported are convergent, showing a significant improvement in the patients' condition, with their autonomy resuming, besides a significant reduction in the number of crises thanks the MST procedure. With the data from the reported cases, can relate the case described by other authors, in whose the LKS was a consequence from a primary disease, such as neurocysticercosis[32], vasculitis[33], tumors[34], demyelinating diseases[35,36] or cortical atrophy[37]. Thus, can note that although the most classic form of LKS presentation is during childhood, the involvement of epileptic foci in the temporal region in adulthood can develop LKS in adults, also causing important functional and social damage to the individual.

As also seen in the literature, LKS cases in adults have a more favorable prognosis after adequate treatment, both in terms of improving aphasia and also in reducing the occurrence of crises, even with different etiologies in the reported cases[36,68-75].

The MST is indicated in the cases reported in this study due to the need for surgical resection of the affected areas in order to resume normal brain activity and enable control of epileptic seizures and maintenance of language, ensuring the maintenance of eloquent brain functions.

Conclusion

Although it is still an uncommon indicated therapy, MST is a more effective treatment with positive results for patients with LKS, with good postoperative evolution and better evolution over time, both for the reduction or extinction of epileptic seizures, as well as for the resumption of speech and

consequently greater autonomy and social independence of the individual. Thus, it is interesting to be constantly updated in order to ensure a good and coherent indication for surgical therapy, both in individuals with a recent diagnosis of LKS, as well as in patients with refractoriness to treatment or progressive worsening of the condition.

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