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Lennox-Gastaut Syndrome and Palliative Surgical Treatment: Bibliographic Review

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Resumen

Introducción: El síndrome de Lennox-Gastaut (SLG) es una de las formas más graves de epilepsia en la infancia debido a la alta frecuencia de convulsiones, resistencia a fármacos y frecuencia asociativa con deterioro cognitivo. Las convulsiones epilépticas más comunes son tónicas, atónicas y atípicas, pero otros tipos pueden coexistir. El tratamiento quirúrgico paliativo de SLG consiste en realizar la calosotomía o estimulación del nervio vago (ENV). **Objetivo:** Revisar qué tratamiento paliativo para el SLG, como la calosotomía y la estimulación del nervio vago, que realiza una mejor respuesta en la remisión de convulsiones. **Métodos:** Revisión bibliográfica de PubMed, LILACS, SciELO y CAPES Journal Platform. Se eligieron artículos principalmente en inglés, publicados desde 2000 y que abarcan el tratamiento quirúrgico paliativo de SLS. Los datos recogidos se organizaron en cuadros. **Resultados**: Se seleccionaron 17 artículos, 8 de calosotomía y 9 de ENV. En cuanto a la calosotomía, se evaluó una respuesta en 327 pacientes y se alcanzó el estado de convulsiones epilépticas libres en 74 pacientes (22,62%). Mientras que en el 70,84% de los pacientes se produjo una mejoría de más del 50%. En cuanto a VNS, se seleccionaron 9 artículos, totalizando 983 pacientes. Obtuvieron una reducción de más del 50% de las convulsiones en el 57,8% de ellas. **Conclusión:** Ambos procedimientos son eficaces en la disminución de la frecuencia y la gravedad de las convulsiones en LGS. La callosotomía parece ser más eficaz para disminuir los ataques atónicos. En los artículos evaluados, no hubo diferencias en la reducción de todos los tipos de convulsiones.

Palabras clave: Epilepsia, Síndrome de Lennox-Gastaut, Estimulación del nervio vago, Calosotomía.

Abstract

Introduction: Lennox-Gastaut Syndrome (LGS) is one of the most severe forms of epilepsy in childhood due to the high frequency of seizures, drug resistance and associative frequency with cognitive impairment. The most common epileptic seizures are tonic, atonic and atypical absences, but other types can coexist. Palliative surgical treatment of LGS consists of performing callosotomy or vagus nerve stimulation (VNS). **Objective:** Review which palliative treatment for LGS, such as callosotomy and vagus nerve stimulation, that performs a better response in the remission of seizures. **Methods:** Bibliographic review of PubMed, LILACS, SciELO and CAPES Journal Platform. It was chosen articles mainly in English, published since 2000 and covering the palliative surgical treatment of LGS. The collected data were organized in tables. **Results:** 17 articles were selected, 8 were about callosotomy and 9 about VNS. Regarding callosotomy, a response was evaluated in 327 patients, and the state of free epileptic seizures was reached in 74 patients (22.62%). While an improvement of more than 50% occurred in 70.84% of the patients. Regarding VNS, 9 articles were selected, totaling 983 patients. They obtained a reduction of more than 50% of the seizures in 57,8% of them. **Conclusion:** Both procedures are effective in decreasing the frequency and severity of seizures in LGS. Callosotomy appears to be more effective in decreasing atonic attacks. In the articles evaluated, there was no difference in the reduction of all types of seizures.

Key words: Epilepsy, Lennox-Gastaut Syndrome, Vagus Nerve Stimulation, Callosotomy.

Introduction

Lennox-Gastaut Syndrome (LGS) is one of the most severe forms of epilepsy in childhood[1] due to the high frequency of seizures, drug resistance and associative frequency with cognitive impairment.

It is characterized by recurrent polymorphic epileptic seizures, neuropsychomotor retardation or involution and a characteristic electroencephalographic pattern, consisting of slowing in the base activity, presence of slow complexes spike - wave (1.5 Hz to 2.5 Hz) of diffuse projection and previous predominance and discharges of diffuse projection polyspikes in electroencephalographic record performed during sleep[1].

Its incidence is about 1 to 10% of childhood epilepsies[2] and 3 to 17% of all patients with epilepsy and psychomotor retardation[3]. It is associated with various etiologies in, at least, 70% of cases, such as brain malformations, hypoxic-ischemic encephalopathy, central nervous system infections, neurocutaneous syndrome and genetic diseases, particularly chromosome abnormalities[4]. It is more frequent in males (5:1)[5] and its onset occurs up to 8 years of age, with a peak between 3 and 5 years[2].

The most common seizures in LGS are tonic and atonic seizures and atypical absences, but other types of epileptic seizures may be associated, such as myoclonic seizures, partial seizures and generalized tonic-clonic seizures[1,6]. Prolonged episodes of atypical absence, with fluctuation of consciousness, occur and have duration of minutes to hours[4]. Drop attacks are common, are most often atonic seizures and may result in repeated craniofacial traumas. Overall, 80% of children will develop tonic seizures, 65% atonic seizures, 60% atypical absences and 55% tonic-clonic seizures[7].

Due to its encephalopathic nature and the multiple types of epileptic seizures present, LGS is a disease of difficult drug control. Many drugs initially reduce the frequency of seizures, but over time, they lose their efficacy.

The *International League Against Epilepsy* (ILAE) have emphasized the importance of early detection of children who are candidates for surgical procedures in LGS treatment and have recommended the immediate referral of them to specialized surgical centers[8].

There are three options in the surgical approach to epilepsy in children: surgical resection, callosotomy, and vagus nerve stimulation.

The main purpose of surgical resection is to remove the brain region where the seizures originate. Surgery may be considered when there is a failure in the control of epileptic seizures, with the use of at least two or three appropriate antiepileptic drugs (AED), or when these crises affect the patient's quality of life[8]. However, because of the multifocal characteristics of the disease or the difficulty in locating a single crisis focus, most patients are not candidates for resection surgery and may undergo two palliative surgeries: callosotomy or vagus nerve stimulation.

Callosotomy aims to partially disconnect the cerebral hemispheres, thus helping to prevent the spread of epileptic discharge between the hemispheres. Currently, it is a particularly effective surgical option for patients with LGS who present atonic, tonic and tonic-clonic seizures, even if it is a palliative treatment[7,8.]

The vagus nerve stimulation consists of the implantation of a programmable electric pulse generator attached to electrodes that are connected to the left cervical vagus nerve. It is an adjunct treatment option that was approved in 1997 by the *Food and Drug Administration* (FDA)[9] and since then has been accepted in clinical practice to decrease the frequency and severity of generalized seizures, especially atonic seizures, although its efficacy in the treatment of other types has also been recognized[10].

Objective

This bibliographic review aims to review which palliative treatment for Lennox-Gastaut syndrome, such as callosotomy and vagus nerve stimulation, presents the best response in the aspect of seizures remission.

Methodology

A bibliographic review was performed through PubMed platform, LILACS, *Scientific Electronic Library Online* (SciELO) and Periodical Portal CAPES. Preferably, articles were chosen in the English language, published from the year 2000 and covering LGS palliative surgical treatment. The terms used were: Lennox-Gastaut syndrome, vagus nerve stimulation, callosotomy and surgical treatment, and preferably with search through index terms.

The data collected were organized into tables (Tables 1 and 2) containing: author, type of treatment (VNS or callosotomy), sample of patients with LGS and seizures reduction rate, categorized according to Engel's classification when available in the article (Figure 1) or their percentages in the articles that did not use this classification

Results

First, 30 articles were selected, 15 about callosotomy and 15 about vagus nerve stimulation. However, 13, in total, were excluded because they did not present enough data for this study or because they were only review articles. Thus, at the end, 17 articles (8 callosotomy and 9 VNS) were analyzed. All were published between the years 2000 and 2016.

Eight articles were selected that addressed the performance of callosotomy, preferably by previous route. In total, the response of 327 patients was evaluated, with average age at surgery ranging from 6 to 12 years of age. After the procedure, these patients were monitored on average for 2 to 4.7 years. Of the total articles selected, 7 reported that the free of epileptic seizures (Engel 1) status, in relation to all types of seizures, had been reached in 74 patients (22.62%). In addition, 3 articles mentioned that an improvement of more than 50% in epileptic seizures occurred in 70.84%. While in relation to atonic seizures, one of the articles reported that there was an improvement of over 50% in 92% of the patients studied.

In relation to vagus nerve stimulation, 9 articles were selected. The total patients presenting LGS in these articles was of 983, and this sample number

Class I	Free of disabling seizures
Class II	Rare disabling seizures
Class III	Worthwhile improvement
Class IV	No worthwhile improvement

Figure 1. Engel Classification[8]

Table 1.
Callosotomy

Authors	Type of treatment	Sample	Results
Shuli Liang, Shaohui Zhang, Xiaohong Hu et al.[16]	Callosotomy and Drug Treatment	60 patients with LGS Average of 9 years of age	Callosotomy: After 1 year: engel 1 = 17.4% Drug: After 1 year: engel 1 = 2.9% After 2 years: engel 1 = 5.9%
Masaki Iwasaki, Mitsugu Uematsu, Yuko Sato et al.[17]	Callosotomy	13 patients with LGS Average of 7 years of age	After 1 year Engel 1: 30.7% Engel 3: 23.07% Engel 4: 46.15%
Ali A. Asadi- Pooya, Zahed Malekmohamadi, Ahmad Kamgarpour et al.[13]	Callosotomy	18 patients with LGS Average of 9.9 years of age	In all types of seizures After 1 year: engel 1 = 16.6% Generalized tonic-clonic seizures After 1 year: engel 1 = 69.2% Tonic seizures After 1 year: engel 1 = 46.1% Absence seizures After 1 year: engel = 88.8% Drop attacks After 1 year: engel 1 = 36.3%
Aimen S. Kasasbeh, Matthew D. Smyth, Karen Steger May et al.[18]	Callosotomy	58 patients with LGS Average of 120.6 months	Previous callosotomy: Engel 1/2: 36% Engel 3: 55% Engel 4: 9% In 2 stages: Engel 1/2: 27% Engel 3: 64% Engel 4: 9% Complete callosotomy: Engel 1/2: 19% Engel 3: 71% Engel 4: 10%
Su Jeong You, Hoon-Chul Kang,Tae Sug Ko el al.[12]	Total callosotomy and VNS	24 patients with LGS	Callosotomy: Reduction > 50%: 64.3% Reduction > 75%: 35.7% VNS: Reduction > 50%: 70% Reduction > 75%: 20%
Arthur Cukiert, Cristine M. Cukiert, José A. Burattini et al.[14]	Callosotomy and VNS	44 patients with LGS Average age: 11.2 years (Callosotomy) and 8.6 years (VNS)	Engel 1 = Callosotomy: 10% VNS: 0%
Arthur Cukiert, José A. Burattini, Pedro Paulo Mariani et al.[11]	Callosotomy	76 patients with LGS Average age: 11.2 years	In all seizures: Engel 1: 9.21% Engel 3: 90.78% Atonic seizure: Engel 3: 92% Atypical absence seizure: Engel 3: 82% Tonic-clonic: Engel 3: 57% Tonic seizure: Engel 3: 51%
Lancman G, Virk M, Shao H et al.[10]	Callosotomy and VNS	203 patients submitted to VNS 145 patients with Callosotomy	Callosotomy is significantly better compared to VNS in achieving 50-75% reduction in atonic seizures Patients who become seizures-free: CC (48%) e VNS (22.8%)

Table 2.
Vagus Nerve Stimulation

Authors	Type of treatment	Sample	Results
Eric HW, Kossoff W, Shields D.[19]	Ketogenic diet and VNS	483 patients with LGS without previous surgery	Of the 483 patients, 55% after 18 months reduced seizures in > 50%
Morris GL, Gloss D, Mack KJ et al.[20]	VNS	113 patients with LGS	Seizure decrease of > 50% in 55% of 113 patients with LGS
Zamponi N, Passamonti C, Cesaroni E.[21]	VNS	14 patients with LGS	After 1 year: Reduction 80 to 100%: 1 pct Reduction 50 to 79%: 2 pct Reduction < 50%: 7 pct Without reduction: 4 pct
Cersósimo RO, Bartuluchi M, Fortini S et al.[22]	VNS	46 patients with LGS	Reduction 80 to 100%: 28 pct Reduction 50 to 79%: 12 pct Reduction < 50%: 6 pct Without reduction: 0 pct No patient was completely free of seizures
Labar D.[23]	VNS	5 studies gathering 28 patients with LGS	Seizure reduction of 55%
Shahwan A, Bailey C, Maxiner W et al.[24]	VNS	9 patients with LGS	7 of 9 patients with LGS (77.7%) had seizure reduction of > 50%
Elliott RE, Morsi A, Kalhorn SP et al.[25]	VNS	24 patients with LGS	Seizure reduction of 57.6%
Frost M, Gates J, Helmers SL et al.[15]	VNS	50 patients with LGS	After 3 months (43 patients): seizures decreased in >75% in 15 (43%), >50% in 24 (56%)
Lancman G, Virk M, Shao H et al[10]	VNS e CC	Meta-analysis with 203 patients with LGS submitted to VNS	VNS Reduction 100%: 142 pct (5.2%) Reduction > 75%: 166 pct (28.6%) Reduction > 50%: 176 pct (49.3%) CC is significantly better compared to VSN in achieving 50 to 75% reduction in atonic seizures There was no statistically significant difference for other types of seizures between VNS and CC

was submitted to VNS treatment. They achieved reduction of more than 50% in epileptic seizures of 57.8% of patients

Discussion

Callosotomy is often oriented to resolve drop attack in children with LGS, leading to a free-falling condition in 10-15% of patients, although effectiveness on other types of seizures has also been recognized. Complications associated with the procedure include: bruising and cerebral infarctions, infections (meningitis and ventriculitis), hydrocephalus, acute disconnection syndrome and neurological deficits, which may be transient[8].

In a retrospective study with seventy-six patients with LGS or Lennox-like who underwent complete callosotomy, the researchers concluded that improvement (> 50%) was achieved in sixty-nine patients (91%). In addition, fifty-two patients (68%) had a ≥ 90% reduction in the frequency of seizures after surgery and seven (9%) were free of seizures. The reduction in the frequency of specific types of seizures

was: atonic (92%), atypical absence (82%), tonic (51%) and tonic-clonic (57%). A consistent increase in the level of attention was also observed in 65 patients (86%)[11].

Su Jeong You[12] et al., described that 5 (35.7%) of 14 patients had an improvement greater than 75%. Likewise, Cukiert et al evaluated the patients' improvement specifically in relation to the decrease in the frequency of atonic seizures, and 92% of the patients in this study (69 people) showed an improvement of more than 50% of atonic seizures after one year of monitoring.

Asadi-Pooya[13] et al., addressed the tonic seizures reduction after callosotomy and found that 6 (46.1%) of the 13 patients were free of seizures after one year. Curkiert et al found a reduction of tonic seizures greater than 50% in 38 patients (51%).

Lancman[10] et al concludes that callosotomy is significantly better compared to VNS in achieving reduction of 50 to 75% in atonic seizures. In this study, a reduction greater than 50% of atonic attacks was observed in 80% of the patients after callosotomy and in 54% after the VNS, whereas a reduction of more than 75% in atonic seizures was observed in 70% after callosotomy and in 26% after VNS.

Authors suggest that VNS should be performed before callosotomy, as it presents a lower morbidity and is a less invasive and reversible procedure and as it presents reduction of the different seizures types similar to callosotomy. Regarding the financial aspects, it is estimated that the costs of VNS are compensated in 2 to 3 years[7].

This device is activated one to two weeks after its implantation and is adjusted periodically. On average, each stimulation lasts 30 seconds, with a frequency of 30 Hz, pulse width of 500 μs, initial output of 0.25 mA, with frequent increases, if tolerated, up to 2.0-2.5 mA. It is considered a useful alternative in patients older than 12 years who are refractory to the use of AED and who are not candidates for surgical treatment. The improvement in seizure control is gradual and continues over time with weekly increments in the stimulation intensity. In addition, improvement in cognition and mood may be associated[7]. The occurrence of adverse effects is low and includes: infections at the site of incision, hoarseness, persistent cough, trachea paresthesia, voice alteration and, most serious, vocal paralysis.

Cukiert[14] et al., describe that both procedures were not effective in controlling tonic seizures and both were effective in controlling atypical absences and generalized tonic-clonic seizures. Callosotomy was more effective in controlling the frequency of atonic seizure while VNS proved to be better for myoclonic seizure control.

Frost[15] et al., evaluates changes in patients' quality of life after VNS. There was improvement in alertness in more than half of patients investigated after 3 to 6 months of treatment. After 6 months, a quarter of patients showed improvement in verbal communication, school performance and post ictal recovery. Some patients also showed improvement in mood, memory and ambulation.

Conclusion

Both procedures are effective in decreasing the frequency and severity of seizures in LGS.

According to the reviewed articles, callosotomy seems to be more effective in decreasing atonic seizures.

In addition, no significant difference was observed in reducing all types of seizures.

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