small
Received: 4 August 2023 | Revised: 1 October 2023 | small Accepted: 9 October 2023
small
DOI: 10.1111/epi.17796

headerOrFooter
Epilepsia™

small
RESEARCH ARTICLE

Title

Added value of corpus callosotomy following vagus nerve stimulation in children with Lennox–Gastaut syndrome: A multicenter, multinational study

Authors

authors
Jonathan Roth[1] | Lottem Bergman[1] | Alexander G. Weil[2] |
authors
Tristan Brunette-Clement[2] | Howard L. Weiner[3,4] | Jeffrey M. Treiber[3,4] |
Ben Shofty[5] | Arthur Cukiert[6] | Cristine Mella Cukiert[7] | Manjari Tripathi[8] |
layout
authors
Poodipedi Sarat Chandra[8] | Robert J. Bollo[9] | Hélio Rubens Machado[10] |
authors
Marcelo Volpon Santos[11] | William D. Gaillard[12] | Chima O. Oluigbo[13] |
authors
George M. Ibrahim[14] | George I. Jallo[15] | Nir Shimony[16,17,18,19] |
Brent R. O'Neill[20] | Marcelo Budke[21] | María Ángeles Pérez-Jiménez[22] |
authors
Francesco T. Mangano[23] | Masaki Iwasaki[24] | Keiya Iijima[24] |
layout
authors
Jorge Gonzalez-Martinez[25] | Kensuke Kawai[26] | Yohei Ishishita[26] |
authors
Samer K. Elbabaa[27] | Luis Bello-Espinosa[28] | Aria Fallah[29] |
authors
Cassia A. B. Maniquis[29] | Ido Ben-Zvi[30,31] | Martin Tisdall[30,31] | Manas Panigrahi[32] |
authors
Sita Jayalakshmi[33] | Jeffrey P. Blount[34] | Georg Dorfmüller[35] | Christine Bulteau[36] |
authors
Scellig S. Stone[37] | Jeffrey Bolton[38] | Ashutosh Singhal[39] | Mary Connolly[40] |
authors
Daad Alsowat[41] | Faisal Alotaibi[41] | John Ragheb[42] | Shimrit Uliel-Sibony[43]

Universities and Publishers

institutions
Correspondence
Jonathan Roth, Department of Pediatric Neurosurgery, Dana Children's Hospital, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv 64239 Israel.
Email: jonaroth@gmail.com

Heading
heading
Abstract

Objective: Lennox–Gastaut syndrome (LGS) is a severe form of epileptic encephalopathy, presenting during the first years of life, and is very resistant to treatment. Once medical therapy has failed, palliative surgeries such as vagus nerve stimulation (VNS) or corpus callosotomy (CC) are considered. Although CC is more effective than VNS as the primary neurosurgical treatment for LGS-associated drop attacks, there are limited data regarding the added value of CC following VNS. This study aimed to assess the effectiveness of CC preceded by VNS.

Methods: This multinational, multicenter retrospective study focuses on LGS children who underwent CC before the age of 18 years, following prior VNS, which failed to achieve satisfactory seizure control. Collected data included

footnote
[Correction added on 18 November 2023, after first online publication: New co-authors, Ashutosh Singhal, Mary Connolly, Daad Alsowat, Faisal Alotaibi, John Ragheb have been added in this version.]

references
For Affiliation refer page on 3210

epilepsy characteristics, surgical details, epilepsy outcomes, and complications. The primary outcome of this study was a 50% reduction in drop attacks.

Results: A total of 127 cases were reviewed (80 males). The median age at epilepsy onset was 6 months (interquartile range [IQR] = 3.12–22.75). The median age at VNS surgery was 7 years (IQR = 4–10), and CC was performed at a median age of 11 years (IQR = 8.76–15). The dominant seizure type was drop attacks (tonic or atonic) in 102 patients. Eighty-six patients underwent a single-stage complete CC, and 41 an anterior callosotomy. Ten patients who did not initially have a complete CC underwent a second surgery for completion of CC due to seizure persistence. Overall, there was at least a 50% reduction in drop attacks and other seizures in 83% and 60%, respectively. Permanent morbidity occurred in 1.5%, with no mortality.

Significance: CC is vital in seizure control in children with LGS in whom VNS has failed. Surgical risks are low. A complete CC has a tendency toward better effectiveness than anterior CC for some seizure types.

KEYWORDS
keywords
corpus callosotomy, Lennox–Gastaut syndrome, refractory epilepsy, vagus nerve stimulation

1 | INTRODUCTION

Lennox–Gastaut syndrome (LGS) is a severe form of epileptic encephalopathy, presenting during the first years of life, and is very resistant to control through antiseizure medications (ASMs). LGS may cause generalized seizure phenotypes, and significantly impact neurodevelopmental aspects such as learning, behavior, alertness, and quality of life.[1] Thus, seizure reduction is of utmost importance, especially in young children.[2] Moreover, drop seizures, which occur in more than half of the patients, are a significant source of morbidity, causing severe injuries, and are among the most disabling factors in this syndrome.[3] Many such patients require close and continuous supervision and head protection with special helmets.

Once conventional ASMs have failed, palliative surgeries such as vagus nerve stimulation (VNS) or corpus callosotomy (CC) should be considered.[4,5] A comparison of the effectiveness and safety of CC and VNS, which are the most common palliative surgical methods, suggests that CC is more effective than VNS in reducing atonic seizure; there is 74%–85% reduction in tonic and atonic seizures following CC, compared to approximately 55% reduction following VNS.[4–6] However, CC is associated with a higher rate of adverse events when compared to VNS. For this reason, in many cases, physicians or family favor VNS over CC as the primary surgical palliative treatment.[7]

Although CC is more effective than VNS as the primary treatment for LGS-associated drop attacks, there are limited data regarding the added value of CC following VNS.

Key Points

- CC has an added value on all seizure subtypes in children with Lennox–Gastaut syndrome who have undergone prior vagus nerve stimulation
- Complete CC has a tendency toward better effectiveness than anterior CC
- Additional studies are needed to ascertain the low morbidity associated with complete callosotomy

The current study evaluates the safety of CC and its effectiveness for drop attacks and other seizure types following prior VNS for LGS.

2 | MATERIALS AND METHODS

This is a multicenter, multinational, retrospective, historical cohort study. Following institutional review board approval, we retrospectively reviewed the files of all children with LGS who underwent CC (complete or incomplete) following a prior VNS. Seventy-one international epilepsy centers were invited to participate based on personal contacts. No institutions were excluded; 27 did not respond, 17 centers had no cases meeting the inclusion criteria, one declined participation, and 26 centers contributed 145 patients (ranging from one to 18 patients from each participating center) operated on between 2003 and 2021.

2.1 | Inclusion and exclusion criteria

Children (up to 18 years of age during CC surgery) undergoing CC surgery, who also underwent a prior VNS for LGS, were included in the study. The LGS diagnosis was based on the criteria of the International League Against Epilepsy.[8] All variations of CC were included (anterior, posterior, complete, open disconnections, and radiofrequency or laser ablation). All LGS etiologies were included. Other epileptic syndromes (unrelated to LGS) and patients who underwent VNS following prior CC were excluded.

2.2 | Collected data

Collected data included demographics, epilepsy etiology, age at seizure onset, and seizure semiology. Surgical data included any prior epilepsy-related surgery (including resections, but not including CC), data regarding VNS surgery (including complications and effectiveness on drop seizures and other seizures), data regarding CC surgery (including technique, extent, complications, and effectiveness), and the need for additional surgeries.

2.3 | Study outcomes

The primary outcome was effectiveness of CC in reducing 50% of drop attacks at the last follow-up despite failure of a prior VNS. Secondary outcome measures were other seizure reductions, role of extent of callosotomy, and safety.

2.4 | Statistical analysis

Data were tabulated in an Excel spreadsheet. SPSS software was used for all statistical analyses (SPSS Statistics, version 25, IBM). Categorical variables are reported as numbers and percentages. Comparison between outcomes of partial and complete callosotomy was done using the chi-squared test. Continuous variables are reported as median and interquartile range (IQR). Correlation between CC outcomes and VNS outcomes was performed using the Fisher exact text. All statistical tests were two-tailed, and $p < .05$ was considered significant.

3 | RESULTS

Of 145 cases submitted by 26 centers, 127 fulfilled the inclusion criteria (0–15 per center). Eighty were males, and 47 were females. Age at epilepsy onset was 0–120 months (median = 6, IQR = 3.12–22.75). Etiology was genetic in 31, structural/congenital in 17, structural/acquired in 15, and unknown or not reported in 64. Dominant seizure types included atypical absence in eight, drop attacks (tonic or atonic) in 102, generalized tonic–clonic in 25, and focal with impaired awareness in 15, in addition to the mandatory tonic seizures. Duration of experiencing drop attacks before VNS was 0–15 years (median = 5, IQR = 2.5–8). Forty-eight children were reported to have severe, 30 moderate, and 22 mild or borderline intellectual disability. Three children had prior resective epilepsy surgeries, and 45 were on the ketogenic diet.

3.1 | Vagus nerve stimulation

Age at VNS surgery was 3 months to 15 years (median = 7, IQR = 4–10). Children were on up to six ASMs (3.1 ± 1.1) before VNS. Apart from two patients who had their VNS setting on 1.5 mA, all other patients were titrated to a minimal output current of 1.75 mA. Seizure outcomes following VNS, and as evaluated before CC surgery (at a follow-up of up to 17 years, median = 3.3, IQR = 2–6), are summarized in Table 1.

3.2 | Corpus callosotomy

A total of 127 children underwent CC surgery at 2–18 years (median = 11, IQR = 8.76–15), up to 17 years following VNS (median = 3.3, IQR = 2–6). Eighty-six underwent a complete callosotomy, and 41 an anterior callosotomy

TABLE 1 Seizure reduction following VNS as evaluated before first corpus callosotomy surgery.

	Drop attacks	Other seizure types
n	106	96
<50% reduction	77 (73%)	74 (77%)
50%–80% reduction	18 (17%)	16 (17%)
>80% reduction	6 (6%)	5 (5%)
Other	5 either temporary improvement or new drop attacks after VNS	1 temporary improvement

Abbreviation: VNS, vagus nerve stimulation.

(40 were of the anterior two thirds, and one of half the callosum extent). We did not collect data regarding the reason for the extent of disconnection. The surgical approach for a complete CC included an open anterior interhemispheric approach ($n=84$) and endoscopic ($n=2$). Of the 41 anterior CCs, 38 were performed via an anterior interhemispheric approach, and three used laser interstitial thermal therapy (LITT).

Ten children underwent additional CC surgery, completing the posterior disconnection. The time from first to second CC surgery was 2–86 months (median = 16.3, IQR = 6.7–34.3). Surgical approaches included anterior interhemispheric in six, posterior interhemispheric in three, and LITT in one. We were therefore evaluating the results following 96 complete CC procedures and 31 partial CC procedures, with a total of 137 surgical procedures. The 137 procedures included an anterior interhemispheric approach ($n=128$), endoscopic ($n=2$), LITT ($n=4$), and posterior interhemispheric ($n=3$).

Surgical complications were reported for 18 of 137 CC procedures (13% [127 primary CCs + 10 CC-completion disconnections]). Following the 127 primary CC procedures, complications included wound complications (four infections, two not specified), pneumonia ($n=2$), neurological (a total of 6 cases, 4 transient, one pericallosal artery infact, and one not specified), one noninfectious fever, one plate removal several years after surgery, and one general deterioration. Following the 10 CC-completion procedures, only one wound infection was reported.

3.3 | Follow-up and seizure outcome

Follow-up after the primary CC was 2–191 months (median = 42.4, IQR = 16–85). The number of ASMs at the last follow-up after the primary CC procedure was similar to that prior to CC (3.3 ± 1.3 after vs. 3.3 ± 1.2 before CC). Seizure outcomes are presented in Table 2. Overall, 83% had at least a 50% reduction in drop attacks, and a 60% reduction in other seizures. Comparing the outcomes between anterior callosotomy and complete callosotomy (including a one or two stage complete callosotomy), extent of disconnection did not significantly affect drop attack control (considering a 50% and an 80% cutoff, and using the chi-squared test). For "other seizure types," a complete callosotomy was significantly associated with a better outcome when compared to anterior callosotomy using the 50% cutoff ($p=.013$) but not using the 80% cutoff.

Outcomes of drop attack control following CC were compared to VNS outcomes according to degree of seizure reduction categories: <50%, between 50% and 80%, and >80%. To verify that sufficient time had elapsed since placing VNS, we focused on patients with 1–2-year follow-up after VNS (prior to CC, $n=27$), and patients with >2 years follow-up after VNS (prior to CC, $n=60$). Using the Fisher exact test, the degree of drop attack reduction following CC was not significantly correlated to the degree of reduction after VNS ($p=.676$ for 1–2 years, and $p=.266$ for >2 years following the VNS before CC).

In addition to the 10 cases undergoing completion of the posterior CC, 10 patients underwent additional surgeries: frontal lobectomy ($n=1$), responsive neurostimulation system (RNS) concurrently with the completion of CC ($n=1$), and deep brain stimulation to the centromedian (CM) nucleus of the thalamus ($n=8$, three of which had an RNS to the CM nucleus).

4 | DISCUSSION

We report here that in children with LGS who fail to achieve seizure control after VNS, CC has an added value, significantly improving seizure control. This is true for drop (tonic and atonic) seizures and other seizure phenotypes. CC-related morbidity was low, and complete CC was associated with higher seizure reduction rates than partial CC.

Prior studies have reported the greater value of CC over VNS as a primary treatment for children with LGS,

TABLE 2 Seizure outcome following corpus callosotomy surgery.

	Drop attacks			Other seizure types		
	<50% reduction	50%–80% reduction	>80% reduction	<50% reduction	50%–80% reduction	>80% reduction
Anterior	9 (26%)	11 (32%)	14 (41%)	15 (62%)	5 (21%)	4 (17%)
Complete [1 stage]	10 (14%)	21 (30%)	39 (56%)	23 (31%)	32 (43%)	19 (26%)
Complete [2 stages]	2 (40%)	0	3 (60%)	4 (80%)	0	1 (20%)
Complete [total]	12 (16%)	21 (28%)	42 (56%)	27 (34%)	32 (40%)	20 (27%)
Total, at the last follow-up	17 (17%)	30 (29%)	55 (54%)	38 (40%)	33 (35%)	24 (25%)

Note: Percentages are given of reported cases only.

especially for atonic seizures.[4,9] However, other studies have found similar effectiveness for both treatments.[5,9,10] Additionally, VNS seems more cost-effective 1 year after surgery and is associated with fewer complications.[4,10,11] However, this study did not evaluate long-term cost-effectiveness (considering the need for VNS battery replacement), which may prove CC is more cost-effective. When both options (CC and VNS) are available, many families will opt for VNS first.[7] Reasons include avoidance of brain surgery, especially because the treatment is palliative and not curative. This is based mainly on the fear of callosotomy-associated risks, including vascular injury, supplementary motor area syndrome, akinetic mutism, disconnection syndrome, and other risks (infection, hydrocephalus, wound-related, and others).

Data are limited regarding secondary treatments (CC following VNS or VNS following CC). Hong et al. reported that half of the patients who underwent CC following VNS reported >50% seizure reduction, with seven of nine patients experiencing total elimination of drop seizures.[12] Guillamón et al.[13] reported a small case series of three patients treated with CC following VNS in severe drug-resistant epilepsy. They reported up to 98% decrease in total seizure frequency following CC. In another small series of seven cases, Arya et al.[14] reported all patients were free of drop attacks, with a 34.7% decrease in total daily seizure frequency at a mean follow-up of 2.6 years. The results of the current series concur with these publications, with approximately 80% having >50% reduction in drop attacks, and 60% having >50% reduction in other seizure types.

Katagiri et al.[15] evaluated 10 children who underwent VNS following failed CC, the reverse of our approach. Six of 10 (60%) patients had ≥50% seizure reduction for all residual seizure types after VNS, and 77.8% showed total resolution of drop seizures.

CC may be performed via various approaches, including interhemispheric, endoscopic-assisted (also done via the interhemispheric route), and LITT.[16–18] LITT approach is minimally invasive, associated with shorter hospitalization and fewer complications, and has similar outcomes to the open approaches.[19] However, LITT is not widely available, and may not be suitable for all corpus callosal anatomy. Open CC, on the other hand, is a widely performed surgery. The microsurgical technique is common to other commonly performed procedures, and is associated with low morbidity if done by experienced surgeons.

There is a long-lasting debate regarding the optimal extent of callosotomy between anterior, complete, and posterior callosotomy.[4,20–22] The basis for this debate is the potential for disconnection syndrome.[23] However, most children with LGS have profound intellectual disability at baseline, and the balance between seizure control (with its positive impact on the quality of life) and the risk of potential disconnection syndrome often favor the goal of seizure control.

This study aim was not to compare CC to VNS as a primary treatment, but to show that VNS failure does not predict the failure of CC, and that CC as the secondary treatment can have a significant benefit.

Interestingly, the outcomes of our series (of secondary CC) concur with the results of primary CC.[4,6] The reasons for the VNS-CC dissonance and added value of CC are unknown but likely involve their different mechanisms of action. Cukiert et al. noted a postsurgical disruption of secondary bilateral synchrony seen on electroencephalographic (EEG) recording in 85% of CC patients, with no EEG modification after VNS insertion.[7] CC disrupts the bilateral synchrony of the hemispheres, whereas the exact mechanisms of VNS are not entirely understood. Based on animal models, it has multiple possible mechanisms of actions, among which is a suppression of cortical hypersynchronization by modulating the synaptic network.[24,25] Other recent data suggest that VNS affects neural networks in three domains: brainstem, limbic system, and cortex.[26] The importance of frequency and amplitude of stimulation on the VNS effect was stated as well. Nevertheless, it should be noted that over time, shorter epilepsy duration and longer VNS therapy time indicted a higher response likelihood, rather than dosing setting.[27] The direct disconnection (achieved with a CC) shows immediate and more effective results. This network disruption not only reduces the general activity associated with drop attacks, but it also reduces other seizures through as yet unknown mechanisms.

This study has several limitations, mainly its retrospective multicenter nature, as well as the lack of a standardized evaluation time point. The lack of a unified time point for outcome evaluation may bias the results. As each center reported data, we could not centrally verify the data, nor verify whether LGS-like cases were included. Detailed neurocognitive assessment was not possible. Disconnection syndrome could not be confirmed in our patients. We did not include EEG data before or following surgery. Thus, the diagnosis of LGS and the effect of surgery on EEG could not be centrally verified. The epilepsy status was based on parental reports during follow-up visits, and the information was incomplete for some patients. The accuracy of seizure detection by parental notification is limited, especially among children, and a possible bias to report better results following surgery cannot be excluded.[28] Reports on seizure outcomes, as well as on the number of ASMs, were not complete. Thus, a bias toward better seizure control cannot be excluded. We did not include dosages of ASM or change to different drugs, possibly affecting seizure outcome. Some of the patients had a VNS battery

change after CC, perhaps contributing to better seizure control, mood, and overall quality of life. We did not collect data regarding the need for VNS battery change, or avoidance of replacement when it was needed.

Despite these limitations, these children were treated for several years with various ASMs. Parents were aware of the seizure semiology; thus, although potentially inaccurate, their report of seizure reduction most likely reflects an actual decline.

5 | CONCLUSIONS

CC has a significant added value in controlling seizures in children with LGS who had prior VNS. Callosotomy resulted in better seizure control considering a >50% cutoff for drop attacks and other seizure types. CC was associated with a low complication rate. Complete callosotomy resulted in better seizure control compared to anterior callosotomy considering a >50% cutoff for other seizure types.

AFFILIATIONS

[1]Department of Pediatric Neurosurgery, Dana Children's Hospital, Tel Aviv Medical Center, Tel Aviv University, Tel Aviv, Israel
[2]Division of Neurosurgery, Department of Surgery, Sainte-Justine University Hospital Centre and University of Montreal Hospital Centre, Montreal, Quebec, Canada
[3]Department of Neurosurgery, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA
[4]Division of Pediatric Neurosurgery, Department of Surgery, Texas Children's Hospital, Houston, Texas, USA
[5]Department of Neurosurgery, University of Utah School of Medicine, Salt Lake City, Utah, USA
[6]Department of Neurosurgery, Epilepsy Surgery Program, Clinica Cukiert, Sao Paulo, Brazil
[7]Department of Neurology and Neurophysiology, Epilepsy Surgery Program, Clinica Cukiert, Sao Paulo, Brazil
[8]Center of Excellence for Epilepsy and MEG, AIIMS, New Delhi, India
[9]Division of Pediatric Neurosurgery, University of Utah School of Medicine, Primary Children's Hospital, Salt Lake City, Utah, USA
[10]Division of Pediatric Neurosurgery, Center for Epilepsy Surgery in Children, Ribeirão Preto Medical School, University of São Paulo, Sao Paulo, Brazil
[11]Division of Pediatric Neurosurgery, Department of Surgery and Anatomy, Ribeirão Preto Medical School, University of São Paulo, Sao Paulo, Brazil
[12]Department of Neurology, Children's National Medical Center, Washington, District of Columbia, USA
[13]Department of Neurosurgery, Children's National Medical Center, Washington, District of Columbia, USA
[14]Department of Surgery, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
[15]Institute for Brain Protection Sciences, Johns Hopkins All Children's Hospital, St. Petersburg, Florida, USA
[16]Department of Surgery, St. Jude Children's Research Hospital, Memphis, Tennessee, USA
[17]Le Bonheur Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, Tennessee, USA
[18]Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, Tennessee, USA
[19]Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[20]Division of Pediatric Neurosurgery, Children's Hospital Colorado, Aurora, Colorado, USA
[21]Department of Neurosurgery, Niño Jesus University Children's Hospital, Madrid, Spain
[22]Department of Neurophysiology, Niño Jesus University Children's Hospital, Madrid, Spain
[23]Division of Pediatric Neurosurgery, Cincinnati Children's Hospital, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA
[24]Department of Neurosurgery, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan
[25]Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[26]Department of Neurosurgery, Jichi Medical University, Tochigi, Japan
[27]Pediatric Neurosurgery, Leon Pediatric Neuroscience Center of Excellence, Arnold Palmer Hospital for Children, Orlando, Florida, USA
[28]Pediatric Neurology and Epilepsy, Leon Pediatric Neuroscience Center of Excellence, Arnold Palmer Hospital for Children, Orlando, Florida, USA
[29]Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[30]Department of Neurosurgery, Great Ormond Street Hospital, London, UK
[31]Developmental Neurosciences, Great Ormond Street Institute of Child Health, University College London, London, UK
[32]Department of Neurosurgery, Krishna Institute of Medical Sciences, Hyderabad, India
[33]Department of Neurology, Krishna Institute of Medical Sciences, Hyderabad, India
[34]Division of Pediatric Neurosurgery, Department of Neurosurgery, University of Alabama at Birmingham, Children's Hospital of Alabama, Birmingham, Alabama, USA
[35]Pediatric Neurosurgery Department, Rothschild Foundation Hospital, Paris, France
[36]University of Paris, MC2Lab, Boulogne-Billancourt, France
[37]Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[38]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[39]Division of Pediatric Neurosurgery, Department of Surgery, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[40]Comprehensive Epilepsy Program, BC Children's Hospital, Vancouver, British Columbia, Canada
[41]Neuroscience Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[42]Department of Surgery, Nicklaus Children's Hospital, University of Miami Leonard M. Miller School of Medicine, Miami, Florida, USA
[43]Pediatric Neurology Unit, Dana Children's Hospital, Tel Aviv Medical Center, Tel Aviv University, Tel Aviv, Israel

ACKNOWLEDGMENTS

We thank Mrs. Adina Sherer for editorial assistance.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

ORCID

Jonathan Roth https://orcid.org/0000-0002-4267-8835
Lottem Bergman https://orcid.org/0000-0002-5447-1751
Alexander G. Weil https://orcid.org/0000-0003-4162-6096
Ben Shofty https://orcid.org/0000-0002-2949-4740
Manjari Tripathi https://orcid.org/0000-0003-2201-5644
Poodipedi Sarat Chandra https://orcid.org/0000-0002-3375-6803
William D. Gaillard https://orcid.org/0000-0001-5709-0033
George M. Ibrahim https://orcid.org/0000-0001-9068-8184
Nir Shimony https://orcid.org/0000-0002-7930-8782
Masaki Iwasaki https://orcid.org/0000-0002-4204-7144
Keiya Iijima https://orcid.org/0000-0002-6249-7732
Kensuke Kawai https://orcid.org/0000-0002-8218-7360
Yohei Ishishita https://orcid.org/0000-0002-9104-2358
Aria Fallah https://orcid.org/0000-0002-9703-0964
Ido Ben-Zvi https://orcid.org/0000-0003-3700-0672
Sita Jayalakshmi https://orcid.org/0000-0001-8630-0896

REFERENCES

1. Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. Epilepsia. 2011;52(Suppl 5):3–9. https://doi.org/10.1111/j.1528-1167.2011.03177.x
2. Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009;8(1):82–93. https://doi.org/10.1016/S1474-4422(08)70292-8
3. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2018;39(3):403–14. https://doi.org/10.1007/s10072-017-3188-y
4. Thirunavu V, Du R, Wu JY, Berg AT, Lam SK. The role of surgery in the management of Lennox–Gastaut syndrome: a systematic review and meta-analysis of the clinical evidence. Epilepsia. 2021;62(4):888–907. https://doi.org/10.1111/epi.16851
5. Ferreira Soares D, Pires de Aguiar PH. Callosotomy vs vagus nerve stimulation in the treatment of Lennox-Gastaut syndrome: a systematic review with meta-analysis. Neuromodulation. 2022;1:518–28. https://doi.org/10.1016/j.neurom.2022.06.005
6. Rolston JD, Englot DJ, Wang DD, Garcia PA, Chang EF. Corpus callosotomy versus vagus nerve stimulation for atonic seizures and drop attacks: a systematic review. Epilepsy Behav. 2015;51:13–7. https://doi.org/10.1016/j.yebeh.2015.06.001
7. Cukiert A, Cukiert CM, Burattini JA, Lima AM, Forster CR, Baise C, et al. Long-term outcome after callosotomy or vagus nerve stimulation in consecutive prospective cohorts of children with Lennox-Gastaut or Lennox-like syndrome and non-specific MRI findings. Seizure. 2013;22(5):396–400. https://doi.org/10.1016/j.seizure.2013.02.009
8. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE task force on nosology and definitions. Epilepsia. 2022;63(6):1398–442. https://doi.org/10.1111/EPI.17241
9. Lancman G, Virk M, Shao H, Mazumdar M, Greenfield JP, Weinstein S, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis. Seizure. 2013;22(1):3–8. https://doi.org/10.1016/j.seizure.2012.09.014
10. You SJ, Kang HC, Ko TS, Kim HD, Yum MS, Hwang YS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. Brain Dev. 2008;30(3):195–9. https://doi.org/10.1016/j.braindev.2007.07.013
11. Abel TJ, Remick M, Welch WC, Smith KJ. One-year cost-effectiveness of callosotomy vs vagus nerve stimulation for drug-resistant seizures in Lennox-Gastaut syndrome: a decision analytic model. Epilepsia Open. 2022;7(1):124–30. https://doi.org/10.1002/EPI4.12570
12. Hong J, Desai A, Thadani VM, Roberts DW. Effcacy and safety of corpus callosotomy after vagal nerve stimulation in patients with drug-resistant epilepsy. J Neurosurg. 2018;128(1):277–86. https://doi.org/10.3171/2016.10.JNS161841
13. Guillamón E, Miró J, Gutiérrez A, Conde R, Falip M, Jaraba S, et al. Combination of corpus callosotomy and vagus nerve stimulation in the treatment of refractory epilepsy. Eur Neurol. 2014;71(1-2):65–74. https://doi.org/10.1159/000353979
14. Arya R, Greiner HM, Horn PS, Turner M, Holland KD, Mangano FT. Corpus callosotomy for childhood-onset drug-resistant epilepsy unresponsive to vagus nerve stimulation. Pediatr Neurol. 2014;51(6):800–5. https://doi.org/10.1016/J.PEDIATRNEUROL.2014.09.008
15. Katagiri M, Iida K, Kagawa K, Hashizume A, Ishikawa N, Hanaya R, et al. Combined surgical intervention with vagus nerve stimulation following corpus callosotomy in patients with Lennox-Gastaut syndrome. Acta Neurochir. 2016;158(5):1005–12. https://doi.org/10.1007/s00701-016-2765-9
16. Smyth MD, Vellimana AK, Asano E, Sood S. Corpus callosotomy—open and endoscopic surgical techniques. Epilepsia. 2017;58:73–9. https://doi.org/10.1111/EPI.13681
17. Doddamani R, Kota R, Ahemad N, Chandra S, Tripathi M. Endoscopic total corpus callosotomy and pan commissurotomy for Lennox-Gastaut syndrome. Neurol India. 2022;70(1):63–7. https://doi.org/10.4103/0028-3886.338654
18. Caruso JP, Janjua MB, Dolce A, Price AV. Retrospective analysis of open surgical versus laser interstitial thermal therapy callosotomy in pediatric patients with refractory epilepsy. J Neurosurg Pediatr. 2021;27(4):420–8. https://doi.org/10.3171/2020.7.PEDS20167
19. Mallela AN, Hect JL, Abou-Al-Shaar H, Akwayena E, Abel TJ. Stereotactic laser interstitial thermal therapy corpus callosotomy for the treatment of pediatric drug-resistant epilepsy. Epilepsia Open. 2022;7(1):75–84. https://doi.org/10.1002/EPI4.12559
20. Liang S, Zhang S, Hu X, Zhang Z, Fu X, Jiang H, et al. Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. Eur J Paediatr Neurol. 2014;18(6):670–6. https://doi.org/10.1016/J.EJPN.2014.05.004
21. Cukiert A, Burattini JA, Mariani PP, Camara RB, Seda L, Baldauf CM, et al. Extended, one-stage callosal section for treatment of refractory secondarily generalized epilepsy in patients with Lennox-Gastaut and Lennox-like syndromes. Epilepsia.

2006;47(2):371–4. https://doi.org/10.1111/J.1528-1167.2006.00430.X

22. Paglioli E, Martins WA, Azambuja N, Portuguez M, Frigeri TM, Pinos L, et al. Selective posterior callosotomy for drop attacks: a new approach sparing prefrontal connectivity. Neurology. 2016;87(19):1968–74. https://doi.org/10.1212/WNL.0000000000003307
23. Jea A, Vachhrajani S, Widjaja E, Nilsson D, Raybaud C, Shroff M, et al. Corpus callosotomy in children and the disconnection syndromes: a review. Childs Nerv Syst. 2008;24(6):685–92. https://doi.org/10.1007/S00381-008-0626-4
24. Ruffoli R, Giorgi FS, Pizzanelli C, Murri L, Paparelli A, Fornai F. The chemical neuroanatomy of vagus nerve stimulation. J Chem Neuroanat. 2011;42(4):288–96. https://doi.org/10.1016/j.jchemneu.2010.12.002
25. Di Lazzaro V, Oliviero A, Pilato F, et al. Effects of vagus nerve stimulation on cortical excitability in epileptic patients. Neurology. 2004;62(12):2310–2. https://doi.org/10.1212/01.WNL.0000131743.45131.AE
26. Carron R, Roncon P, Lagarde S, Dibué M, Zanello M, Bartolomei F. Latest views on the mechanisms of action of surgically implanted cervical vagal nerve stimulation in epilepsy. Neuromodulation. 2023;26(3):498–506. https://doi.org/10.1016/J.NEUROM.2022.08.447
27. Fahoum F, Boffini M, Kann L, Faini S, Gordon C, Tzadok M, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;15(3):814–21. https://doi.org/10.1016/J.BRS.2022.05.016
28. Akman CI, Montenegro MA, Jacob S, Eck K, Chiriboga C, Gilliam F. Seizure frequency in children with epilepsy: factors influencing accuracy and parental awareness. Seizure. 2009;18(7):524–9. https://doi.org/10.1016/J.SEIZURE.2009.05.009

How to cite this article: Roth J, Bergman L, Weil AG, Brunette-Clement T, Weiner HL, Treiber JM, et al. Added value of corpus callosotomy following vagus nerve stimulation in children with Lennox–Gastaut syndrome: A multicenter, multinational study. Epilepsia. 2023;64:3205–3212. https://doi.org/10.1111/epi.17796