LETTER TO THE EDITOR

To the Editor

Delayed Response to Corpus Callosotomy

Keywords: Corpus callosotomy, Epilepsy surgery, Refractory epilepsy, Intractable epilepsy, Delayed response

The corpus callosum is an important pathway for interhemispheric spread of epileptiform activity.[1] Corpus callosotomy (CC) was first introduced in 1940 as a palliative surgical treatment involving partial or complete disconnection of the corpus callosum.[2] Studies have shown that CC improves outcomes in terms of seizure control within six months, but it is well reported that many patients can respond immediately after the procedure.[3] CC is not a first-line treatment due to its associated high morbidity, especially in regard to disconnection syndrome and other potential complications.

We report a 23-year-old right-handed female who first presented with seizures at the age of 16. Her first event was a generalized tonic-clonic seizure. She did not have any past medical conditions, and she did not have a family history of epilepsy. She was born at 32 weeks and hospitalized for 2 months because she had apneic episodes. She did not experience any seizures as a child. Her neurological exam was unremarkable. Her cognition was average in all functions. Some seizures were triggered by menstruation.

Her initial investigations included normal laboratory work, while CT and MRI showed bilateral subepedymal heterotopic nodules in the temporal, occipital and posterior horns of the lateral ventricles (Figure 1). Her routine EEGs showed generalized epileptiform activity, sometimes preceded by focal spikes from both posterior temporal regions, more commonly from the left (secondary bilateral synchrony) (Figure 2A). She was initially treated with phenytoin followed by valproate and clobazam, with inadequate control of seizures.

Within a year of her seizure onset, she had malignant evolution with the addition of two different types of seizures. She began to develop atypical absences manifested by staring spells with oral and bimanual automatisms. In some absences, the patient had postictal confusion. She would drop objects from her hands during these episodes. She experienced two to three absences per day. In addition, she began to experience weekly drop attacks. She also had fractured multiple facial bones and shoulder joints secondary to the drop attacks. The generalized tonic-clonic seizures were less frequent—approximately one every three to four months. She had multiple video-EEG telemetries, which showed generalized spike-and-wave at 2.5-3 Hz during her atypical absences and drop attacks. We never recorded a focal seizure from the areas where the MRI abnormalities were located. She failed the following antiepileptic drugs (AEDs): lamotrigine, levetiracetam, phenobarbital, carbamazepine, ethosuximide, topiramate, Diamox, lacosamide and rufinamide. She had also failed a ketogenic diet and addition of hormonal agents to the AED regimen. The combination that produced some improvement was carbamazepine 400 mg BID, lamotrigine 150 mg BID and phenobarbital 60 mg PO o.d. In 2009, she had a vagal nerve stimulator implanted with multiple titrated levels to a maximum of 2.75 mA as an output current. However, she did not respond adequately to the procedure for four years. The patient was referred to neurosurgery for a potential callosotomy. She received an anterior corpus callosotomy at the age of 23. There was some hesitation in doing the procedure due to her normal cognition. The EEG following corpus callosotomy showed generalized epileptiform activity with evidence of disruption of interhemispheric synchrony (Figure 2B). Her response to the procedure was inadequate at the end of the first year post-surgery. She then began to experience progressive improvement. No change in dose or addition of new AEDs was done after the callosotomy. Also, no other intervention was performed after the callosotomy. At present, the patient is free of drop attacks and has a reduced number of absences that interfere with her lifestyle. Since the procedure, she has not had any generalized tonic-clonic seizures at around 30 months post-surgery. Her neuropsychological testing after surgery showed no significant changes.

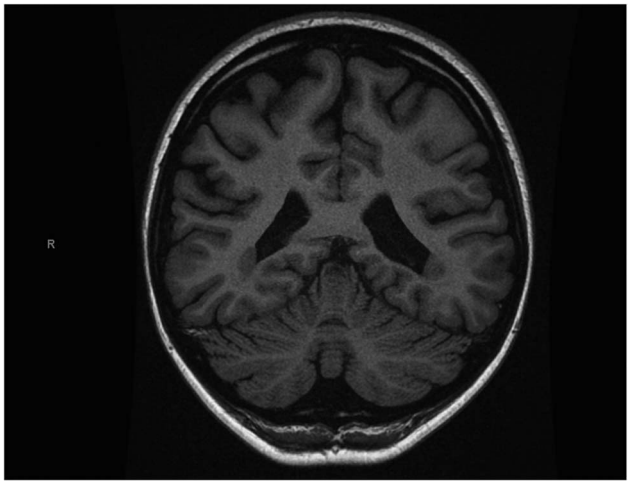

Figure 1: *MRI T1-weighted sagittal brain. Bilateral subependymal heterotopic nodules.*

Corpus callosotomy was first introduced in 1940 by van Wagenen and Herren as a treatment for intractable epilepsy.[2,3-7] It involves the section of the corpus callosum that is involved in interhemispheric spread of epileptiform activity.[2,3,7] Anterior corpus callosotomy sparing the splenium is generally the preferred procedure.[2,6] It has a relatively acceptable side-effect profile compared to complete corpus callosotomy.[5,8] Some of the complications include disconnection syndrome, alien hand syndrome, motor deficits, language impairment and memory deficit.[7,8]

There are no randomized control trials assessing the efficacy of corpus callosotomy. However, a recent meta-analysis suggested that corpus callosotomy may be significantly more effective than vagal nerve stimulation in achieving 50 and 75% reductions in atonic seizures associated with Lennox–Gastaut syndrome.[6] There was no statistically significant difference in tonic, generalized tonic-clonic, complex partial and myoclonic seizures.[6] Most studies have consistently reported a >75% reduction in drop attacks and a >56% rate of complete freedom from drop attacks.[8] In addition, the procedure has shown a >50% reduction in generalized tonic-clonic seizures and complex partial seizures.[7,8] In one study,[3] corpus callosotomy demonstrated a >80%

https://doi.org/10.1017/cjn.2016.313 Published online by Cambridge University Press

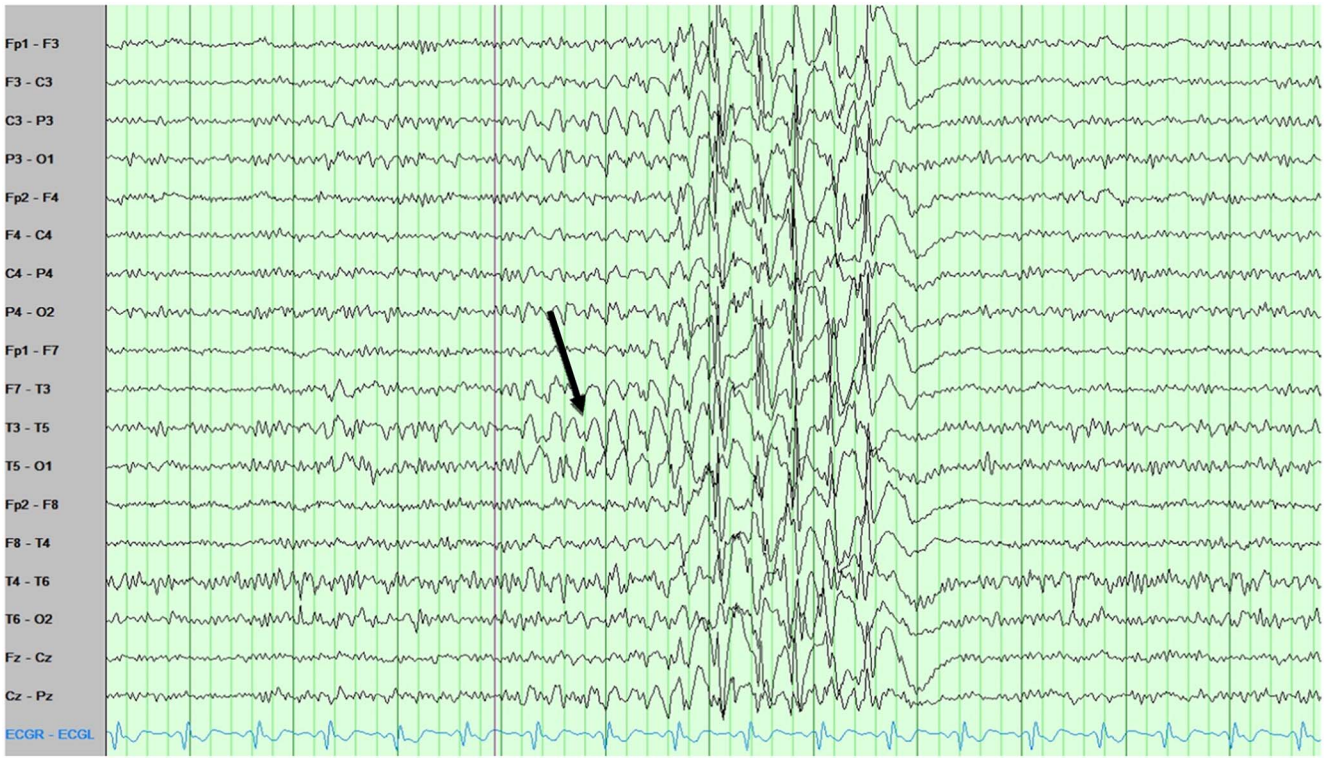

Figure 2A: *Anterior–posterior bipolar montage pre-corpus callosotomy. Interictally, the EEG shows focal spikes from the left posterior temporal region maximum at T5 followed by secondary generalized discharges (arrow). Ictal recordings show the presence of generalized spike and wave at 2.5–3 Hz during drop attacks and absences with no focal onset. Parameters: sensitivity 7 μV/ml, time base 60 mm/sec.*

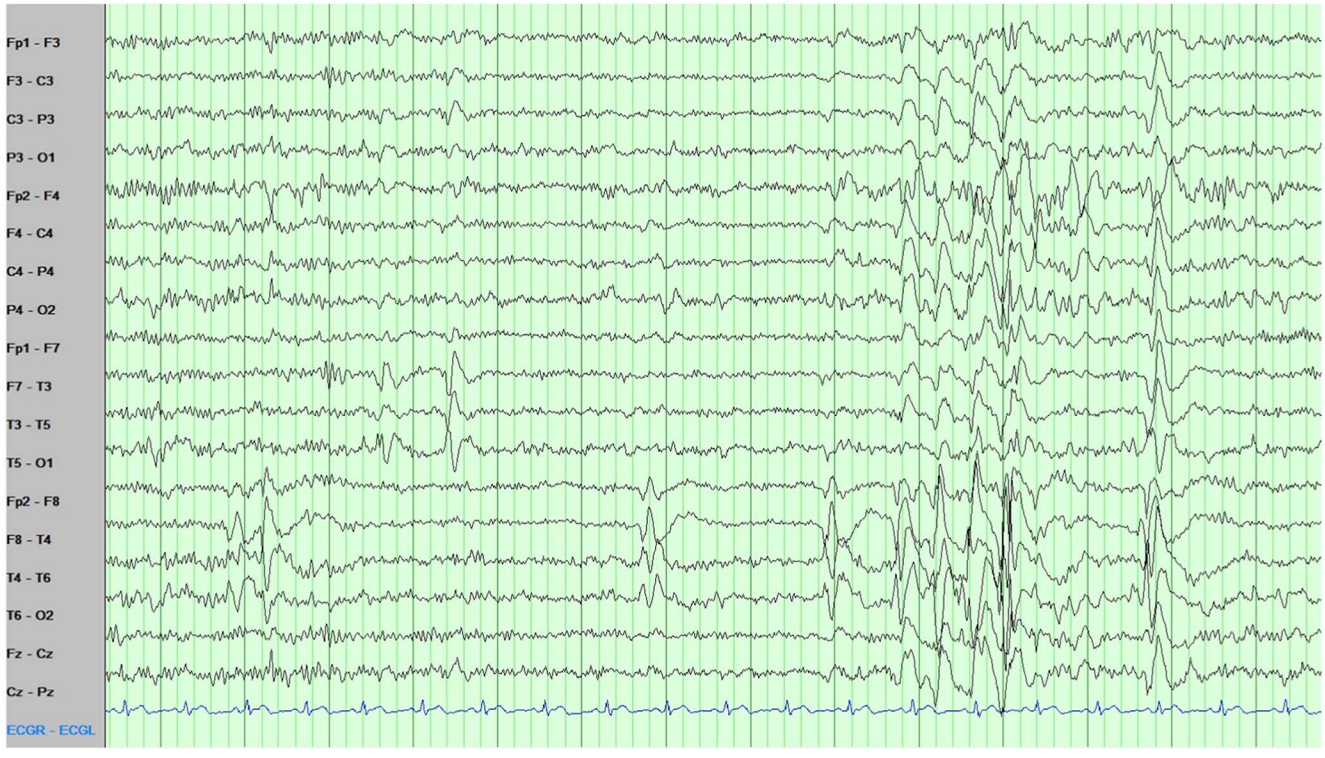

Figure 2B: *Anterior–posterior bipolar montage post-corpus callosotomy. Generalized epileptiform activity with evidence of disruption interhemispheric synchrony post-corpus callosotomy. Parameters: sensitivity 7 μV/ml, time base 60 mm/sec.*

https://doi.org/10.1017/cjn.2016.313 Published online by Cambridge University Press

reduction in seizures when all seizure types were considered. In general, the procedures have shown favourable results. Our case is unique because the patient had average cognition. The literature that describes the use of callosotomy is almost entirely in patients with developmental delay and Lenox–Gastaut syndrome, and the procedure is rarely performed in patients with normal cognition.

Multiple studies have shown that the timing of the response is fast after CC. A 2014 retrospective study showed that, among the 64% of subjects who achieved seizure improvement, 78% achieved this result immediately after surgery.[3] The mean interval of improvement was four months post-CC.[3] Other evidence shows that the response is seen in more than 90% of patients within the first year after the procedure.[6] Our case is an exception to the usual course of patients with a CC. The most intriguing factor in our case is that the response to the corpus callosotomy was seen almost two years after the procedure. This delayed effect may be related to a delayed restructuring of interhemispheric pathways, which contributed to the spread of epileptiform activity. Our case is unusual, but it should nonetheless alert physicians to a possible delayed response to the callosotomy. It also suggests that the procedure can be done in patients with normal cognition, although this aspect has to be clarified in the future with more evidence.

Acknowledgments

Dr. Téllez-Zenteno receives grants from the University of Saskatchewan, the Saskatchewan Health Research Foundation and the Royal University Hospital Foundation in Saskatoon, Saskatchewan.

Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

Statement of Authorship

José F. Téllez-Zenteno, Pragma Laboni Roy, Adam Wu and Chelsea Dash have participated in the medical care of the patient. All took part in writing this document, and all reviewed its final version.

Disclosures

José Téllez-Zenteno has the following disclosures: University of Saskatchewan Health Research Foundation and Royal University Hospital Foundation: grant recipient.

Pragma Laboni Roy, Adam Wu and Chelsea Dash do not have anything to disclose.

Pragma Laboni Roy
Saskatchewan Epilepsy Program, Department of Medicine
Division of Neurology, University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Adam Wu
Saskatchewan Epilepsy Program. Department of Surgery
Division of Neurosurgery, University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Chelsea Dash
Clinical Neurophysiology Department
Royal University Hospital
Saskatoon, Saskatchewan, Canada

J.F. Tellez-Zenteno
Saskatchewan Epilepsy Program, Department of Medicine
Division of Neurology, University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Correspondence to: José F. Téllez-Zenteno, Department of Medicine, Division of Neurology, Royal University Hospital, Saskatoon, Saskatchewan, S7N 0W8 Canada.
E-mail: jose.tellez@usask.ca

References

1. 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. Epub ahead of print Sep 18.
2. Asadi-Pooya AA, Malekmohamadi Z, Kamgarpour A, Rakei SM, Taghipour M, Ashjazadeh N, et al. Corpus callosotomy is a valuable therapeutic option for patients with Lennox–Gastaut syndrome and medially refractory seizures. Epilepsy Behav. 2013;29(2):285-8. Epub ahead of print Sep 5.
3. Bower RS, Wirrell E, Nwojo M, Wetjen NM, Marsh WR, Meyer FB. Seizure outcomes after corpus callosotomy for drop attacks. Neurosurgery. 2013;73(6):993-1000.
4. Iwasaki M, Umatsu M, Sato Y, Nakayama T, Haginoya K, Osawa S, et al. Complete remission of seizures after corpus callosotomy. J Neurosurg Pediatr. 2012;10(1):7-13. Epub ahead of print Jun 8. Available at: http://thejns.org/doi/pdf/10.3171/2012.3.PEDS11544.
5. Kasasbeh A, Smyth M, Steger-May K, Jalilian L, Bertrand M, Limbrick DD. Outcomes after anterior or complete corpus callosotomy in children. Neurosurgery. 2014;74(1):17-28.
6. 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. Epub ahead of print Oct 12, 2012. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3655762/.
7. Malmgren K, Rydenhag B, Hallbook T. Reappraisal of corpus callosotomy. Curr Opin Neurol. 2015;28(2):175-81.
8. Park MS, Nakagawa E, Schoenber MR, Benbadis SR, Vale FL. Outcome of corpus callosotomy in adults. Epilepsy Behav. 2013;28(2):181-4. Epub ahead of print Jun 7.

https://doi.org/10.1017/cjn.2016.313 Published online by Cambridge University Press