Case Report

Elimination of anxiety after laser interstitial thermal ablation of the dominant cingulate gyrus for epilepsy

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ABSTRACT

Background: Anxiety is a common symptom of mental health disorders. Surgical treatment of anxiety-related disorders is limited by our understanding of the neural circuitry responsible for emotional regulation. Limbic regions communicate with other cortical and subcortical regions to generate emotional responses and behaviors toward anxiogenic stimuli. Epilepsy involving corticolimbic regions may disrupt normal neural circuitry and present with mood disorders. Anxiety presenting in patients with mesial temporal lobe epilepsy is common; however, anxiety in patients with cingulate epilepsy is not well described. Neurosurgical cases with rare clinical presentations may provide insight into the basic functionality of the human mind and ultimately lead to improvements in surgical treatments.

Case Description: We present the case of a 24-year-old male with a 20-year history of nonlesional and cingulate epilepsy with an aura of anxiety and baseline anxiety. Noninvasive work-up was discordant. Intracranial evaluation using stereoencephalography established the epileptogenic zone in the left anterior and mid-cingulate gyrus. Stimulation of the cingulate reproduced a sense of anxiety typical of the habitual auras. We performed laser interstitial thermal therapy of the left anterior and mid-cingulate gyrus. At 8 months following ablation, the patient reported a substantial reduction in seizure frequency and complete elimination of his baseline anxiety and anxious auras.

Conclusion: This case highlights the role of the cingulate cortex (CC) in regulating anxiety. Ablation of the epileptic focus resolved both epilepsy-related anxiety and baseline features. Future studies assessing the role of the CC in anxiety disorders may enable improvements in surgical treatments for anxiety disorders.

Keywords: Cingulate epilepsy, Epilepsy surgery, Ictal anxiety, Laser interstitial thermal therapy, Stereoeencephalography, Stereotactic laser ablation

INTRODUCTION

Anxiety is a debilitating symptom that occurs in 28% of adults and up to 60% of epilepsy patients.⁵,¹⁹,²⁰ Anxiety on its own is not a surgical disease; however, anxiety presenting as part of a more complex disorder, such as obsessive compulsive disorder (OCD), may be treated surgically in select cases. Surgical treatment is limited by our current understanding of neural circuits responsible for emotional states and heterogeneous phenotypic presentations of anxiety disorders.⁶,¹⁰,¹⁷ Several studies in humans and animal models have shown that limbic structures, such as the amygdala and hippocampus, play a central role in forming emotional responses to aversive stimuli.
Connections between limbic areas and subcortical and cortical areas, including the bed nucleus of the stria terminalis, hypothalamus, ventromedial prefrontal cortex, insula, and cingulate cortex (CC), allow for interpretation of emotional responses and subsequent action to address anxiogenic stimuli. Neuromodulation and surgical ablation targeting these networks have been used to treat medically refractory OCD, but have not yet been extended more broadly to other anxiety disorders. Before possible surgical treatment of anxiety-related disorders can be advanced, a better understanding of the neural mechanisms regulating excessive aversive response to benign stimuli is required.

In epilepsy with foci located in corticolimbic structures, disruption of normal circuitry may result in anxiety presenting concurrently with epilepsy or as part of the seizure. Anxiety and anxious auras are common in mesial temporal lobe epilepsy (MTLE); however, anxiety in cingulate epilepsy is poorly characterized. The CC is an important relay center between temporal limbic structures and other cortical regions in the emotional regulation network; thus, disruption of circuitry in cingulate epilepsy may also present with anxiety. Neurosurgical cases with rare clinical presentations may provide insight into whether disrupted CC function promotes anxiety and ultimately lead to improvements in surgical treatments.

Here, we describe a case of a young patient with nonlesional, focal, dominant cingulate epilepsy with strong anxious auras, and high baseline anxiety. We utilized stereoelectroencephalography (sEEG) and laser interstitial thermal therapy (LITT) to localize and ablate, respectively, epileptogenic foci in the anterior CC (ACC) and middle CC (MCC). Following surgical ablation, the patient reported complete elimination of baseline anxiety and anxious auras along with adequate seizure reduction. The patient’s clinical presentation, treatment outcome, and a discussion of the literature are presented.

CASE PRESENTATION

History and presentation

A 24-year-old right-handed man with no relevant medical history presented with a history of epilepsy since 4 years of age. Initially, his seizures occurred at night accompanied by bouts of crying and bad dreams. His semiology then progressed to seizures consisting of loss of balance, increased muscle tension, and “zoning out.” In the 3 years before epilepsy surgery, his seizure semiology changed and consisted of an aura of confusion and anxiety followed by an ictal period of arousal, body tingling, leg extension, and thrashing of the arms and legs lasting 30–50 s. Sometimes, the thrashing would progress to generalized bilateral tonic-clonic seizures, followed by post ictal confusion. His seizures mainly occurred while asleep and occurred up to every other night. Since turning 21, the patient’s seizures have become more frequent, and he reported increased anxiety associated with the seizures despite no clear life events that may have triggered the increase in anxiety. The patient reported avoiding situations or conversations that may cause distress, such as attending college courses or discussing his health condition. The patient took sertraline to manage his anxiety, which provided moderate relief of baseline anxiety but had no therapeutic effect on his anxious aura. His anxiety-induced avoidance behavior substantially impaired his quality of life.

Following his initial diagnosis, the patient was treated with oxcarbazepine and was seizure-free for 1 year between 6 and 7 years of age. After his seizures returned, the dosage of oxcarbazepine was increased without benefit. Topiramate, levetiracetam, zonisamide, and laosamide were added to his antiepileptic drug regimen at various points but were discontinued due to side effects. Before surgery, the patient was on oxcarbazepine and cannabidiol for his epilepsy.

Phase 1 evaluation: Noninvasive work-up

The patient was admitted to the epilepsy monitoring unit for scalp EEG, during which he had six habitual seizures. EEG was nonlocalizing, as no clear ictal pattern was discerned. However, the clinical characteristics of nocturnal predominance, brief duration, maintained awareness, and hyperkinetic features suggested a mesial frontal epileptogenic zone. The patient’s head turning to the right suggested lateralization to the left hemisphere, but a “Figure of 4 sign” seen late in the generalized seizure with the left arm extended was suggestive of a right hemisphere source. Complex bilateral and hyperkinetic movements suggested a midline or supplementary motor area involvement. As there were no clear ictal EEG changes or interictal epileptiform discharges, deeper structures such as the mesial parietal or frontal areas were hypothesized to be involved. Observations of ictal tachycardia further suggested a mesial temporal source.

Brain magnetic resonance imaging (MRI) appeared normal. Positron emission tomography showed hypometabolism in the temporal lobes bilaterally, with a greater reduction in the right temporal lobe. Magnetoencephalography showed a single right-sided posterior insular cluster. Both magnetoencephalography and positron emission tomography findings were discordant with the semiology. Neuropsychiatric evaluation showed elevated baseline anxiety and poor distress tolerance.

The patient’s case was presented to a multidisciplinary epilepsy surgery conference. Given that the data obtained from the noninvasive work-up were non-conclusive, the clinical team decided that the patient would be a suitable candidate for intracranial evaluation using sEEG for further localization of the seizure focus.
Phase 2 evaluation: Stereoecephalography

The patient underwent a sEEG study with bilateral frontotemporal and parietal coverage including the insular cortex and CC [Figure 1]. Initially, 20 SEEG electrodes were placed using robotic guidance with ROSA planning software (Zimmer, Montpellier, France). After 1 week in the epilepsy monitoring unit, sEEG captured three electroclinical seizures. All three seizures consisted of slowing with attenuation of background EEG signal and superimposed low voltage fast activity over the two deepest contacts in the left cingulate electrode. Due to the observed activity in the left CC and poor lateralization and localization of onset and spread of seizure activity, the clinical team opted for expanded electrode coverage in the left CC. Consequently, four additional depth electrodes were inserted targeting the left ACC, MCC, and posterior CC to better localize the epileptogenic foci within the cingulate gyrus [Figure 1]. After expanding left CC coverage, six seizures were captured, all localized to the left ACC and MCC. On EEG, all nine seizures showed spread to the insula and mesial temporal lobe bilaterally. All seizures were preceded by a patient-described anxious aura. Intercital repetitive sharp spikes and high-frequency oscillations were seen in the left CC, right insula, and bilateral hippocampi. Electrical stimulation of the deepest ACC and MCC contacts reproduced a strong sense of anxiety typical of his habitual auras. In addition, stimulation of the deepest contacts in the posterior CC reproduced the sense of confusion that was typical of the post ictal period.

Throughout his hospital stay, the patient expressed an overwhelming sense of anxiety regarding constant pain, headaches, and desires to leave the hospital. Notably, the severity of his anxiety increased as he was weaned off antiepileptic drugs to induce seizures.

LITT

After intracranial evaluation, the patient had nightly habitual seizures with a strong aura of anxiety. Based on Phases 1 and 2 evaluations, we presented the patient with laser ablation, surgical resection, responsive neural stimulation, or deep brain stimulation as treatment options. After deliberation, the patient chose to proceed with laser ablation. Roughly 3 months after his discharge from the intracranial evaluation, the patient underwent LITT ablation of his epileptic focus.

Under general anesthesia, the patient’s head was affixed to the ROSA using a Leksell (Elekta, Atlanta, GA, USA) frame, and fluoroscopic computed tomography (CT) was performed (O-arm O2, Medtronic, Minnesota, United States). The images were fused with the preoperative planning MRI and CT. The preoperative plan was loaded into the ROSA stereotactic robot and the robot was registered using the frame pins as skull fiducials. Our full stereotactic workflow has been described in detail.[18] Two trajectories were planned for ablation: left ACC and left MCC. A parasagittal posterior approach was used to insert both optical fibers and cooling cannulas with robotic guidance. Intraoperative CT was used to confirm probe placements. The patient was placed in the MRI scanner for ablation under MRI thermometry control. Background images were obtained to verify catheter probe placements before ablation. A test dose of 30% power was used to confirm the fiber location, after which power was increased to 80% to create a lesion. For the ACC trajectory, a primary lesion was made followed by a secondary lesion after one pull back to cover the desired area in the ACC. For the MCC trajectory, six pull backs were performed to cover the entire region [Figure 2, Video 1]. Total ablation volume was 17.86 cm$^3$ [Figure 3]. The patient was transferred to the postanesthesia care unit for further postoperative care and was discharged the following day in satisfactory condition.

Figure 1: Stereoecephalography electrode placement. (a) Anterior view of bilateral electrode placement in frontal and temporal lobes with insular and cingulate coverage. Yellow and blue lines represent electrodes targeting the cingulate gyrus and non-cingulate regions respectively. (b) Left cingulate electrode coverage with the cingulate gyrus highlighted in yellow.

Figure 2: Laser interstitial thermal therapy trajectory and ablation volume. (a) Sagittal view of the left anterior cingulate trajectory. (b) Coronal view of left anterior cingulate trajectory. (c) Sagittal view of the left middle cingulate trajectory. (d) Axial view of the left middle cingulate trajectory. Orange mask over the brain indicates the ablation volume of the trajectory.
Postoperative follow-up

After surgery, the patient reported complete elimination of his anxiety. For 3 weeks after laser ablation, the patient experienced transient right upper and lower extremity weakness, congruent with ablation of the posterior MCC near the left supplemental motor area. After 4 months, the patient reported a constellation of nonhabitual seizures consisting of abnormal sensations starting in both feet moving up through the body. Anxiety was not present in the semiology of seizures after laser ablation. The patient had a dramatic reduction in seizure frequency from daily seizures to a total of four seizures since ablation. The patient's outcome at 8 months was categorized as Engel Class IIB.

DISCUSSION

Anxiety is a debilitating symptom caused by disruption of complex interconnected neural networks responsible for stimulus and emotion processing and integration. Defining brain regions and networks responsible for anxiety are necessary for developing effective therapies. Neurosurgical cases like ours, much like historical, and accidental lesion cases, provide a unique opportunity for understanding fundamental neural mechanisms that underlie complex human behavior. In the present case, we determined that the CC was responsible for anxiety regulation. Two prior studies describe four patients with cingulate epilepsy presenting with similar semiology consisting of auras of anxiety. In all four cases, patients presented with anxious auras followed by hypermotor ictal activity with abnormal electrographic activity localized to the ACC. Psychic auras consisting of fear, laughter, or crying were localized throughout the CC; however, cases presenting specifically with anxiety were reported to originate from the ACC.

Neurological substrate of anxiety

The ACC plays a role in mood regulation and cognitive control. The ACC is important for the induction of emotional response to pain, modulation of affect, and regulation of anxiety and depression. Stimulation of the ACC during awake craniotomies has been found to provide significant anxiolysis, whereas stimulation more posteriorly along the ACC has induced mirth and significant motor activation. In addition, cingulotomy in OCD has resulted in significant reduction of anxiety symptoms.

The basis of the ACC’s contribution to anxiety can be attributed to its role as a hub for communication among areas responsible for emotional regulation and goal-oriented cognitive control. For example, in nonpathological states, areas responsible for the detection of and response to aversive stimuli (i.e., amygdala, prefrontal cortex, and orbitofrontal cortex) are functionally connected to the ACC, which then sends signals to areas responsible for the removal of these stimuli (i.e., supplemental motor area, thalamus, and striatum). In pathological states such as OCD or anxiety disorders, the ACC may be aberrantly active, sending superfluous signals of negative affect and discomfort to efferent systems. In cingulate epilepsy, activation of the ACC during ictal events may produce the anxiety felt persistently by OCD patients and could be a reason for the anxiolytic effect of cingulum ablation. Furthermore, anxiety presenting in MTLE may result from desynchrony between the ACC and the amygdala. Direct activation of the amygdala can induce primal emotions such as fear; however, disruption of pathways from the amygdala to functionally connected brain regions in MTLE may lead to higher-order emotional dysregulation manifesting as anxiety. Although MTLE and cingulate epilepsy have different epileptogenic foci, they may involve the same mood regulation network and present with similar psychiatric symptoms.

In the present case, LITT of the ACC provided complete elimination of ictal and baseline elevated anxiety levels. On
initial presentation, the relationship between the patient's anxiety and epilepsy was not clear. Before sEEG, increased anxiety, reported by the patient as his epilepsy burden increased, was characterized as a common comorbidity of increased seizure frequency rather than temporarily linked to his seizures. After surgical ablation, it was evident that his baseline anxiety could have been a result of ictal activity in the ACC without progression to motor seizures. Furthermore, elimination of anxious auras with development of new semiology without anxiety after ablation provides more evidence that the patient's anxiety was temporally and spatially linked to neural activity in the ACC. This case corroborates prior neuromodulation studies and further characterizes the role of the ACC in regulating anxiety.

Current surgical treatments for anxiety disorders are limited by the heterogeneity of phenotypes of anxiety disorders and poor characterization of the underlying neural circuitry. Given the role of the ACC as a hub for communication within emotional regulation networks and the dramatic results seen in this case, the ACC may serve as a general target for anxiety treatment through neuromodulation or surgical ablation. Few studies have assessed the effects of ACC neuromodulation for anxiety disorders; however, the future work that better defines the role of the ACC in anxiety may lead to therapeutic breakthroughs.\[15,34\]

**Limitations**

Although we provide strong evidence for the role of the ACC in regulating anxiety through a lesional study, findings arising from a single patient may limit the generalizability of the phenomenon. Still, our case supports prior findings in the literature regarding this causal relationship, which should be further studied in larger series of patients with similar ailments.

**CONCLUSION**

We present the case of a 24-year-old man with a 20-year history of dominant hemisphere focal nonlesional cingulate epilepsy with elevated baseline anxiety and anxious auras. The patient underwent sEEG with successful localization of the epileptogenic zone followed by LITT to ablate seizure foci in the ACC and MCC. Surgical ablation eliminated the patient's baseline anxiety and anxious auras and provided significant seizure reduction 8-months postoperatively. This case provides further evidence supporting the central role of the ACC in anxiety disorders.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent.

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**Conflicts of interest**

SAS is a consultant for Boston Scientific, Neuropace, Abbott, and Zimmer Biomet. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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