Anterior Cingulate Epilepsy in an 18-Year-Old Woman

-1- Deepak Madhavan, Tracey Liebman, Siddhartha Nadkarni, Orrin Devinsky

Department of Neurology, New York University School of Medicine, New York, NY

Anterior cingulate epilepsy is a diagnostic and therapeutic challenge, with a broad range of nonspecific symptoms. Seizures can arise from any region of the anterior cingulate cortex (ACC) and manifest distinctive features based on the area of onset and pattern of spread. Although these features may provide insight as to the origin of the seizures, because the ACC integrates information from several networks involving emotional and executive functions and has a diverse cytoarchitecture, functional-structural correlates are far from clear. Further, the location of the ACC within the interhemispheric fissure limits the capacity of scalp electrodes to record seizure activity from this region. This case review illustrates one part of the spectrum of cingulate epilepsy and discusses clinical features of the disorder.

[Rev Neurol Dis. *2006;3(4):XX-XX*]

Key words: Anterior cingulate cortex • Seizures • Cingulate epilepsy

The anterior cingulate cortex (ACC) is the largest region of limbic cortex and integrates information from several networks involving emotional and executive functions, including motivational behaviors, affect, perception of pain, emotional responses, motor activity, and response selection.[1] It has a diverse cytoarchitecture, with different anatomical regions projecting to or connecting to distinct networks. The ACC has two major subdivisions: a dorsal cognitive division and a rostral–ventral emotional division. The dorsal ACC has robust connections to the dorsolateral prefrontal cortex and also contains the cingulate motor area. The rostral–ventral ACC is divided into the subgenual ACC (autonomic functions) and the posterior ACC (experience of emotion).[2]

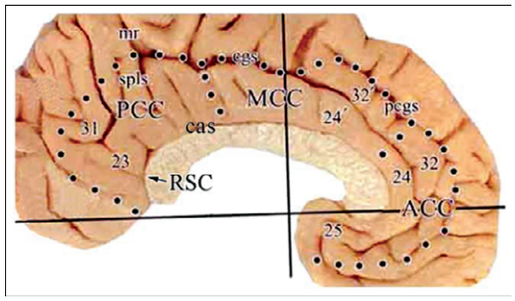

Figure 1. *Cingulate cortex, outlined by black dots. Brodmann areas are numbered. mr, marginal ramus of the cingulate sulcus; spls, splenial sulci; PCC, posterior cingulate cortex; RSC, retrosplenial cortex; cas, ; cgs, cingulate sulcus; MCC, mid-cingulate cortex; pcgs, paracingulate sulcus; ACC, anterior cingulate cortex. Image courtesy of Brent A. Vogt, PhD.*

-2- Cingulate seizures can arise from any region of the ACC and manifest distinctive features based on the subregion of onset as well as the pattern of spread within and beyond the ACC. The diagnosis of ACC seizures is difficult[1,3,4] and is usually made only if a structural lesion is identified or if invasive electrodes are used. Its location within the interhemispheric fissure limits the capacity of scalp electrodes to record seizure activity from this region -3- (Figure 1). If interictal or ictal activity is recorded, it often reflects spread rather than a localized ACC discharge.[5] Even when extensive depth or subdural electrode arrays are used, only a small percentage of the ACC and other mesial cortical areas are sampled. There are few cases of ACC epilepsy documented with discrete structural lesions or invasive electrodes.[1,5]

We report a case of ACC epilepsy and review the clinical features of this disorder.

Case Report

An 18-year-old right-handed woman was well until December 2004, when she had her first seizure. It began with a sensation of tightness and fluttering in her chest, and a feeling of anxiety. She was then witnessed to have mouth tightening and grabbing movements with both hands. She maintained awareness throughout the episode but was unable to interact with those around her. The seizure lasted approximately 5 seconds. She began having identical episodes once per month, increasing up to 6 times per day by December 2005. Seizure frequency increased around menses. She was started on levetiracetam (Keppra®; UCB, Inc., Smyrna, GA), but became depressed, irritable, and aggressive. She was then switched to oxcarbazepine (Trileptal®; Novartis, East Hanover, NJ).

She had no epilepsy risk factors by history. Medical and neurologic examinations were normal. Magnetic resonance imaging revealed a poorly defined area of abnormal enhancement along the left anterior cingulate gyrus extending into the lateral genu of the corpus callosum (Figure 2), suggesting a low-grade astrocytoma or ganglioglioma.

Video-electroencephalogram (EEG) monitoring revealed no interictal discharges. Multiple ictal events were recorded, lasting 7 to 10 seconds each; all were preceded by an aura of "butterflies" in her stomach. She then displayed speech arrest, bilateral -5- hand automatisms (left greater than right), with preserved comprehension. EEG showed left frontotemporal onset of rhythmic alpha activity spreading quickly to the right hemisphere (Figure 3).

Discussion

This patient illustrates part of the spectrum of cingulate epilepsy and the challenges in diagnosing this disorder. Typical of seizure arising from the prefrontal region were the short duration of the seizures, their tendency to cluster, and preservation of consciousness during automatisms. The EEG features revealed a widespread area of activation at seizure onset and rapid spread to the contralateral hemisphere—again typical, but not specific, for prefrontal seizures.

No clinical feature of the history, neurologic or psychiatric examination, or seizure semiology is pathognomonic for cingulate epilepsy. Slightly increased contralateral reflexes, slight contralateral grasp reflex, depressed contralateral nasolabial fold, or asymmetric emotional smile or laugh may be observed but are not specific. Auras are also nonspecific and include warmth, abdominal sensation, pallor, tachycardia, mydriasis, piloerection, fear, feeling of suffocation, urge to void, forced urination,

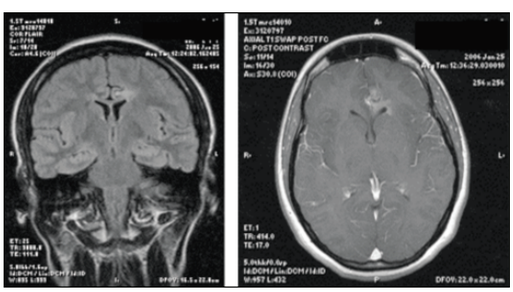

Figure 2. *Coronal fluid attenuated inversion recovery (left) and axial post-gadolinium T1 magnetic resonance imaging (right) of left cingulate lesion.*

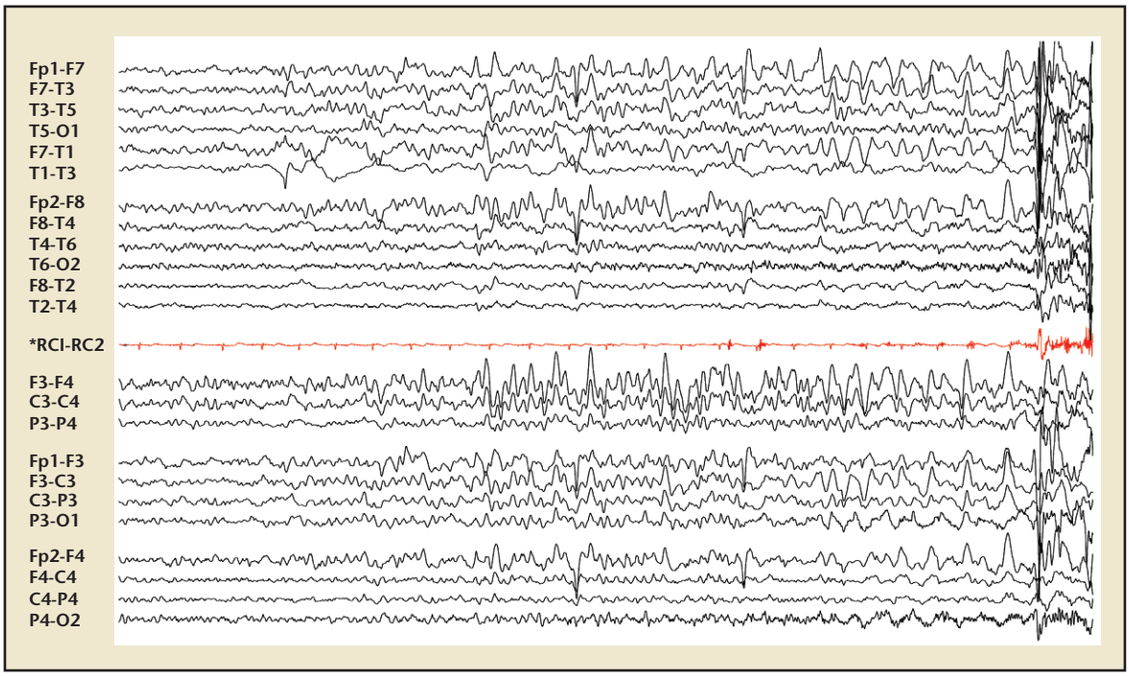

Figure 3. *Typical seizure captured during video-electroencephalogram monitoring.*

or apnea that can be voluntarily overcome.[2,4,6-9]

The clinical features of a patient's seizures often provide insight into the specific region of the ACC from which the seizures arise.[10] Subgenual ACC foci are often accompanied by autonomic phenomena such as piloerection or respiratory changes; posterior ACC foci often evoke emotional experiences such as fear with early impairment of consciousness. -4- Posterior ACC seizures can change in motivation, thought, or the feeling of control over one's actions. Simple and complex partial seizures arising from ACC are often frequent, brief, stereotyped, nocturnal, and may be associated with automatisms ranging from simple acts, such as repetitive hand motions, to complex motor acts. Motor automatisms include bizarre or sexual features leading to misdiagnosis of conversion nonepileptic seizures or movement disorder.[11,12] Stimulation of the cingulate may evoke restlessness and semi-elaborate movements, principally of the contralateral leg.[4] Pedaling, face rubbing, picking, and lip movements have been documented.[5,6] This may indicate spread of ictal activity to frontal networks that receive projections from the ACC.

The clinical features of a patient's seizures often provide insight into the specific region of the anterior cingulate cortex from which the seizures arise.

The continued effects of repeated epileptiform activity in the ACC, often combined with structural pathology, can disrupt personality, emotional regulation, social cognition, and cohesion of thought. Psychiatric comorbidity is reported, with problems including emotional lability, psychosis, aggression, obsessive-compulsive behaviors, and sociopathy. Even restricted cingulate resections may improve behavior in patients with cingulate epilepsy and psychopathology.[13]

Cingulate epilepsy remains a diagnostic and therapeutic challenge. Greater recognition is critical, because many of these patients have medically refractory epilepsy that may be amenable to surgical resection. Diagnostic tools such as magnetoencephalography may help to noninvasively identify cases without pathology on neuroimaging studies.[14] Further study of the functional–structural correlates of cingulate epilepsy may provide new insights about this disorder and its relation to other prefrontal and limbic epilepsies. ■

-6- References

1. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behavior. *Brain*. 1995;118:279-306.
2. Geier S, Bancaud J, Talairach J, et al. The seizures of frontal lobe epilepsy: a study of clinical manifestations. *Neurology.* 1977;27:951-958.
3. Escobedo F, Fernández-Guardiola A, Solis G. Chronic stimulation of the cingulum in humans with behavior disorders. In: Laitinen LV, Livingston KE, eds. *Surgical Approaches in Psychiatry*. Baltimore, MD: MTP; 1973:65-68.
4. Geier S, Bancaud J, Talairach J, et al. Clinical note: clinical and tele-stereo-EEG findings in a patient with psychomotor seizures. *Epilepsia*. 1975;16:119-125.
5. McConachie NS, King MD. Gelastic seizures in a child with focal cortical dysplasia of the cingulate gyrus. *Neuroradiology.* 1997;39:44-45.
6. Bancaud J, Talairach J, Geier S, et al. Manifestations comportementales induites par la stimulation electrique du gyrus cingulaire anterieur chez l'homme. *Rev Neurol (Paris).* 1976;132:705-724.
7. Penfield W, Jasper H. *Epilepsy and Functional Anatomy of the Human Brain*. Boston: Little Brown; 1954.
8. Seo DW, Lee HS, Hong SB, et al. Pilomotor seizures in frontal lobe epilepsy: case report. *Seizure*. 2003;12:241-244.
9. Talairach J, Bancaud J, Geier S, et al. The cingulate gyrus and human behaviour. *Electroencephalogr Clin Neurophysiol*. 1973;34:45-52.
10. Nadkarni S, Devinsky O. Cingulate cortex seizures. In: Vogt BA, ed. *Cingulate Neurobiology and Disease*. Oxford, UK: Oxford University Press. In press.
11. Kanner AM, Morris HH, Luders H, et al. Supplementary motor seizures mimicking pseudoseizures: some clinical differences. *Neurology.* 1990;40:1404-1407.
12. Williamson PD, Spencer DD, Spencer SS, et al. Complex partial seizures of frontal lobe origin. *Ann Neurol*. 1985;18:497-504.
13. Levin B, Duchowny M. Childhood obsessive-compulsive disorder and cingulated epilepsy. *Biol Psychiatry*. 1991;30:1049-1055.
14. de Jongh A, de Munck JC, Gonclaves SI, Ossenblok P. Differences in MEG/EEG epileptic spike yields explained by regional differences in signal-to-noise ratios. *J Clin Neurophysiol*. 2005; 22:153-158.

Main Points

- Seizures can arise from any region of the anterior cingulate cortex (ACC) and, because the ACC integrates information from several networks involving emotional and executive functions, it can be difficult to trace the point of origin. The clinical features of a seizure can provide insight. Subgenual ACC foci are often accompanied by autonomic phenomena such as piloerection or respiratory changes, whereas posterior ACC foci frequently evoke emotional experiences such as fear with early impairment of consciousness.
- Simple and complex partial seizures arising from ACC are often frequent, brief, stereotyped, nocturnal, and may be associated with automatisms ranging from repetitive hand motions to complex motor acts. Auras are common and consciousness typically is preserved during automatisms. Electroencephalograms may show a widespread area of activation at seizure onset and rapid spread to the contralateral hemisphere. None of these features, however, is specific for ACC seizures.
- Diagnostic tools such as magnetoencephalography may help to noninvasively identify cases of cingulate epilepsy without pathology on neuroimaging studies, and further study of functional–structural correlates may provide new insights about this disorder and its relation to other prefrontal and limbic epilepsies. At this time, however, cingulate epilepsy remains a diagnostic and therapeutic challenge.

AUTHOR QUERIES

AQ1. Please provide degrees for all authors.
AQ2. Can they arise in other areas of the CC or just the ACC?
AQ3. OK to "call out" Figure 1 here?
AQ4. Change to "can *cause* changes"? Please clarify.
AQ5. Figure 1 caption: Please define "cas".
AQ6. The following references were not used in the article; insert these anywhere?

Bush G, Vogt BA, Holmes J, et al. Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc Natl Acad Sci U S A*. 2002;8;99:523-528.

Halgren E, Walter RD, Cherlow DG, Crandal PH. Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdale. *Brain*. 1978;101:83-117.

Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex*. 1992;2:435-443.