

SURGERY FOR HETEROTOPIA: A SECOND LOOK

Electroclinical, MRI, and Neuropathological Study of 10 Patients with Nodular Heterotopia, with Surgical Outcomes

Tassi L, Colombo N, Cossu M, Mai R, Francione S, Lo Russo G, Galli C, Bramerio M, Battaglia G, Garbelli R, Meroni A, Spreafico R

Brain 2005;128:321–337

We present the results of a retrospective study on 10 patients operated on for intractable epilepsy associated with nodular heterotopia, as identified by high-resolution MRI. Seven patients had unilateral heterotopia, one patient had symmetrical bilateral heterotopia, and two patients had asymmetrical bilateral heterotopia. By stereoelectroencephalogram (SEEG; nine patients), interictal activity within nodules was similar in all cases, and ictal activity never started from nodules alone but from the overlying cortex or simultaneously in nodules and cortex. Excellent outcomes (Engel class Ia, 1987) were achieved in the seven patients with unilateral heterotopia, showing that surgery can be highly beneficial in such cases when the epileptogenic zone is carefully located before surgery by MRI and particularly SEEG. For the bilateral cases, surgical out-

comes were Engel IIa (one patient) or Engel IIIa (two patients).

Histologic/immunohistochemical studies of resected specimens showed that all nodules had similar microscopic organization, even though their extent and location varied markedly. The overlying cortex was dysplastic in nine patients, but of normal thickness. We suggest that nodule formation may be the result of a dual mechanism: (1) failure of a stop signal in the germinal periventricular region leading to cell overproduction; and (2) early transformation of radial glial cells into astrocytes, resulting in defective neuronal migration. The intrinsic interictal epileptiform activity of nodules may be due to an impaired intranodular GABAergic system.

The Role of Periventricular Nodular Heterotopia in Epileptogenesis

Aghakhani Y, Kinay D, Gotman J, Soualmi L, Andermann F, Olivier A, Dubeau F

Brain 2005;128:641–651

A temporal resection in patients with periventricular nodular heterotopia (PNH) and intractable focal seizures yields poor results. To define the role of heterotopic grey matter tissue in epileptogenesis and to improve outcome, we performed stereoencephalography (SEEG) recordings in eight patients with uni- or bilateral PNH and intractable focal epilepsy. The SEEG studies aimed to evaluate the most epileptogenic areas and included the allo- and neocortex and at least one nodule of grey matter. Interictal spiking activity was found in ectopic grey matter in three patients, in the cortex overlying the nodules in five, and in the mesial temporal structures in all. At least one heterotopia was involved at seizure onset in six patients, synchronous with the overlying neocortex or ipsilateral hippocampus. Two patients had their seizures originating in the mesial tem-

poral structures only. Six patients had surgery, and the resected areas included the seizure onset, with follow-up from 1 to 8 years. An amygdalohippocampectomy was performed in two (Engel classes Id and III), an amygdalohippocampectomy plus removal of an adjacent heterotopia in two (class Ia), and a resection of two contiguous nodules plus a small rim of overlying occipital cortex in one patient (class Id). One patient with bilateral PNH had three adjacent nodules resected and an ipsilateral amygdalohippocampectomy, resulting in a reduction of the number of seizures by 25 to 50%. The best predictor of surgical outcome is the presence of a focal epileptic generator; this generator may or may not include the PNH. Invasive recording is required in patients with PNH; it improves localization and is the key to better outcome.

COMMENTARY

Malformations of cortical development are commonly associated with medically intractable epilepsy. Many developmental abnormalities are potentially amenable to resective epilepsy surgery. With appropriate evaluation and surgical treatment, patients with focal cortical dysplasia of Taylor (1), tuberous sclerosis (2), and hemimegalencephaly (3) have a reasonable chance for complete seizure control. Until recently, however, it appeared that patients with periventricular nodular heterotopia (PNH) had far less hope of a good surgical outcome. Initial reports of resective surgery in patients with PNH suggested that poor outcomes could be expected by using standard surgical techniques. Li and colleagues (4) reported poor outcomes in 10 patients with PNH who had temporal resections, and Dubeau et al. (5) reported that just 2 of 7 patients did well with seizure surgery. Patients appear to have fared much better in the most recent series by Tassi et al. and Aghakhani et al. Whereas both groups used aggressive intracranial monitoring techniques, they differed significantly in their surgical approach. Nevertheless, each group achieved favorable outcomes.

Together, the two groups studied 17 patients with multiple, stereotactically placed depth electrodes used to record from neocortex, medial temporal structures, and heterotopic nodules. When these series are examined side by side, some common patterns emerge. Both groups found stereoencephalography to be invaluable in guiding the development of their surgical approaches. Furthermore, their EEG findings were similar. Specifically, neither group found ictal patterns initiated from the heterotopic tissue. However, both found frequent instances in which the ictal EEG patterns could be detected within the heterotopic nodules, coincident with either the neocortical or medial temporal structures. Ictal patterns in the heterotopia were similar to patterns noted from other seizure foci.

In total, 16 patients had surgery; all but one patient had surgery based on stereoencephalographic findings. Both groups performed medial temporal resections on most of their patients. Aghakhani's group typically performed aggressive resection of the adjacent heterotopic gray matter, whereas Tassi's group resected a portion of the heterotopic gray matter along with an aggressive resection of the overlying neocortex. Based on these findings, it is impossible to be certain of the relative contribution of each component of the resection—with the exception of the one patient in Aghakhani's series who had a good outcome after an amygdalohippocampectomy alone. Taken together, these case series suggest that aggressive surgical management will ameliorate seizures in approximately two thirds of patients with intractable partial epilepsy and PNH.

Because the different surgical approaches in these series led to similar outcomes, it is not possible to recommend a specific surgical plan. Together, the studies support the need for includ-

ing heterotopic tissue in the resection, however. It is clear from prior studies that standard resections are unlikely to prove helpful in patients with PNH, even those with coexistent mesial temporal sclerosis (4). All but three patients in these series (two with amygdalohippocampectomy in the series by Aghakhani and colleagues and one with a frontal resection in the study of Tassi et al.) had at least partial resection of the heterotopic tissue. Only one of the patients who did not have heterotopic tissue resected had a good outcome. Aghakhani et al. were unable to explain this patient's successful outcome, particularly given the consistent failure of the technique reported by their institution in the past. Presumably, the depth electrode recordings allowed them to limit this patient's resection. In light of their past experience of poor outcome with limited resections for PNH, however, one might reasonably ask whether it is ever a good idea to omit adjacent heterotopic nodules from the resection. Apparently Tassi and colleagues had similar concerns, because they typically resected at least some of the adjacent heterotopic tissue, even in the patients who did not have early ictal EEG involvement of the PNH.

Although stereoencephalography may not be essential to deciding whether the nodules should be incorporated into a resection, it is overly optimistic to suggest that invasive recordings might be unnecessary for these patients. Given the experience with scalp recordings in these and prior series, invasive monitoring will likely be required to document the epileptogenic region and, depending on the surgical approach, to guide the extent of neocortical resection. It remains to be seen whether tailoring the resection of heterotopic tissue, based on depth-electrode recordings (as opposed to aggressively resecting adjacent heterotopic tissue, regardless of recordings), will be helpful.

Although the number of patients in these series is small, the similar finding of poor outcomes in patients with bilateral heterotopia may be important. When combined, these studies show that 11 of 11 patients with unilateral heterotopia became seizure free, whereas none of five patients with bilateral nodules had resolution of their seizures (Fisher's exact test, $p < 0.001$). Aghakhani and colleagues have planned further resection of nodules contralateral to the initial resection in these patients to attempt to ameliorate the seizures.

From a practical standpoint, it appears that the stereoencephalographic findings in both series, as well as the dramatically improved surgical outcomes, support an aggressive surgical approach to patients with PNH. Aggressive operations should lead to surgical results similar to those performed in patients with other cortical malformations. Invasive EEG recordings will often be necessary. For now, patients with bilateral PNH should continue to be advised that surgery is unlikely to provide complete freedom from seizures.

by Paul A. Garcia, MD

References

1. Lawson JA, Birchansky S, Pacheco E, Jayakar P, Resnick TJ, Dean P, Duchowny MS. Distinct clinicopathologic subtypes of cortical dysplasia of Taylor. *Neurology* 2005;64:55–61.
2. Weiner HL, Ferraris N, LaJoie J, Miles D, Devinsky O. Epilepsy surgery for children with tuberous sclerosis complex. *J Child Neurol* 2004;19:687–689.
3. Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, de Bode S, Yudovin S, Shields WD, Vinters HV, Mathern GW. Cerebral hemispherectomy: Hospital course, seizure, developmental, language, and motor outcomes. *Neurology* 2004;62:1712–1721.
4. Li LM, Dubeau F, Andermann F, Fish DR, Watson C, Cascino GD, Berkovic SF, Moran N, Duncan JS, Olivier A, Leblanc R, Harkness W. Periventricular nodular heterotopia and intractable temporal lobe epilepsy: Poor outcome after temporal lobe resection. *Ann Neurol* 1997;41:662–668.
5. Dubeau F, Tampieri D, Lee N, Andermann E, Carpenter S, Leblanc R, Olivier A, Radtke R, Villemure JG, Andermann F. Periventricular and subcortical nodular heterotopia: A study of 33 patients. *Brain* 1995;118:1273–1287.