

Secondary Epileptogenesis in Cerebral Arteriovenous Malformations

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• **There is debate as to whether secondary epileptogenesis occurs in humans. As part of a series of patients with cerebral arteriovenous malformations and epilepsy, we identified two patients with probable secondary epileptogenesis in the mesiotemporal regions, ipsilateral but anatomically distant from an arteriovenous malformation causing seizures. Both patients had arteriovenous malformations outside the mesiotemporal region and resection of the arteriovenous malformation and epileptogenic areas identified by electrocorticography produced initial freedom from seizures. Three to 6 months later both patients developed a different seizure pattern that proved to be mesiotemporal in origin by video/electroencephalogram (one with depth electrodes) and both patients are seizure free after a second resection of anterotemporal and mesiotemporal regions. Findings indicating a secondary epileptogenic focus include (1) different seizure type by patient history, (2) second seizure type by ictal video/electroencephalographic recordings, and (3) lack of pathologic abnormalities in the resected mesiotemporal specimens.**

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The incidence of patients with arteriovenous malformations (AVMs) presenting with epilepsy and with no clinical evidence of intracranial hemorrhage varies between 17% and 40% in published series.¹⁻³ The result of surgical treatment for seizure control in patients who have cerebral AVMs are not satis-

factory.⁴⁻⁷ Since 1982 we have performed a prospective study in 36 patients who had supratentorial AVMs who presented with epilepsy and without a history of intracranial hemorrhage. All of the patients had been treated medically before surgery. They were considered disabled because of side effects or failure of anticonvulsant therapy or the effect on their professional lives of even infrequent seizures. They underwent preoperative electroencephalographic (EEG) evaluation in addition to computed tomography scanning or magnetic resonance imaging and cerebral angiography. Most of these operations were performed with the patients under local anesthesia for an accurate intraoperative electrocorticographic recording. Cortical excision in addition to removal of AVMs was performed in 19 patients if epileptic discharges were demonstrated adjacent to or at a distance from the AVMs. Two patients, one with a large AVM in the right frontal region and the other one with a thrombosed AVM in the right posterior temporal region, presented with complex partial seizures due to a remote epileptic focus in the ipsilateral mesial temporal region after the initial procedure of excision of AVMs. Both patients had a second surgery to remove the remote seizure focus.

REPORT OF CASES

CASE 1.—A 30-year-old man presented with a 9-year history of medically intractable seizures. The seizures were not preceded by an aura, but consisted of sudden onset of unconsciousness, followed by generalized tonic-clonic convulsions that lasted for 1 to 2 minutes. Frequency of seizures was about one to two per week despite adequate anticonvulsant therapy. Computed tomography

showed a 2-cm calcified lesion located in the right posterior temporal region (Fig 1). Ictal EEG recordings showed seizure onset from the right posterotemporal region.

He underwent a right frontotemporoparietal craniotomy under local anesthesia for excision of the thrombosed AVM from the posterior portion of the right superior temporal gyrus at University Hospital in Cincinnati (Ohio) on February 13, 1986, and the intraoperative electrocorticography revealed epileptiform activity from the inferior portion of the right parietal lobe that was resected. The patient has not experienced generalized seizures since surgery.

Three months after surgery the patient developed complex partial seizures, characterized by eye blinking, staring, and loss of consciousness. There were no generalized tonic-clonic seizures. He became disabled because of increasing frequency of the attacks despite trials of various antiepileptic drugs at serum concentrations producing clinical toxicity.

Sixteen months following the first procedure, video/EEG monitoring was performed and showed five clinical complex partial seizures with an initial blank stare, automatisms, and postictal confusion. Each seizure was associated with a clear rhythmic sharp-wave discharge from the right sphenoidal electrode, starting simultaneously with the clinical alteration in behavior. Intraoperative acute surface and depth electrode electrocorticography showed active epileptiform discharges and polymorphic delta activity from both the amygdala and hippocampus, as well as from the anterior portions of the middle and inferior temporal gyri. There was no evidence of epileptiform activity or abnormal slowing in the 3 to 4 cm of temporal lobe lying between the previously resected AVM and the electrophysiologically abnormal anterior temporal lobe. Six centimeters of the right anterotemporal lobe, including the amygdala and the anterior 1.5 cm of pes hippocampus, were resected en bloc. Neuropathologic analysis of the antero/mesiotemporal lobe was unremarkable. The patient has remained sei-

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ture free for 3 years following the second procedure.

CASE 2.—A 39-year-old right-handed man presented with a 20-year history of generalized seizures. He had denied warning symptoms and had 4 to 6 generalized tonic-clonic seizures per week despite treatment with phenytoin and carbamazepine at serum concentrations producing clinical toxicity. Cerebral angiogram showed a large AVM in the right anterofrontal region (Fig 2, left). An electroencephalogram showed rhythmic sharp and slow activity in the right anterofrontal region.

A right frontotemporal craniotomy was performed at University Hospital in Cincinnati on June 27, 1986. Intraoperative electrocorticography showed active spike and sharp wave activity in the right frontal cortex posterior to the AVM. The AVM and the cerebral cortex showing epileptiform activity were both resected. Pathologic study revealed an AVM and gliosis of the removed parenchyma. Postoperative angiogram showed complete excision of the AVM (Fig 2, right). The patient has not experienced seizures after surgery.

During a follow-up visit 6 months after surgery, he mentioned that he had experienced intermittent episodes of unpleasant and strange smells. Despite serum concentrations of phenytoin and carbamazepine causing clinical toxicity, he continued to have episodes of unpleasant smells followed by complex partial seizures characterized by altered consciousness and automatism. He developed two episodes of generalized tonic-clonic seizures preceded by lightheadedness and a bad smell. Retrospectively, he admitted that he has occasionally experienced transient episodes of a "rusty smell" before surgery, but he did not think that was a symptom of epilepsy.

Neither a magnetic resonance scan nor angiography revealed abnormalities in the temporal lobe. Two years later the patient was readmitted for video/EEG monitoring. Four complex partial seizures were recorded showing an initial aura of an unpleasant smell followed by staring, alteration in consciousness, lip smacking, then secondary generalization. Ictal EEG recording with scalp and sphenoidal electrodes did not adequately localize seizure onset, so the patient was readmitted for chronic depth electrode recordings that showed seizure onset from the right hippocampus and amygdala. The patient underwent a right anterotemporal lobectomy with resection of the amygdala and hippocampus. He has been seizure free for 24 months. Pathologic evaluation of the right temporal lobe was unremarkable.

COMMENT

Secondary epileptogenesis and kindling have been observed in experimental animal studies, but are not well documented in humans.^{8,9} Kindling was first observed in rats by Goddard¹⁰ as the progressive enhancement of electrical and behavioral response to a low-intensity initially ineffective electrical brain stimulation. The limbic system structures, especially the amygdala, are the

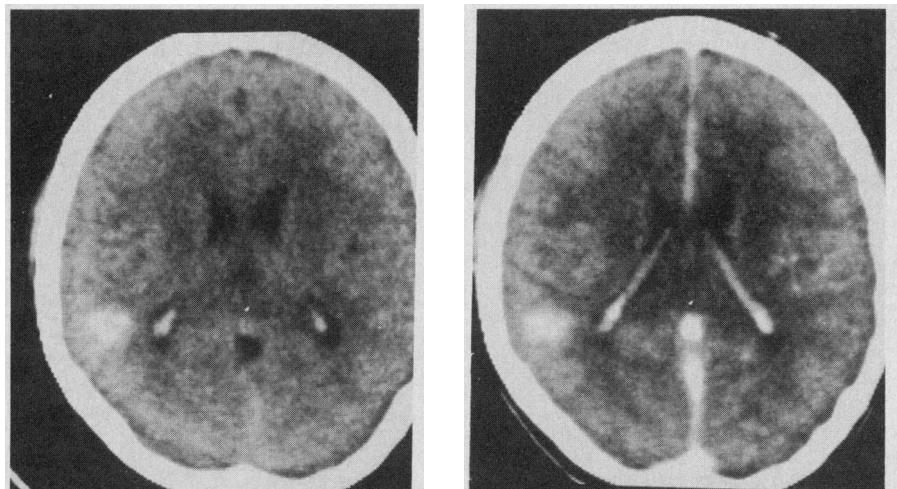


Fig 1.—Computed tomography without (left) and with (right) contrast showed a 2-cm calcified thrombosed arteriovenous malformation in the right posterotemporal region.

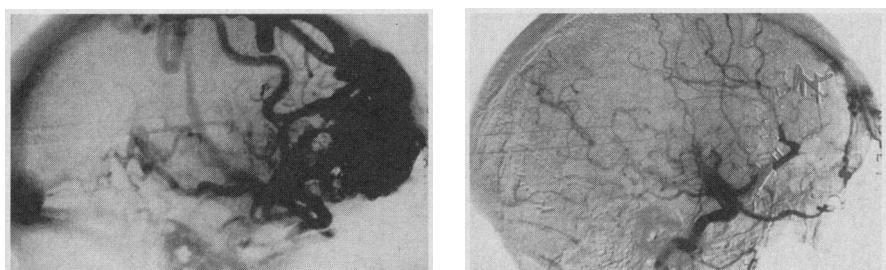


Fig 2.—Cerebral arteriogram (lateral view) disclosed a large arteriovenous malformation in the right anterofrontal region (left). The postoperative study showed a complete excision of the arteriovenous malformation (right).

most sensitive to electrical kindling.¹¹ The duration of stimulation required for seizures varies in different species; an average of 14 days is needed in rats, 25 days in cats, and 248 days in rhesus monkeys.¹² The interictal electrical discharges propagate and appear independently at distant sites for an indefinite period of time in the animals with kindling in the amygdala. As in kindled animals, a similar distant independent epileptic discharge is believed to occur in humans with partial seizures.¹³ Mechanisms similar to those in animal kindling may cause some poorly controlled seizures in humans. The mirror focus is described as an independent secondary epileptogenic lesion in the brain contralateral and homotopic to the primary focus.¹⁴ The question of secondary epileptogenesis in humans, especially in patients who had epilepsy caused by tumor of the brain, has been addressed.^{15,16} Twenty-one percent to 36% of patients with epilepsy caused by tumors in varied locations of the human brain had evidence of secondary epileptogenesis. After surgical removal of the primary lesion, in approximately one third of the

patients secondary foci persisted and continued to give rise to clinical seizures.

The clinical course and EEG findings in these two patients provide evidence of a remote, independent epileptic focus after removal of the primary lesion. In both cases, an abnormality outside the mesiotemporal region gave rise to seizures that were initially controlled by resection of the AVM; however, an independent seizure focus developed in the mesiotemporal region and seizures were stopped by a second surgical resection of anterior and mesiotemporal structures. The change in the manifestations of the seizures by history, clinical observation on video, and ictal EEG all support a region of epileptogenicity anatomically distinct from the region of the AVM capable of producing clinical seizures. Both regions were capable of producing clinically distinct seizures, not merely interictal spikes. Furthermore, pathologic analysis did not demonstrate any AVM or residual hemosiderin in the resected mesiotemporal regions, indicating the epileptogenicity was not due to a preexisting structural

abnormality of mesiotemporal structures.

Secondary epileptogenesis presumably occurred prior to the surgical excision of AVMs. The symptoms from the secondary seizure focus may have existed earlier, but were not recognized initially in case 2. The first patient denied complex partial seizures before the first surgery. Perhaps the second seizure pattern was clinically enhanced after excision of the primary focus, which was associated with more prominent and disabling seizures.

Morrell¹⁷ postulated that "the density of the excitatory synaptic connections of the cells of the primary focus and the excitability of the target cells appear to exert a major influence on the likelihood of development of secondary foci." In the kindling model, the amygdala is the most sensitive site for development of seizures, and in humans, the mesiotemporal region is the most common site for complex partial seizures.¹⁸ In case 1, the epileptic discharges may have reached the mesiotemporal region via the fibers of the inferior longitudinal fasciculus, which extend from the occipital lobe, pass through the length of the temporal lobe, terminate in the temporal pole, and reach the amygdala by the arcuate fibers. In case 2, discharges may have spread from the orbitofrontal region to the rostral part of the ipsilateral temporal lobe by the uncinate fasciculus.

Several investigators have reported cases where ipsilateral secondary epileptogenesis was inferred but not proven. In the cases of Falconer et al¹⁹ removal of a lesion outside the mesiotemporal lobe produced gradual resolution of presumed mesiotemporal onset seizures. Falconer and coworkers' patients may have had what Morrell¹⁷ refers to as "reversible" secondary epileptogenesis where removal of the primary region produces freedom from seizures. Our two cases may have reached the irreversible stage where the secondary focus continues to produce clinical seizures after removal of the primary focus.

Sperling et al²⁰ and Olivier et al²¹ presented cases with predominantly mesiotemporal seizures and presumed primary epileptogenic regions outside the mesiotemporal region. In Sperling and coworkers' case, a tumor involved language areas of the posterotemporal region, but the patient became seizure free after anterotemporal and mesiotemporal resection. Olivier and coworkers' patient had an initial seizure pattern indicating occipital lobe onset, but after some years also developed independent temporal lobe complex partial seizures. Depth electrode recording

demonstrated independent epileptogenic regions in the occipital and in the mesiotemporal areas, and the patient was almost completely seizure free after only anterotemporal and mesiotemporal resection. In these two cases, the primary abnormality was not resected, yet removal of a presumed secondary epileptogenic lesion produced a good outcome.

It has been postulated that the following mechanisms are active in the pathophysiology of epilepsy associated with cerebral AVMs: (1) ischemia of the adjacent cerebral cortex due to arteriovenous shunting in the large AVMs; (2) gliosis of the brain surrounding the AVM because of previously subclinical hemorrhage or hemosiderin deposits; and (3) secondary epileptogenesis, especially AVMs in the temporal lobe in association with remote epileptogenic foci.²² Therefore, thorough preoperative and intraoperative EEG studies should be carried out, especially in patients who have cerebral AVMs and present with chronic epilepsy. Video/EEG monitoring of seizures is important to demonstrate whether independent regions of seizure onset exist. According to our previous experience with a favorable result of seizure control of surgically treated patients associated with cerebral AVMs, excision of the AVM along with adjacent or remote epileptogenic cortex should be considered to optimize seizure control after surgery.²³ As in Sperling and coworkers' case, if a lesion is in eloquent cortex that cannot be resected but seizures originate in an accessible area, resection of only the region producing seizures may produce good seizure control. Continuous long-term follow-up and reevaluation of patients who still have seizures after initial resection of cerebral AVM, either the same type or a new type, are important. As we have shown, some patients may benefit from a second surgery to excise the secondary epileptogenic focus to achieve good seizure control.

Our cases are unique in that a focal structural abnormality initially causing seizures was removed, seizures improved, but then recurred with a different seizure pattern indicating a region of secondary epileptogenesis; removal of the pathologic normal secondary region stopped the new seizure pattern.

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