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Delayed Diagnosis of Lesional Epilepsy: Utility of Modern Imaging

■ Although MRI examination is generally recommended in patients with focal epilepsy, we have encountered a population of individuals with chronic epilepsy who have never undergone a high-resolution imaging examination. We sought to identify factors in the history and prior evaluation that led to an incorrect diagnosis of cryptogenic epilepsy with overlooked lesions. We identified and retrospectively reviewed 10 patients referred to a tertiary-care hospital-based epilepsy clinic from 1993–1999 with longstanding localization-related epilepsy in whom initial brain MRI, obtained years after seizure onset, demonstrated focal lesions. Structural lesions were identified on MRI in each case that were concordant with the clinical, interictal, and when available, ictal electrographic localization of their seizure foci. Lesions included gray matter heterotopia, low-grade glioma, nonspecific gliosis, congenital encephalomalacia, remote intraparenchymal hemorrhage, cavernous malformation, and mesial temporal sclerosis. Lesions identified in each case were potentially amenable to surgical treatment. In every case, the recognized lesion was probably present decades before discovery. The median duration of epilepsy prior to MRI examination in this population was 26 years, indicating that the epilepsy diagnosis was assigned before MRI became widely available. We conclude that there is a population of "MRI-naïve" epilepsy patients whose diagnosis predates the widespread availability of MRI and who harbor chronic lesions that are causally related to their seizures and are amenable to surgical resection. MRI may be underutilized in patients with longstanding epilepsy. Identification of unsuspected lesions may decrease epileptic morbidity and mortality. ■

Key Words: Epilepsy, Intractable, MRI, Diagnosis, Lesion

INTRODUCTION

Both diagnosis and treatment of localization-related epilepsy have been greatly improved by modern neuroimaging methods (Scheuer and Pedley, 1990). In 1968, Schmidt and Wilder suggested that all individuals with adult-onset focal seizures be evaluated with "contrast studies," which at that time meant angiography or pneumoencephalography (Schmidt and Wilder, 1968). In 1973, Hounsfield and Ambrose introduced computerized axial tomography (CT) into medicine (Hounsfield, 1973; Ambrose, 1973) and a few years later, Bogdanoff and colleagues (Bogdanoff et al., 1975) and Gastaut and Gastaut (Gastaut and Gastaut, 1976) demonstrated the utility of CT in patients with epilepsy. The benefit to patients was readily accepted without clinical trials, and within a few years, fourth-generation scanners were widely available and frequently used in the evaluation of patients with isolated seizures or chronic epilepsy (Scheuer and Pedley, 1990). By 1984, within just a year of its introduction into clinical medicine, Oldendorf predicted that magnetic resonance imaging (MRI) would replace CT in everyday epilepsy patient management (Oldendorf, 1984). That year there were 50 units in operation. Early studies rapidly demonstrated the superiority of MRI over CT in detecting cerebral lesions (McLachlan et al., 1985; Laster et al., 1985; Latack et al., 1986; Berkovic et al., 1986; Radtke et al., 1986; Hyman and Gorey, 1988), and by 1988, MRI had become readily accessible and recognized as the neuroimaging technique of choice for the evaluation of patients with seizures (Scheuer and Pedley, 1990).

Advanced neuroimaging has resulted in the detection of previously unrecognized and ever-smaller lesions that have forced reclassification of many "idiopathic" or cryptogenic epilepsies into localization-related, lesional epilepsies. Importantly, many of these epilepsies are amenable to surgical treatment with the potential for cure or significant reduction in seizure frequency. Thus, the current recommendations of the International League Against Epilepsy (ILAE) suggest that every patient with epilepsy, excepting those with a definite diagnosis of a so-called "benign" epileptic syndrome, undergo brain MRI examination (ILAE Neuroimaging Commission, 1997). In our tertiary epilepsy referral clinic, however, we regularly meet patients who carry a diagnosis of "idiopathic" or cryptic partial epilepsy who have never undergone MRI examination, despite its wide availability. Many have had a normal CT scan at some point in their illness. Here we present 10 patients in whom initial high-resolution MRI examination conducted years after seizure onset revealed focal lesions. We describe features common to

this group of patients, and include the reasons for and effect of diagnostic delay.

METHODS

All patients attending the Epilepsy Clinic at Massachusetts General Hospital are reviewed at a weekly conference. Patients in whom structural lesions were identified between 1993 and 1999 were reviewed to determine whether they had ever undergone brain MRI examination. Only cases without a previous MRI examination were studied. Duration of epilepsy, seizure type, time of initial examination, previous CT examination and results, and clinical course were retrospectively reviewed and abstracted. No attempt was made to define a denominator for this population.

Case Reports

The average age of our patients at the time of seizure onset was 13.5 (SD 9.4) years. The average age at the time of their first MRI was 39.2 (SD 10.5) years. Clinical details of 10 patients are summarized in Table 1. The following are representative case histories.

Case 1

A 38-year-old right-handed man presented to us in 1993 with seizures since age 7 consisting of a recurrent thought, visualization of an object, intense nausea, and spitting automatisms, all followed by an intense feeling of pleasure. Seizures lasted 30–60 sec with no definite loss of awareness. At age 12 he was evaluated by a neurologist, and treated with phenytoin. Over the years his seizures proved refractory to numerous anticonvulsants. He developed psychiatric illness and was intermittently homeless. At the time of our evaluation, seizures were occurring weekly. Examination revealed hypergraphia, an obsessive, paranoid personality, and tangential thinking. Formal visual-field testing revealed a subtle left superior quadrantic deficit. An EEG showed right temporal slowing with right anterior and mid-temporal spikes. MRI examination demonstrated an irregular 3-cm-diameter heterogeneous cystic mass centered in the right mesial temporal lobe, appearing to arise from the hippocampus itself (see Fig. 1A). Its appearance was most consistent with a hamartoma or low-grade astrocytoma. Continuous EEG/video monitoring yielded a record of eight of his habitual seizures, all of which originated from the right mid-temporal region maximal at T4 and T2. Despite multiple opinions urging him to have the lesion resected, the patient declined surgery and has remained intermittently homeless with persistent seizures.

Case 6

A 53-year-old left-handed woman presented to us in 1993 with a 20-year history of trance-like spells consisting of staring, loss of contact, hand-wringing, throat clearing, and wandering. Spells lasted 1–2 min and were followed by several minutes of confusion. A CT scan in 1985 was normal. She had been treated with many anticonvulsants, but continued to have 3–5 seizures per week. Neurological examination revealed minimal drift of the outstretched right arm, and right-arm posturing with stressed gait. Multiple EEGs had shown left fronto-temporal theta, but no clear epileptiform activity. MRI examination revealed a 2-cm-diameter infiltrating lesion in the left mesial temporal lobe at the level of the amygdala. There was a small cystic component, but minimal mass effect or edema. Its appearance was consistent with a low-grade glioma (see Fig. 1B). A left temporal lobectomy was performed in 1993. Pathological examination of the resected specimen revealed an astrocytoma. She has been seizure-free and off anticonvulsants since surgery.

Case 7

A 34-year-old right-handed woman was referred in 1994 with seizures since age 18. Her first seizure was a generalized tonic-clonic convulsion. A CT scan in 1978 was normal. Since then, she had had 15–20 generalized convulsions. More problematic, however, were almost daily minor spells, one of which occurred during the initial office visit. She suddenly stopped interacting, began to blink rhythmically, and fumble with her hands. After 20 sec, she rapidly returned to normal and was able to recall by name four objects that had been spoken to her during the seizure. She did not recall a warning. She was taking phenytoin, phenobarbital, and valproic acid. Her neurological examination was normal except for an equivocal right plantar response. An EEG showed an irregular high amplitude 3-Hz spike and slow wave discharges, sometimes in clusters, widely represented across the head with a bifrontal maximum, sometimes with a left-sided predominance. MRI showed a 2–3-cm-diameter mass contiguous with the head of the left caudate that had signal characteristics similar to gray matter (see Fig. 1C). Three of her typical ictal events recorded during continuous EEG/video monitoring demonstrated maximal ictal activity in the left anterior quadrant, but no clear localizing or lateralizing features. An [18]FDG-PET study revealed mild hypermetabolism in the region of the lesion. Because the ictal scalp recordings were inconclusive, bilateral depth electrodes were placed into the frontal lobes and amygdala, and several seizures were recorded. Several seizures appeared to arise electrographically from the lesion itself. In 1994 she underwent a left anterior and parasagital frontal resection, which included the lesion and the cingulate gyrus. Postoperatively she has been seizure free. Pathological examination of the specimen confirmed a gray-matter heterotopia.

Table 1 Clinical Features in Identified Cases

Case	Age (years), Handedness, Sex	Age (year) of Seizure Onset	Age (year) of MRI	CT Scan	MRI Findings	Action/Outcome	Pathology
1*	38, RH, G	7 (1962)	38 (1993)	N	3-cm irregular heterogeneous cystic mass, centered in the right mesial temporal lobe c/w hamartoma	Declined surgery	N/A
2	45, RH, G	4 (1953)	45 (1998)	Y	Cortical-based area of T2 hyperintensity in the left parieto-temporal region; nonspecific, c/w gliosis	Underwent invasive monitoring and intra-operative cortical mapping; to preserve language, partial lesionectomy performed; not seizure-free.	Focal cortical dysplasia
3	56, RH, G	21 (1963)	56 (1998)	N	1.7-cm lesion centered in the right inferior frontal gyrus c/w cavernous malformation	Surgical candidate	N/A
4	28, RH, E	1 (1971)	28 (1998)	Y	Right hippocampal T2 hyperintensity with volume loss c/w mesial temporal sclerosis	Right anterior temporal lobectomy scheduled	N/A
5	38, RH, G	12 (1972)	38 (1998)	Y	Encephalomalacia involving the left frontal and parietal lobes, the left outflow tracts, basal ganglia, and thalamus c/w remote ischemia	Surgical candidate	N/A
6*	53, LH, E	33 (1973)	53 (1993)	Y	2-cm infiltrating lesion in the left mesial temporal lobe c/w low-grade cystic glioma	Left temporal lobectomy in 1993. Off anticonvulsants; seizure-free.	Astrocytoma
7*	34, RH, E	18 (1978)	34 (1994)	Y	2–3 cm left frontal mass with gray-matter signal characteristics, contiguous with left caudate head	Large left frontal resection including medial structures and cingulate gyrus; seizure-free to date.	Neuronal heterotopia
8*	39, RH, G	16 (1975)	39 (1995, 1998)	Y	1995 MRI normal; 1998 MRI showed a 7-mm lesion in the right superior temporal gyrus c/w cavernous malformation	Lesionectomy performed; seizure-free to date.	Cavernous angioma
9	25, RH, E	7 (1980)	21 (1994)	Y	Well-circumscribed T2 hyperintense cavity with surrounding hemosiderin in the left anterior frontal lobe. Bi-occipital encephalomalacia	Surgical candidate	N/A
10	40, LH, G	16 (1974)	40 (1999)	N	Left fronto-temporal encephalomalacia, post-traumatic	Surgical candidate	N/A

* See case history in text for detailed description.

Case 8

A 39-year-old right-handed man presented to us in 1997 with seizures since age 16. Attacks began with 10 sec of anxiety and "butterflies" in his stomach, followed by complex automatisms. Post-ictally he was completely amnestic for the events. In spite of his attacks, he was able to hold a job as a computer systems administrator. At evaluation he was having about four seizures a month on topirimate, carbamazepine, and lamotrigine. Neurological examination was normal. An EEG showed right fronto-temporal spikes. Several CT scans performed during the 1980s were normal. An MRI performed in 1995 was initially thought to be normal, but on review demonstrated a subtle abnormality in the right temporal neocortex. A high-resolution MRI using 1.2-mm-thick axial and

(A)

(B)

(C)
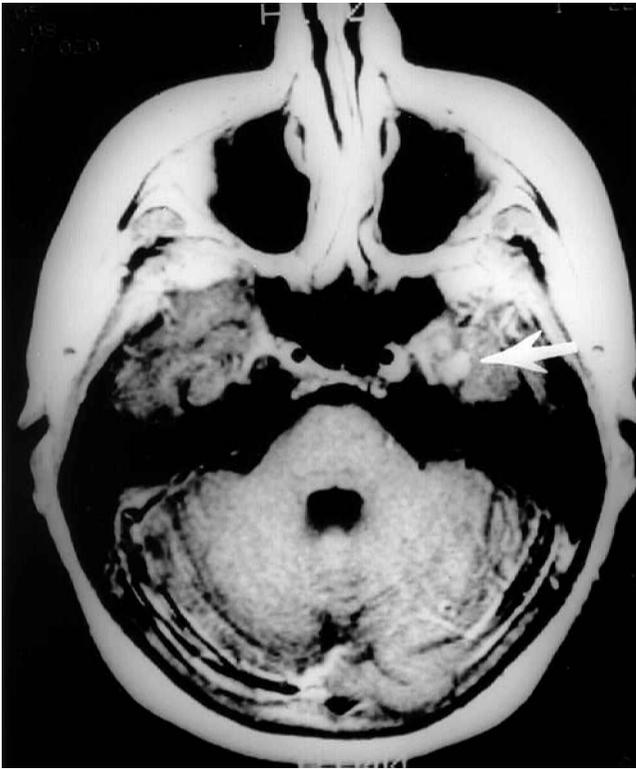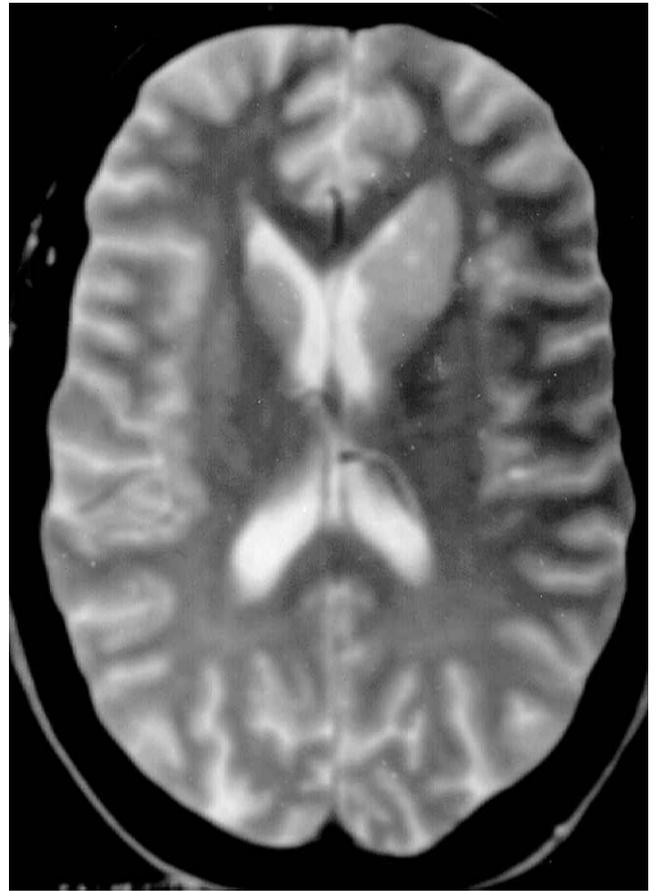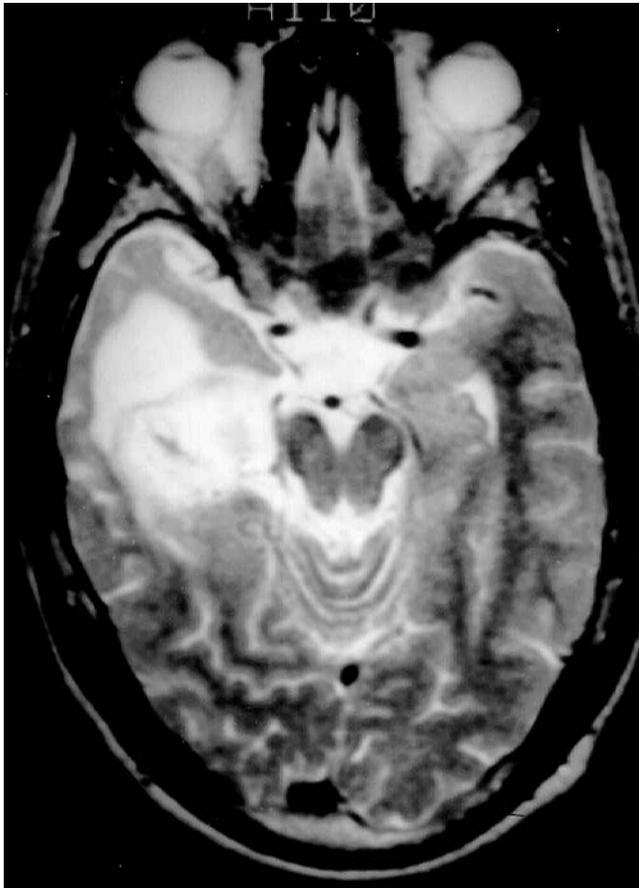
(D)

FIGURE 1. Representative MRI images demonstrating previously unsuspected lesions. (A) T2-weighted image from Case 1, demonstrating right temporal mass. (B) T1-weighted image after gadolinium infusion from Case 6, demonstrating left inferomesial temporal enhancing nodular mass. (C) Proton-density image from Case 7, demonstrating left periventricular mass with gray-matter signal characteristics. (D) Coronal T2-weighted fast spin echo image from Case 8, demonstrating right superior temporal gyrus cystic lesion. Clinical details of each case are provided in the text. Case numbers refer to entries in Table 1.

coronal fast spin echo images in 1998 revealed a lesion in the right superior temporal gyrus consisting of a 7-mm-diameter region of heterogeneous signal on T2 weighted images with susceptibility related signal loss (see Fig. 1D). Four of the patient's seizures recorded during continuous video/EEG monitoring arose from the right anterior sylvian region maximal at F8. An ^{18}FDG-PET study revealed mild decreased glucose uptake in the right mesial temporal region. The lesion was surgically excised, and the diagnosis of cavernous angioma was pathologically confirmed. The patient experienced a single early postoperative seizure, but has remained seizure-free since, although follow-up has been brief.

DISCUSSION

The main finding of our study is that a number of patients with chronic partial epilepsy are followed for many years without ever undergoing MRI examination, but when appropriate imaging studies are conducted, even many years after onset, causative and often treatable pathologies may be identified. Although recommendations to perform MRI on certain patients with epilepsy began to appear by 1986 (McLachlan et al., 1985; Laster et al., 1985; Berkovic et al., 1986; Radtke et al., 1986) and were widely disseminated by 1988 (Hyman and Gorey, 1988), among the patients reported here, the median delay between initial diagnosis and MRI examination was 26 years. As these patients were previously followed elsewhere, we can only speculate about why these patients with clear focal epilepsy may not have undergone MRI examination. Examination of the clinical data revealed that virtually all of these patients began having seizures before the introduction of MRI, and by the time MRI techniques became widely available these individuals were known as chronic epileptics who appeared neurologically stable except for their seizures. Moreover, the lesions eventually identified were indolent and produced relatively little in the way of neurological signs. We therefore conclude that the delay in discovering lesions in our cases was most likely related to the perceived chronicity, and by inference, the presumed idiopathic nature of their epilepsy. While idiopathic focal epilepsy has been well described and is reasonably common, our data emphasizes the importance of obtaining high-resolution MRI images in all patients with seizures of definite or possible focal origin, as indicated by either clinical semiology or focal EEG findings.

There are many reasons to pursue the early identification of structural lesions in patients with epilepsy. Few would disagree that metastases, hemorrhages, progressive infiltrative lesions, and lesions with the potential to produce mass effect are best identified early so as to undertake prompt definitive treatment.

In the case of indolent lesions, the absence of progressive neurological deterioration may suggest an underlying lesion's benign nature, but seizure disorders associated with structural abnormalities may take a malignant course and become progressively more difficult to control. Even without evidence of neurological progression, psychosocial deterioration is a frequent consequence of uncontrolled epilepsy, as in our first case. Recurrent focal seizures may also produce progressive neuronal injury. Finally, it is likely that chronic anticonvulsant drug treatment over many years may result in detrimental neurological and systemic effects. For all of these reasons, definitive surgical treatment is often considered when a resectable lesion can be identified, and these patients are often among the best candidates for epilepsy surgery, as cure rates are typically highest in patients with fully resectable lesions (Li et al., 1997; Smith et al., 1997). Of our 10 patients with surgically accessible lesions, 4 have had resections, 1 is awaiting surgery, 4 are undergoing presurgical evaluation, and 1 has refused surgical treatment.

Although CT may have a role in the acute management of seizures, especially when a space-occupying lesion or hemorrhage is suspected and MRI is not readily available, the CT scan is an insensitive test for the detection of lesions in patients with chronic partial epilepsy (Laster et al., 1985). CT may not detect subtle lesions, including hippocampal sclerosis, low-grade tumors, small cavernous angiomas, or developmental abnormalities. In seven of our patients, lesions ultimately detected on MRI were not identified on CT scans. The improved sensitivity of MRI was reported as early as 1986 when Latack and colleagues imaged 50 patients with complex partial seizures with both CT scans and MRI. Of the 23 patients with abnormalities on MRI, 10 had normal CT scans (Latack et al., 1986). We therefore agree with the most recent ILAE guidelines, published in 1997, that recommend brain MRI for all epileptic patients except those with definite idiopathic epilepsy syndromes, eg, benign myoclonic epilepsy in infancy, juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, and benign epilepsy of childhood with centro-temporal spikes (ILAE Neuroimaging Commission, 1997). The utility of MRI in patients with apparent benign idiopathic epilepsy syndromes is less clear. However, if atypical features are present, or if seizures fail to respond to standard treatment, an MRI investigation should be obtained. This point is illustrated by Patient 7, who was thought for many years to have a primary generalized epilepsy syndrome with absence and occasional generalized attacks.

To maximize the yield from MRI examination in epilepsy, a combination of sequences should be cho-

sen to allow sharp gray-white differentiation, to reveal increased magnetic susceptibility, and to allow careful volume comparisons. The imaging protocol we utilize consists of axial 5-mm spin echo proton density and T2-weighted sequences, coronal 3–4 mm-thick fluid attenuated inversion recovery (FLAIR) T2-weighted images, coronal 4–5-mm-thick multiplanar gradient echo (MPGR), a coronal 1.5-mm-thick 3D spoiled gradient echo (SPGR) volumetric dataset of the whole brain, and coronal 3-mm-thick T2 fast spin echo (FSE) images targeted to the lobe of interest. Gadolinium contrast is not routinely employed, because most of the lesions responsible for chronic epilepsy do not enhance, and can be identified on the thin-section noncontrast protocol described (Cascino et al., 1989). Of course, slightly different protocols may be required depending on the scanner and software available.

Neuroimaging technology is constantly changing. Although the resolution of expertly directed MRI today would have been difficult to imagine even 5 years ago, it is likely that 5 years from now it will be even better. Because the technology is constantly changing, the question arises, When, if ever, is it appropriate to repeat neuroimaging studies on patients who have had negative studies in the past? We can offer no specific guidelines to address this issue, but suggest that practitioners review patients with so-called idiopathic or cryptogenic epilepsy on an annual basis to determine whether and when recent advances justify re-examination.

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