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Brain Structure and Epilepsy: The Impact of Modern Imaging

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After the pioneering work of Hans Berger in the 1930s (1), electroencephalography (EEG) opened a new window on epilepsy. This led to its general acceptance and now widespread use. It provided an invaluable new dimension to the ability to locate epileptogenic abnormalities in patients with focal or partial epilepsy. The presence of structural lesions in patients with partial epilepsy had, of course, been long realized but there evolved a widely held concept that the lesion was not nearly as important as the electrographically defined epileptogenic abnormalities.

In the early days of neuroradiology, the founding fathers, like Arthur Childe and Donald McCrae, soon realized that asymmetries in skull growth and identification of lesions by pneumoencephalography and arteriography contributed to our study of patients with intractable epilepsy. Nevertheless, imaging continued to labor in the shadow of the EEG until the advent of computed tomography, which ushered in the era of modern imaging in patients with epilepsy (2–8). First came the recognition of disorders or cortical organization such as polymicrogyria and pachygyria (4–7) and the beginning of the explosion of diagnosis by imaging of small inert lesions, some calcified, like the cavernous angiomas (8). It was at that time that we finally realized that electrographic localization, whether from the surface or from intracranial recording, might not provide as reliable an answer as one had anticipated (2, 3). Patients with posterior temporal or temporal occipital lesions and anterior and inferomesial temporal epileptogenic foci had disappointing results after resection of the electrically defined epileptogenic area (9), and it became progressively clearer that the lesion and its immediate surround was much more important in epileptogenesis than we had suspected (8–10).

Then came the era of magnetic resonance (MR), which led to important insights into the structural basis of temporal epilepsy, the most common form of the intractable disease, and recognition of a wide range of structural cortical abnormalities, often developmental, leading to seizures which were often difficult or impossible to control. The introduction of MR coincided with a period of renewed and widespread interest in the surgical treatment of epilepsy. Advances in epileptology made it very clear that in as many as 20% of epileptic patients medical control of seizures was not possible with the available pharmacologic armamentarium (2, 3). Advances in surgical technique and, above all, in preoperative electrographic studies and neuropsychological investigation held out the promise of improved results of surgical treatment. There was, in North America, a proliferation of centers hoping to embark on surgical treatment (2, 3). We now see an improved balance between the enthusiasm of the physicians and surgeons and the recognition of the essentialness of searching imaging, EEG, and neuropsychological investigations. Functional imaging is also increasingly used (10).

MR imaging is now the standard of reference in the investigation of patients with epilepsy, particularly those with intractable seizures (4). Computed tomography retains a role in recognition of calcifications. It is not a sufficient screening procedure because of the difficulty of recognizing temporal lobe abnormalities and parenchymatous changes.

Neurologists and neurosurgeons are now beginning to recognize that referring patients for routine MR imaging is inappropriate. To obtain maximal usefulness, the problem should be discussed in advance with the neuroradiologists and the procedures tailored to the specific clinical problem.

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In patients with a clinical history of temporal lobe epilepsy, evaluation of the size and measurement of the volume of the amygdala and hippocampus greatly outweighs the radiologist's ability to assess these structures visually (11–13). The technique has been well validated. When the mesial temporal structures are unilaterally small (below 2 standard deviations in our center), there is a very high correlation with an excellent surgical outcome (14). When electrographic and volumetric studies appear to be contradictory, recordings with depth electrodes have shown that the small volume is clinically more significant than the surface EEG findings (15, 16), which may result from lower amplitude and rapid contralateral spread from a shrunken hippocampus.

When there is bilateral atrophy, the trend is for greater likelihood of the clinically significant seizures to originate in the smaller hippocampus and amygdala. There are, however, a number of patients who have seizures originating in both temporal lobes, and it appears that in exceptional cases the majority of seizures can arise in the less atrophic mesial structures (15, 16). This is obviously an area that requires further clarification; some of these patients present the most difficult temporal epileptic problems.

Patients with temporal lobe epilepsy and with normal volume of hippocampus and amygdala are a minority and they, like the ones with bilateral atrophy and bilateral seizures, do not do as well after surgical resection than those patients who have good evidence of mesial temporal sclerosis (14–16). Mild pathologic changes may be found in patients without atrophy. Some of these patients have abnormalities on MR spectroscopy, a technology that is rapidly gaining clinical acceptance and that can contribute to the lateralization of temporal epileptogenic processes (4, 17–19). Abnormalities of signal and disturbed organization of the internal structure of the hippocampus have also been recognized (4). In their preoperative investigation, different centers emphasize different groups of imaging studies. This is similar to the variation in the electrographic investigations and especially in the perceived need for invasive recording and neuropsychological studies.

Another major area of progress has been the recognition of lesions. Before modern imaging, about a third of patients with intractable epilepsy were found to have lesions at surgery. The original descriptions of cortical dysplasia by

Taylor, Falconer, and the pathologists Bruton and Corsellis (20, 21) were based on pathologic findings in surgical specimens. They referred to small areas of dysplasia totally included in the resected tissue.

Dysplastic lesions of varying configuration and pathologic severity have now been increasingly recognized. The ones containing balloon cells were previously considered to represent the "forme fruste" of tuberous sclerosis. The molecular relationship of these lesions to the genetic form of tuberous sclerosis is not yet clarified, though the affected patients do not have the multiple lesions or involvement of other systems or a family history of tuberous sclerosis. Dysplastic lesions usually, though not always, produce extremely active epileptogenic EEG abnormalities with a characteristic bursting pattern (22, 23). It has become clear that for surgical treatment of intractable epilepsy, the areas of brain generating this bursting pattern had to be resected in addition to the visible lesion in order to obtain a good result. Dysplastic lesions are somewhat like the tip of an iceberg. Lesser pathologic changes, invisible by modern imaging (24), may extend beyond the visible lesion and likely account for some of the less successful outcomes after surgical treatment. Recording with invasive techniques may not necessarily solve this problem, because some of these abnormalities may involve areas that cannot be resected. The challenge is to find such areas of lesser but still significant pathologic abnormality.

Looking for smaller lesions with the help of surface coils has led Grant et al (25), in this issue of *AJNR*, to be able to see small but important areas of structural abnormality. Currently, patients with intractable partial epilepsy and completely normal MR images represent a major challenge, particularly when seizures seem to arise in extratemporal areas. Thus in such patients, even when invasive EEG recordings seem to show an epileptogenic area, there is often a poor outcome when this region is resected. The recently recognized familial frontal epilepsy with predominantly nocturnal seizures (26) may account for some, but by no means all, of these poor results. The important lesson from the paper by Grant et al is that one would not accept a normal study using a head coil as sufficient evidence of structural normality. The identification of even small structural lesions could influence a decision regarding sur-

gical treatment with all that this implies for the patient's future. One may, with some justification, wonder what the clinical significance of such small lesions is. This must be assessed by the congruence of the imaging findings with all other available information: clinical, electrographic, neuropsychological, and that derived from functional imaging.

There is currently a great deal of discussion about the effect of resection of the epileptogenic lesion. Some forms of cortical dysplasia are in themselves epileptogenic, whereas other lesions, such as glial tumors, are probably not (4, 8, 27). In that case, the epileptogenic abnormality arises in surrounding brain. Other lesions, such as cavernous hemangiomas, are surrounded by a rim of hemosiderin-impregnated tissue, which is epileptogenic. It is likely, though not conclusively proved, that when both the cavernous angioma and the rim are completely resected, patients become seizure free irrespective of the presence of more widespread epileptogenic EEG abnormalities.

The surgical results of lesionectomy for the treatment of intractable epilepsy have improved progressively. The need for invasive recording and wide resection is increasingly questioned. Some of the inadequate results of lesionectomy, however, can be explained by the presence of dual pathology (8, 27). This term is used to describe the association of mesial temporal sclerosis or atrophy in association with a lesion not directly impinging on these mesial temporal structures. When both the mesial temporal structures and the lesion are resected, the results are optimal. Resection of the mesial structures alone is generally inadequate, whereas resection of the lesion alone in the presence of mesial temporal atrophy may also not be sufficient. Obviously, greater experience is needed to clarify further the optimal treatment of patients with such dual pathology.

Imaging has brought to light a number of epileptic syndromes. Thus, patients with posterior periventricular nodular heterotopia and more anterior temporal mesial epileptogenic foci have a specific natural course and response to mesial temporal resection. In a series of 10 such patients similar to patient 17 reported by Grant et al, only one has become seizure free and that after only a 6-month follow-up (28). All others continued or again developed attacks, suggesting that these lesions may be in themselves epileptogenic. This has been shown in at

least one patient. The more anterior and inferomesial temporal epileptogenic abnormalities may be attributable to secondary epileptogenesis or abnormality of the cortex overlying the nodule.

An analogous syndrome, with what one might call *pseudotemporal epileptic discharges*, is found in patients with hypothalamic hamartomas (29). These patients sometimes have temporal and, more rarely, frontal EEG abnormalities. When these areas were resected after studies with depth recording or other invasive techniques, there was no improvement. The situation was further clarified when the hamartomas were shown to be in themselves epileptogenic by recording directly from them. This also explained the secondary generalized epileptic pattern with deterioration and drop attacks that often develops late in the first decade. This is yet another example suggesting secondary epileptogenesis caused by a lesion whose tendency to cause laughing attacks was never understood until recently.

Another group of lesions diagnosed with MR are the micropolygyrias (7). These are unilateral or bilateral; patient 25 in the paper by Grant et al illustrates that these lesions may be very asymmetric and that a small abnormality contralateral to the major one may be present. The lesions are often perisylvian but are at times bilateral mesial occipital. Others, again often bilateral, extend from the perisylvian region along the sylvian fissure into the parietooccipital region (5, 7, 30).

Bilateral perisylvian polymicrogyria might be genetically determined; there are several sibling pairs reported (31). In the majority of cases, a prenatal watershed vascular abnormality is suspected to cause the micropolygyria. There has been some reluctance to consider surgical resection in patients with very widespread areas of micropolygyria, because the whole area cannot be removed. Evidence is beginning to appear that in some patients, depending on accurate clinical and EEG location, improvement can be obtained by resection of the area of maximal epileptic discharge. In the majority of patients with bilateral perisylvian polymicrogyria, however, there is no evidence of such a focal process. These patients can show a bilateral or generalized epileptic process with drop attacks that respond to callosotomy.

Imaging has recently brought to light at least two autosomal sex-linked migration abnormal-

ities: band heterotopia and periventricular nodular heterotopia (7, 31, 32).

Most of the patients with band heterotopia are female (31). Some have affected daughters whose lesions are similar to those of the mother, and sons with lissencephaly (33). Contiguous periventricular nodular heterotopia can also be found in several generations of female patients. In these families, the abnormalities are probably lethal for the male. A small number of male subjects with band heterotopia have been described, and in at least one of these, radial structures probably representing persistent glial guides can be seen, connecting the band to the cortex.

An area still being explored is computerized morphometry of both temporal and frontal structures (34, 35). The clinical significance of a reduced volume of white matter or of an asymmetric cortical pattern is still not entirely clear. These studies are extremely time consuming and their clinical applicability is as yet uncertain. Cooperative studies at several centers might clarify the issue of their usefulness.

It is often difficult, as Grant et al have stressed, to decide whether a small irregularity of cortical structure represents a real abnormality or whether it is attributable to the incidence of the tomographic sections through one or more gyri. This can often be clarified by curvilinear reconstruction of the brain cortical structure after global MR acquisition (36), a method of image processing that displays the cortical ribbon along curved surfaces. This avoids partial volume effect and provides better comparison between individual gyri and homologous brain regions. At times, it allows recognition of small cortical lesions that had not been recognized by inspection of the usual conventional reformatting.

Not all structural lesions can be demonstrated by current imaging techniques. Microdysgenesis has been described in patients with both generalized and partial epilepsy, and its significance in the causation of the idiopathic form remains uncertain (7, 21, 37). It is equally unclear whether its presence in patients with temporal lobe epilepsy is genetically determined or acquired. There has been remarkably little said in recent years about these abnormalities, which can still be shown only pathologically.

It is readily apparent that MR imaging has opened yet another window on intractable epi-

lepsy. The clinical significance of these findings has allowed identification of new syndromes and the development of new strategies for surgical treatment. With the aid of surface coils, the identification of progressively smaller and smaller lesions has been well illustrated in the paper of Grant et al. It is an important contribution because it has led to recognition of yet another group of lesions, which previously defied detection. Such elegant studies aid in the decision-making process, to the benefit of affected patients.

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