Differential diagnosis and treatment of intractable seizures

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Not all intractable seizures are due to epilepsy, and episodes of uncertain origin call for assessment by appropriate diagnostic methods. Once the disorder is found to be epileptic in nature, seizures can be controlled in many patients. Techniques of diagnosis and treatment are reviewed.

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In recent years, there have been significant advances in the methodologies available for the diagnosis and treatment of seizure disorders. Although the techniques involved are of interest for their theoretical implications, we wish to concentrate on their application to clinical care of patients with intractable seizures.

Diagnosis

If seizures are rare and well controlled with ordinary doses of medication, many of these considerations may not seem relevant. On the other hand, if a patient has had frequent and recurrent seizures, no evidence of an underlying structural lesion, good evidence for adequate anticonvulsant blood levels, and normal routine electroencephalograms (EEGs), the diagnosis should be reassessed before continuing therapy. One consideration should always be syncope (for example, orthostatic hypotension, hyperventilation syndrome, or a vasovagal reaction).1–5 The EEG
can help in differentiating syncope from a seizure disorder; for example, one channel can be devoted to recording the electrocardiogram, facilitating evaluation of possible cardiac arrhythmia, which can be especially important if an episode occurs during the EEG.

Once syncope has been considered, the EEG is also the primary tool for evaluation of patients with intractable epileptic or psychogenic seizures. However, it is important that only definite seizure discharges are taken as evidence of epilepsy; nonepileptiform transients such as psychomotor variant, "six-per-second spike-and-wave," small sharp spikes or benign epileptiform transients of sleep, 14- and 6-per-second positive spikes, wicket spikes, slow-wave transients of the elderly, temporal-parietal rhythmic discharge of adults, hyperventilation responses, and hypnagogic or hypnopompic hypersynchrony are all common in persons with no history of seizures and cannot be considered to support a diagnosis of epilepsy (Figs. 1-3). The EEG will often reveal no epileptiform abnormalities on a single record, particularly in patients with infrequent seizures. Since normal variants do not clarify the etiology of intractable seizures, additional monitoring may be needed to arrive at a specific diagnosis.

Sleep: In 1947, Gibbs and Gibbs reported that of 174 patients with grand mal seizures, 19% had seizure discharges while awake and 63% had them while asleep. Subsequent studies showed that sleep was necessary to define an epileptiform abnormality in 226 of 667 cases, 23 of 36 patients, 30 of 89 cases, and 23 of 73 patients. However, Bagchi and Jones found that only 10% of their 150 patients had a normal awake EEG followed by an abnormal sleep record, while Gloor et al. found that sleep records were necessary in only 5%-6% of patients with temporal lobe epilepsy and therefore did not have to be obtained routinely. This latter
study involved patients referred for epilepsy surgery, who might be expected to have more frequent seizures and thus more frequent epileptiform discharges on the EEG, whether awake or asleep. Nonetheless, the authors agreed that "in patients in whom the waking record remains negative or doubtful...especially patients suffering from a high incidence of nocturnal attacks...a sleep record is certainly indicated." We have reviewed the records of 30 children with complex partial seizures and focal seizure discharges and found that 8 records showed definite seizure discharges only during sleep while the abnormality was increased in 14 others. Whatever the percentage of patients whose seizure discharges are activated by sleep, its use during the EEG involves little risk to the patient and can be of significant diagnostic benefit.

Sleep deprivation: Sleep deprivation for 24 hours has also been used as a method of activating seizure discharges in patients with normal routine records, and previous reports indicated this technique to be successful in 47 of 114 patients in Pratt's series and 31 out of 42 studied by Scollo-Lavizzari et al. Sleep deprivation increases the diagnostic yield even when the patient does not sleep during the recording; again this involves minimal risk and can be of significant diagnostic help.

Repeated and prolonged recordings: One problem in evaluating the effectiveness of techniques involving a second recording is sampling, i.e., a second record may be abnormal simply because additional recordings have been obtained, with sleep, sleep deprivation, or other techniques being incidental. Pratt et al had 33 patients with normal initial EEGs return for a second routine awake record and found that 6 of these were now abnormal, emphasizing the value of obtaining additional information regardless of the state of consciousness of the patient before or during the recording. Therefore, besides additional recordings, we often obtain a longer trace (anywhere from several hours to several days, depending on the frequency of the seizures) in an attempt to document rare epileptiform activity.

Special electrodes: Gloor et al stated that they routinely use nasopharyngeal leads in the evaluation of complex partial seizures, and that accurate localization of the seizure focus was possible only with these leads in 71 out of 177 patients who later underwent a temporal lobectomy; some patients also required sphenoidal leads. Pampiglione and Kerridge found that sphenoidal leads demonstrated seizure discharges in 72 patients with normal or nonspecific scalp recordings. In our laboratory, we always try to use nasopharyngeal electrodes in the diagnosis of intractable seizures. While we have found that it

Fig. 3. Wicket spikes in a 71-year-old woman who had experienced fainting spells six months earlier and had not been placed on anticonvulsants. Note run of sharp transients in the left temporal region, one of which is of higher amplitude than the others.
is very unusual to see epileptiform discharges only at the nasopharyngeal electrode, not infrequently the abnormality is much better defined there or at the sphenoidal lead, helping to clarify the epileptiform nature of discharges which are defined more poorly at the scalp electrodes. In addition, electrodes placed between or below the standard 10–20 placements can be of value. The best known of these electrodes is that described by Silverman, which generally overlaps the anterior temporal region in an area relatively distant from the standard placement sites.

**Drug withdrawal:** Anticonvulsants sometimes "mask" seizure discharges during EEG recordings. Although there is a possibility that drug withdrawal might activate areas which were not previously epileptogenic, Spencer et al found that the results after abrupt withdrawal were consistent with those prior to withdrawal in 25 patients. We often withdraw drugs more gradually, over a period of weeks, but our findings regarding the localizing value of the EEG have been identical. Withdrawal of anticonvulsants is often essential in diagnosing intractable seizures of obscure origin.

**Chemical activation:** Merlis et al reported that pentylenetetrazol activated seizure discharges in 7 out of 16 patients with psychomotor seizures and nondiagnostic awake recordings. However, only 3 patients had focal discharges, which is important since this drug is well known to produce generalized discharges in persons with no history of seizures. Nevertheless, it may be of help diagnostically in selected cases if it produces focal epileptiform discharges or produces a seizure of focal onset which is typical for that patient. Gloor et al employed pentylenetetrazol in 11 of 163 awake recordings to localize the seizures, suggesting that chemical activation may be of value in patients who are being considered for surgery of focal epilepsy and did not have seizures when other methods of activation were employed. However, other authors have reported discrepancies between the location of chemically induced and spontaneous seizures.

**Environmental activation:** A variety of environmental factors have been reported to produce seizures in susceptible patients, including a flickering light, touch, visual patterns, musical passages, and video arcade games. Under these circumstances, one should test the patient with the specific activating agent during the EEG and reproduce the conditions which normally produce a seizure episode as closely as possible.

**Video–EEG monitoring:** Simultaneous recordings of clinical seizures and epileptiform EEG changes have been used successfully in a number of centers to determine which symptoms occur during seizure episodes. In patients with intractable seizures of uncertain origin, this technique can be crucial in demonstrating that epileptiform EEG changes accompany clinical seizure episodes, since one can define the exact time at which a clinical seizure begins and then precisely correlate it with the EEG. It can also be beneficial in demonstrating the etiology of seizure episodes in some patients.

**Activation by suggestion:** If psychogenic causes are suspected, a typical seizure can frequently be induced by suggestion. The combination of a continued normal EEG with a typical unresponsive episode in this setting is highly indicative of a psychogenic seizure disorder (Fig. 4). However, it is important to emphasize that an epileptic seizure can occur during the induction procedure, either due to the stress of the procedure or by chance, so that careful analysis of the record is essential.

Because of the considerations outlined above, we routinely ask that patients thought to have seizure disorders sleep no longer than three hours the night before the EEG. We use nasopharyngeal leads and attempt to induce sleep on the first recording, thereby increasing the yield of definite diagnostic findings at the outset with no increase in examination time. When the EEG is normal in a patient with intractable seizures, the patient may be asked to return for a more prolonged recording (2 to 3 hr, 24 hr, or even several days), also under sleep deprivation and using nasopharyngeal leads. Where appropriate, he or she may be asked to taper medication prior to returning.

When drug withdrawal is employed, we usually taper medication over a period of weeks, lowering the drug with the longest half-life first, and try to have the patient remain on the drug with the shortest half-life. For example, if a patient was on both phenobarbital and phenytoin at the time of referral, we would first taper and then discontinue phenobarbital and continue the patient on phenytoin, discontinuing it just prior to EEG. We have encountered no marked increases in seizure frequency during the tapering-off period in patients with previously normal records and one or fewer seizures per week, although we caution patients about this possibility. Our goal...
is to record definite epileptiform discharges, but not necessarily a seizure. If a patient has had a normal EEG but is experiencing several seizures a week, we might conduct an EEG over a 24-hour period in an effort to record epileptiform discharges or make prolonged recordings over several days in an effort to record an actual episode; moreover, we might taper medication minimally or not at all, since our goals could be achieved without modifying medication. If no epileptiform discharges or seizures occur, we then taper the anticonvulsants. Our objective is to alter the activity of the seizure focus enough to document the etiology of the seizures, but not enough to cause undue clinical deterioration. When a psychogenic seizure disorder is suspected, we attempt to induce an episode during EEG by means of suggestion. Of 50 patients with seizure episodes documented as psychogenic on the basis of absence of epileptiform changes during a typical seizure episode, which included loss of responsiveness, only 5 had evidence of epilepsy. In another study, epileptiform discharges were noted in 6 out of 51 similar patients. These data indicate that patients with documented psychogenic seizures have a higher incidence of epilepsy than the general population, but the great majority of our patients with psychogenic seizures did not have evidence of epilepsy. No matter what the frequency of epilepsy may be in patients with psychogenic seizures, however, the individual approach remains the same. Diagnosis of concurrent psychogenic and epileptogenic seizures requires EEG evidence of each.

**Medical therapy**

**General concepts:** If intractable symptoms are shown to be due to epilepsy, it is necessary to determine why they are intractable. Reynolds et al indicate that control of seizures correlates highly with plasma anticonvulsant levels. Patients with untreated grand mal seizures had an average of approximately one attack per month. When phenytoin levels were less than 10 μg/mL, the seizure rate fell to one every 10 months, while with levels greater than 10 μg/mL it fell to one every 100 months, implying that the first consideration should be not the dosage but rather the drug level in the blood. Furthermore, many patients with intractable seizures fare as well or better on monotherapy, taking a single drug but at the highest tolerated dose, when compared to polytherapy, taking multiple drugs. In part, this appears to be so because these patients can tolerate a higher dose of medication if they are using a single drug, without the development of side effects, whereas if they are taking several drugs, drowsiness, ataxia, or other problems are more likely to develop. Anticonvulsant drug lev-
els are guides which help in evaluating the success of therapy, but they are by no means the final word as to optimal therapy in a given patient. If a patient is seizure-free and has a phenytoin level of 8 μg/mL, one should not automatically increase the dose to obtain an anticonvulsant level in the “therapeutic range.” By the same token, it appears that some patients may need to have a phenytoin level of more than 20 μg/mL to achieve complete seizure control without adverse reactions. Terms such as “therapeutic range” are misleading, since they falsely suggest that all levels within that range are equally therapeutic, whereas a higher drug level may be more effective than a lower one in an individual case. The commonly quoted ranges reflect general clinical experience rather than precise experimental studies, and for this reason, some authors have instead emphasized effective blood levels or the levels at which toxic reactions begin.62-64

Thus in a patient whose seizures continue at lower doses, regardless of the drug levels obtained, the goal of therapy should be to increase the dosage of a single drug to the highest level tolerable without side effects. Drug levels can help in assessing patient compliance, rate of drug metabolism, and patterns of absorption and excretion and assist in establishing the level at which control was achieved for the purpose of comparison if new seizures develop or toxicity occurs.62-64

Reasons for variation in effective or toxic drug levels between patients have been extensively reviewed.62-65 Although compliance, absorption, and excretion are of concern in many cases, it is particularly important to be aware of the effect of altered protein binding,66-68 particularly in uremic patients who characteristically have a much higher unbound plasma fraction of drugs such as phenytoin69 or valproic acid.70 In such cases, the free drug level in the plasma is important because it is this fraction of the total anticonvulsant load which is readily available for penetration of the brain.62,65 A low total drug level may result in a high free drug level in these patients. Conversely, in patients with a low free drug fraction, high-dose monotherapy is effective for improving seizure control because standard doses and plasma levels result in relatively low amounts of medication in the central nervous system.81 Thus if one patient has a total phenytoin level of 40 μg/mL (5% free), a second patient 20 μg/mL (10% free), and a third patient 4 μg/mL (50% free), all three would have an identical free level (2 μg/mL) and thus an identical amount of drug able to interact with receptors within the brain. Once technical problems are resolved,64,71,72 free levels may be obtained routinely with total anticonvulsant drug levels (or even replace them) in assessing seizure control and assessing toxicity because of their greater precision in determining the anticonvulsant load to the brain. At the same time, it is important to be aware of the necessity of adequate laboratory support. Pippenger et al73 demonstrated a wide variation between laboratories with regard to the accuracy of anticonvulsant drug level determinations. In order to improve matters, the Epilepsy Foundation of America and then the American Association for Clinical Chemistry developed a quality assurance program. Although technical proficiency has improved,74 it is still essential that the laboratory participates in this program or has other methods of quality assurance.

Choice of anticonvulsants: Although authors differ in their choice of antiepileptic drugs,75-81 most prefer phenobarbital, primidone, phenytoin, carbamazepine, or sodium valproate for generalized tonic–clonic seizures and ethosuximide or sodium valproate for absence seizures. For seizures of focal onset, most employ primidone, phenytoin, and carbamazepine as first-line drugs. If generalized tonic–clonic or partial seizures remain intractable despite high-dose monotherapy using each of these drugs, one can add methsuximide,82 clorazepate,83,84 or occasionally sodium valproate as a second drug.85-87 Our procedure is to determine which first-line drug is most effective and then add either another first-line drug or (if high-dose monotherapy proves ineffective) one of the second-line drugs. We decrease the first drug enough to avoid side effects such as lethargy and ataxia, which become more prominent when two drugs are used, and increase the second drug to the maximum tolerable dose.60,61 If that drug is not helpful, we try another. Finally, Sterman et al88,89 have reported that biofeedback is occasionally helpful in patients with intractable complex partial seizures. Although further confirmation is necessary, these reports emphasize that psychological methods may have a place in the management of selected epileptic patients.

Surgical therapy

Patients with medically intractable seizures may be candidates for surgical therapy, provided that there is a reasonable chance that surgery...
Because of the potential morbidity with any intracranial procedure, it is important to first gain as much information as possible using noninvasive means, which can document the topographic distribution of interictal epileptiform discharges and the origin of ictal events. It should be kept in mind that the skull and scalp attenuate the amplitude of the discharge and can slightly alter the distribution of the focus as determined by surface electrodes; however, this potential disadvantage is outweighed by the capability of assessing the extent and distribution of the seizure focus, the likelihood of multiple seizure foci, and the potential relationship of the focus to nonresectable “functional” cortical areas (e.g. primary motor strip, speech area, etc.) by noninvasive means. In order to increase the precision of surface localization, our laboratory uses the standard electrode array (International 10-20 System) plus additional electrodes midway between the 10-20 positions over the area(s) of specific interest. In addition, rows of electrodes are placed below the 10-20 positions and nasopharyngeal and/or sphenoidal leads employed in patients with temporal lobe foci to record epileptiform activity from the basal and mesial regions of the temporal lobe (Figs. 5-9). Based on cadaver studies, Jasper has noted the location of scalp electrodes in relation to the underlying brain. In

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**Fig. 5.** Schematic map of the terminology used for scalp electrodes [modified from Chatrian]. Extra leads are placed between the standard International 10-20 System electrodes.

**Fig. 6.** Placement of electrodes on a patient with intractable seizures who had been admitted for prolonged monitoring.
addition, we obtain skull radiographs with the electrodes in place so that we can determine their precise relationship to the anterior and middle fossae in each patient. Ictal and interictal discharges of definite epileptiform significance are then analyzed as to frequency and distribution by recording referentially between the closely spaced scalp electrodes and one distant from the epileptiform focus (or foci). The amplitude of the discharge at each electrode is measured, the point of maximum amplitude determined, and those at the other electrodes expressed as a percentage of the maximum. An isopotential map can then be drawn, indicating the distribution of measured activity. In general, epileptiform discharges are accurately localized at the scalp in the case of convexity foci, compared to the findings with implanted electrodes. However, in the case of mesial or basal foci, there are alterations in surface distribution. For example, mesial and anterior temporal epileptiform discharges tend to be recorded over the inferior frontal or even fronto-polar region as well as over the tip of the temporal lobe. Nasopharyngeal and sphenoidal leads are helpful in patients with mesial temporal foci, but not foci localized to the tip. Seizures of focal origin may not be reflected at the surface (Figs. 10 and 11), presumably because a relatively large area of the cortical surface must be generating a spike before it can be recorded with scalp.

**Figs. 8 and 9.** Two topographic maps of interictal epileptiform discharges (same patient as in Fig. 6) The extra electrodes help to define the presence of a posterior temporal focus.
For this reason, epileptiform activity may not be detectable at the scalp at the onset of seizures if the activity is restricted to a relatively small area of the cortex. In this context, Lieb et al. have noted that the scalp EEG may not record epileptiform activity during auras, or during episodes not accompanied by altered behavior. It is precisely these (simple partial) seizure episodes which may be limited to restricted areas. Thus at the time a seizure is reflected at the scalp surface, it may have projected from the initial focus to a large number of other areas on both sides of the head. Video-EEG monitoring can be helpful in this regard, since it can determine whether the clinical episode occurs before, during, or after the onset of the EEG seizure pattern and whether the topographic distribution of interictal epileptiform discharges is similar to that seen at seizure onset. Functional tests, such as psychological evaluation, dichotic auditory stimulation, decrease of fast activity on pentothal activation, memory testing after intracarotid amobarbital injections (Wada test), and investigation for areas of hypometabolism on positron computed tomography (PCT) have been advocated as additional methods for determining the location of the ictal focus. Engel et al. concluded that the latter three tests provided information which complemented that obtained with stereotactically implanted depth electrodes.
Fig. 12. Subdural 8 × 8 electrode array with centers separated by 1 cm; 1 × 4 electrode strips are also routinely employed and the size of the larger electrode array is modified according to the needs of the patient.

(SEEG). Electrical and chemical techniques for inducing interictal or ictal epileptiform activity do not appear to be consistently accurate.32

Because of the limitations of surface EEGs and other noninvasive techniques, a number of centers use SEEGs to further lateralize seizure onset, either routinely or in cases where noninvasive studies do not provide definite data.102–104 Most such probes have multiple contacts stretching from the convexity to the depth of the brain, suggesting that they would be of value in assessing a variety of structures. However, these electrodes have particularly been used to assess activity in mesial cortical structures. One possible difficulty is that each contact along the probe assesses activity from a relatively restricted region. Also, even with precise stereotaxic placement, slight anatomical variations between hemispheres may result in the contacts on each side not being in precisely homotopic regions. In practice, seizures appear to originate in a wide enough region that such slight variations are not clinically relevant. However, in other circumstances, they may be more significant. For example, in case 107 of Engel et al.,102 surface ictal epileptiform activity was recorded only on the side opposite the temporal lobe eventually selected for removal on the basis of PCT and other functional data.102 Although depth recorded ictal onset and PCT data were concordant, the authors noted that the former “consisted of very low voltage fast activity reflected in only a few electrodes and could easily have been missed if another montage had been used.” Apparently, then, minor differences in activity may dramatically affect the recorded physiological information. Presumably not only different recording montages, but also slight differences in placement or underlying regional anatomy could be important.

Although time of onset is critical in lateralizing the seizure focus, interictal epileptiform activity is also recorded by depth electrodes. However, Wieser et al.32 found that interictal lateralization information agreed with that obtained from spontaneous ictal events in only two thirds of seizures, and the data from depth recordings of Engel et al.102 indicated that the side of seizure onset agreed with interictal spike frequency in only 2 out of 7 patients and with interictal spike autonomy in only 4. These conclusions would seem to suggest that interictal spikes recorded from depth electrodes are unreliable as indicators of the seizure focus; however, it is possible that morphological data (i.e., “what is a spike”) might demonstrate that certain types of interictal discharges are more reliable in this regard.

Since Wieser et al.32 found that the epileptogenic zone included the lateral temporal cortex in 58% of cases, the limited coverage of SEEGs could affect surgery in a large number of cases and might explain some of the discrepancies reported from studies with depth electrodes. In addition, although it is important to know which temporal lobe to remove, it is also necessary to determine how much of the lobe to remove to achieve optimal seizure control in view of the evidence for multiple potentially epileptogenic areas within the lobe of interest as opposed to a single small focus.

For the past several years, we have placed plates of disc electrodes over the convexity to provide wider coverage in patients with intractable seizures93,105–107 (Fig. 12). In addition, strips of electrodes can be placed under the frontal or temporal lobe, directed toward the basal and mesial structures.93,105 These electrodes are used
to record ictal and interictal epileptiform activity, and the use of multiple contacts over the convexity provides wide coverage of this region. Both groups of electrodes are also used for cortical stimulation and for recording evoked potentials and thus for location of areas crucial in controlling motor, sensory, language-related, or other functions. As they are left in place continuously, these electrodes can be used to record spontaneous ictal events as well as for functional localization outside the surgical setting. The electrodes are stainless steel disks 7 mm in diameter imbedded in Dow–Corning MDX clean-grade elastomer with a center-to-center separation of 1 cm. The entire grid is tailored to fit each patient according to the clinical problem. To increase the flexibility and compliance of the grid in relation to the underlying cortex, our current array is “waffled,” with the elastomer between two electrodes being thinner than that at the electrodes. This grid allows the physician to evaluate for the presence of significant epileptogenic areas in the lateral temporal cortex as noted by Wieser et al and supported by the finding by Engel et al of lateral temporal hypometabolism during PCT scanning of patients with complex partial seizures. Since memory testing during intracarotid amobarbital administration and psychological evaluation can be used to infer the safety of removing mesial structures presumably related to memory, the next crucial question is: how much of the lateral temporal cortex is epileptogenic and how much can be safely removed without affecting speech and other complex psychological functions? Although experience has suggested that standard anatomical landmarks can be used to determine the limits of the cortical excision in most patients with temporal lobe epileptic foci, there are well-described exceptions which emphasize the importance of considering that the speech-related region of the cortex may be located farther anteriorly or posteriorly than usual in some patients. Speech testing can be performed in the operating room, but time is limited; moreover, this is only possible in cooperative or older patients who can remain awake during surgery. Chronic subdural electrode arrays allow detailed testing (including both evoked potentials and cortical stimulation) to be performed outside the operating room over a period of several days, thus increasing the precision with which crucial functional areas can be localized and the confidence with which the remaining cortex can be excised. This technique also allows delineation of crucial functional areas outside the temporal lobe, e.g., near the motor strip or in the occipital lobe. In such cases, we stimulate the cortex and use evoked potentials to delineate those structures which cannot be removed without producing clinically significant deficits and then remove as much of the epileptogenic focus as possible, leaving functionally crucial areas intact. We have employed this approach in about 50 patients over the past five years, revising our technique as experience was gained. The Montreal experience suggests that follow-up for at least four years is necessary in assessing the results of surgery, and we are only now beginning to accumulate this expertise in a significant number of patients. However, our initial results have been comparable to those reported by other groups. This technique has been particularly helpful in patients with epileptogenic foci involving regions which otherwise might have seemed too risky to remove.

**Conclusion**

In some patients, intractable seizures are best treated by using diagnostic techniques which demonstrate that they are of syncopal or psychogenic origin, cannot be treated with anticonvulsants, and require other therapeutic approaches. In many other patients the disorder is not cured but rather controlled through modification of medication. If seizures remain uncontrolled, surgery can significantly reduce their frequency in selected patients, but surgery should be thought of as a complement to, rather than as a replacement for medication until complete control is demonstrated for a sufficient length of time. The fact that some patients are not candidates for surgery, or do not improve despite such measures, underscores the need for further drug trials, improved surgical techniques, and the development of alternative approaches.

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