Intractable seizure disorders of childhood[1]

A. David Rothner, M.D.

The evaluation of the child with intractable seizures is reviewed. Important in this diagnosis are a review of the history to classify seizures and rule out nonepileptiform conditions; a review of the general physical and neurological examinations to rule out any previously undiagnosed conditions; repeating laboratory studies to make sure no etiologies have been undiscovered; and the use of multiple therapies, including combinations of antiepileptic drugs, the ketogenic diet, and seizure surgery. Infantile spasms, myoclonic seizures, and complex partial seizures have the most unfavorable prognoses.

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The goal of the treatment of epilepsy is the complete suppression of seizures without the development of medication-related side effects.[1] Drug therapy results in good seizure control in approximately 70% of patients with epilepsy. At least 20%–30% of patients have seizures which are refractory to available anticonvulsant drugs.[2] The frequency of seizures in these intractable patients may be diminished by medication, but they are not totally controlled. The term "intractable seizures" is relative and may be used to describe patients who are having 70–100 seizures per day or three to four seizures per month. The incidence of intractable seizures seems to be higher in children than in adults, although no definitive data are available. Uncontrolled, recurrent seizures have a lasting effect on cognition, psychosocial development, and quality of life and interfere with all environmental interactions.

[1] Department of Neurology, The Cleveland Clinic Foundation. Submitted Dec 1983; accepted Feb 1984.

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The medical model for the evaluation of the patient with refractory seizures includes repeating the history, general physical and neurological examinations, and laboratory tests. Critical to the process is the rethinking of the differential diagnosis.

The goal of re-evaluating children with intractable seizures is to reduce their seizure frequency, seizure severity, and seizure duration. This improved seizure control should aid in the patient's social and vocational adjustment, as well as decrease side effects and toxicity. Approaching such a difficult problem requires a multidisciplinary effort. Patients with intractable seizures are best evaluated at epilepsy centers, where many specialists can interact, both when diagnosing and treating the disorder, as well as when rehabilitating, educating, and psychosocially supporting the patient.

The re-evaluation[3]

The *history* should include data concerning the actual seizure itself. Important questions should deal with the frequency of spells, precipitating factors, times of occurrence, presence of an aura, duration of spells, a description of the ictal activity, and a description of the postictal state. It should be determined if more than one seizure type has taken place, and an effort must be made to properly classify the spells as this is critical for later treatment.[4] In reviewing the history, special attention should be given to past and present factors known to be associated with intractable seizure disorders, such as mental retardation, focal or generalized cortical pathology, previous central nervous system infection or injury, cerebral palsy, birth trauma or prematurity, central nervous system neoplasms, degenerative disorders, a metabolic disorder, a congenital anomaly of the nervous system, a genetic disorder associated with seizures, a past history of status epilepticus, or a positive family history of epilepsy.

During the *systems review*, disorders of other organ systems which may predispose to seizures should be carefully considered. These include congenital cardiac defects, chronic pulmonary disease, chronic infection, hepatic disorders, gastrointestinal disorders with malabsorption, renal disease and/or electrolyte imbalance, non-central nervous system neoplasms, endocrinological disorders, and psychological disorders which may predispose to hysterical seizures or noncompliance.

The *drug history* must be reviewed, stressing exposure to previous antiepileptic drugs (AEDs), their maximum amounts in milligrams per kilogram, and maximum drug levels (free and bound). If the patient is taking drugs other than AEDs, their types, amounts, and possible interactions with AEDs should be reviewed. Queries concerning motor and/or developmental regression, as well as questions regarding symptoms of increased intracranial pressure, such as headaches, vomiting, weakness, ataxia, mental changes, and visual changes, complete the history. If the disorder seems progressive, the evaluation process must be accelerated.

The *general physical examination* should be repeated carefully, keeping in mind that any organ system may have an effect on the central nervous system and may affect seizure frequency and drug metabolism. The neurological examination[3,5] is repeated in an attempt to determine if the patient is functioning normally or if focal or generalized neurological deficits exist. The neurological examination should include evaluation of the patient's mental status and intellect, gait, cranial nerves, motor system, sensory system, and cerebellar function. Diagnostic skin lesions, intracranial bruits, microcephaly or macrocephaly, or other dysmorphic features should be noted. The behavior and affect of the patient are important since behavioral disorders are more common in patients with chronic central nervous system problems and may contribute to poor seizure control.

After compulsively reviewing the history and re-performing a detailed general physical and neurological examination, one should *rethink* the *differential diagnosis*. Does the patient suffer from a paroxysmal nonepileptiform disorder and not true epilepsy? Disorders to be considered are apneic spells, breath-holding spells, gastroesophageal reflux, syncope, head banging, cardiac arrhythmias, hydrocephalus with episodic increased intracranial pressure, hypoglycemia, temper tantrums, vertigo, masturbation, atypical behavioral mannerisms, narcolepsy, hyperventilation, postural hypotension, pseudoseizures, atypical migrainous attacks, the periodic syndrome, sleep disorders, and other periodic events such as paroxysmal choreoathetosis. If the patient is believed to have true epilepsy, an attempt should be made to classify its specific type to provide more effective therapy.[4]

The *laboratory tests* should be chosen on the

basis of the differential diagnosis. Even if some have been previously performed, repetition may be necessary. Basic tests such as blood sugars or blood calciums drawn at the time of the seizure may produce unexpected results. Specific metabolic testing (such as amino-acid chromatography) of both blood and urine should be done. If the patient is dysmorphic, chromosome testing is indicated. Unusual historical information or atypical or unusual physical findings may dictate the need for other less frequently ordered tests, for example, arsenic or lead levels. Determination of blood levels of AEDs is necessary; blood may be drawn at different times of the day to determine peak and trough levels. The blood levels may determine whether or not the patient has complied with the prescribed drug treatment program or whether drug-drug interaction is a problem and whether the levels are at maximal tolerance. One must be sure that the laboratory performing the AED levels is reliable and accurate. If a recent computed-tomographic (CT) scan has not been obtained, one should be repeated, using the injection of contrast material to see if a structural deficit of the central nervous system is present. At the present time, the additional value of magnetic resonance imaging, positron emission tomography, and digital subtraction angiography is not known. If one suspects a degenerative process, a lumbar puncture with special studies may be helpful. Other studies of patients suspected of harboring a degenerative disease include evaluation of evoked potentials, electromyography, biopsy of the skin or other tissue, evaluation of lysosomal enzymes, and electroretinography. Especially helpful in patients with intractable seizures are prolonged electroencephalographic recordings with closed-circuit television monitoring, evocative procedures, and telemetry. In this way, one may actually be able to record a seizure, determine its origin, and elucidate the nature of the patient's ictal and interictal activity. This procedure may determine whether or not the patient has a true seizure disorder or pseudoseizures.

Discussion

My own experience indicates that therapeutic failures are most often due to the basic underlying nature of the patient's seizure disorder. Certain seizure disorders, such as generalized tonic-clonic seizures,[6,7] classic absence or petit mal seizures,[8] and benign focal epilepsy of childhood,[9] in the otherwise normal patient have an excellent prognosis and are not usually intractable. Also, patients with any long-standing or mixed uncontrolled seizure disorder, especially infantile spasms, the myoclonic seizures, and complex partial seizures, have a much poorer prognosis.[6,7,10–14] The presence of neurological deficits, mental retardation, and of certain electroencephalographic (EEG) patterns such as hypsarrhythmia, slow spikes and waves, multifocal spikes, and a disordered, slow background also suggests a seizure disorder which may prove to be intractable.[11–13]

Infantile spasms are the seizure component of a syndrome consisting of the spasms, mental retardation, and a hypsarrhythmic EEG and occur in from 1 per 2,500 to 1 per 6,000 births. They usually begin when the child is between three and nine months old. The seizure consists of a quick flexion contraction at the trunk and limbs, followed by relaxation. The spasms tend to occur in clusters and are most frequently noticed when the child is awakening from or falling to sleep. They last one to three seconds. The disorder may either be idiopathic or symptomatic. The latter category includes disorders which may occur in utero, during the perinatal period, or postnatally. Many of these youngsters are abnormal at the time or before diagnosis. The patients seem to "deteriorate" when the spasms begin. The EEG abnormality consists of a chaotic mixture of irregular high-voltage slow spikes and waves combined with multifocal sharp waves and burst suppression. The background is abnormal as well. Despite treatment, most patients are retarded at follow-up examination. Great differences in the literature exist concerning the percentage of patients with normal intellectual function at the time of follow up. The evaluation of these youngsters is as outlined above. Treatment of these youngsters involves the use of intramuscular ACTH (varied dosage, from 20–120 mg/day for 4 wks to 6 mo). Many authors advocate the use of major anticonvulsants along with the ACTH injections; other authors recommend the concomitant administration of medication such as nitrazepam, clonazepam, or valproic acid.[12]

Myoclonic seizures, which include akinetic seizures, atonic seizures, and myoclonic seizures, occur in the first decade of life, but usually not during the first year. Their incidence is approximately 1 per 1,000 children. The disorder has also been called the Lennox-Gastaut syndrome,

atypical petit mal, slow spike and wave epilepsy, and minor motor epilepsy. These seizures are usually associated with other forms of seizures such as focal motor, grand mal, and complex partial seizures.[11,12] They all have similar characteristics (brevity [a matter of milliseconds or seconds] and repetition [occurring several hundred times per day]). They are associated with mental retardation, either at the onset of the seizure disorder or once the seizure disorder has been established. They are associated with an abnormal EEG, either showing slow spike and wave discharges or multifocal spike discharges and a disordered background. The differential diagnosis of this disorder includes congenital anomalies of the central nervous system, degenerative disorders, central nervous system infections, other metabolic disorders, toxic disorders, and trauma. The evaluation, in addition to the routine history, physical examination, and laboratory studies, includes a metabolic work-up, study of lysosomal enzymes, CT scanning, a lumbar puncture, and TORCH titers. This disorder is refractory to treatment. Unfavorable signs include seizures which have an onset when the patient is less than two years old, the presence of tonic seizures, the presence of an abnormal neurological examination, and the presence of slow spike and wave or multifocal spikes on the EEG. In addition to the usual medications, such as phenytoin, phenobarbital, primidone, and carbamazepine, medications such as valproic acid, prednisone, ACTH injections, the benzodiazepines (nitrazepam, clonazepam, and diazepam), ethosuximide, and acetazolamide (Diamox) have been used. Unfortunately, their use has not met with much success. The prognosis for seizure control and intellectual normalcy in this group of patients is poor.

Complex partial seizures frequently begin in childhood. The seizures consist of a blank stare, a period of unresponsiveness, and amnesia. Many of the patients will have an aura, and many will have automatisms. Postictally, the patients are lethargic or confused. Associated behavioral problems may be present. Electroencephalographic findings include sharp waves or spikes located in the temporal derivations. The evaluation of these patients includes routine laboratory studies, as well as a CT scan with and without the injection of contrast material. Phenytoin, phenobarbital, primidone, and carbamazepine, administered either singly or in combination, are the most commonly used medications. Many of these patients will be refractory to medical therapy and will require surgery.[13]

If, however, the patient is a therapeutic failure, and causes other than the basic seizure disorders discussed previously may be possible, one should suspect the following factors and investigate them one by one in great detail:

The correct diagnosis has not been established. Critical to a thorough re-evaluation is re-investigation of the differential diagnosis and the ordering of laboratory tests not previously done to rule in or rule out those disorders deemed likely. Prolonged EEG monitoring, combined with closed-circuit television monitoring, is absolutely necessary to evaluate this group of patients. In my experience, drug withdrawal and evocative procedures, although potentially hazardous, have been helpful. Only in this way can the diagnosis of seizures, the exact type of seizure, and the possibility of pseudoseizures be established.

Medication-related problems are also common.[15–17] The patient may purposely not take the medication regularly; unwittingly not take the medication regularly; not use the proper form of the medication; take inadequate amounts of medication; take the medication at inappropriate times; take other drugs which interfere with the AEDs; have an abnormal metabolism which affects drug absorption, binding, distribution, metabolism, and excretion; take the wrong drug for the seizure type; or overmedicate with resultant drug toxicity. The problem of the patient in relation to his or her medication can be solved by hospitalizing the patient; personally administering the correct drug in the correct amount, at the correct time, in the correct form; and obtaining frequent drug levels. All other unnecessary competing medications should be discontinued if possible. Sequential, peak, and trough drug levels can be measured to rule out abnormal metabolism, toxicity, and malabsorption.

It is important to review with the patient in his or her own terms the importance of avoiding *seizure-inducing factors.*[18] Tension and stressful situations, certain stimulatory medications, sudden discontinuation of medications, hyperventilation that occurs with athletic activity, sleep deprivation, chronic lethargy and fatigue, flashing lights, fever, central nervous system overstimulation, hypoxia, hypoglycemia, alcohol ingestion, and the degree of hydration and acidosis can play a role in causing uncontrollable seizures. Every

one of these factors must be investigated. The patient must be helped to better understand the nature of his or her seizure disorder, the factors which may precipitate or aggravate the attacks, and most importantly, the reasons for daily administration of medication for an indefinite, sometimes lifelong, period.[12,14] Many patients require psychological help to avoid consciously or unconsciously continuing seizure-inducing behavior.

Pseudoepilepsy and factitious seizures are more common than previously suspected.[19,20] Patients may have "pure" pseudoepilepsy or a combination of real seizures and pseudoseizures. It is indeed difficult to differentiate clinically between pseudoepileptic and real seizures. The use of a historical profile, behavioral observations, psychological and personality testing, and prolonged EEG-video recording helps differentiate the patient with pseudoepileptic seizures from the patient with true epilepsy. The absence of any interictal epileptiform activity helps confirm the diagnosis, as does a normal EEG during the "seizure." Methods of activation include suggestion, photic stimulation, hyperventilation, or saline infusion.[21] Treatment is difficult and the prognosis is variable.

If the patient truly has intractable epilepsy and other disorders and problems (non-pseudoepilepsy and noncompliance) have been ruled out, the type of epilepsy should be classified.[4] The appropriate drug for that type of seizure should be prescribed in the proper amount, proper form, and with the proper schedule.[17,22] The patient should be instructed to avoid situations which may precipitate seizures and to avoid other drugs which interfere with the metabolism of the drug controlling the seizure disorder. The patient should be informed regarding side effects and the consequences of noncompliance. In some patients, higher dosages of a single drug are more useful in bringing the seizure disorder under control than is the use of multiple drugs. Side effects are minimized by this technique as well. The therapeutic program should be initiated and the patient monitored closely so that the patient is exposed to a variety of AEDs over a period of time, both singly and in combination, using maximally tolerated dosages and measuring levels. In this way, many so-called intractable seizures can be brought under better control. The use of any and all AEDs should be considered. Retrial of previously tried AEDs is sometimes successful. Discontinuation of AEDs with maximal side effects is helpful. If this methodology fails, exposure to newer, possibly unapproved anticonvulsant drugs is indicated, and referral to a medical center specializing in the use of these drugs may be necessary.

In certain selected patients with a focal cerebral cortical lesion, surgery for epilepsy is a "conservative" approach to bringing the seizures under control.[23] Patients may be considered for surgical treatment if: (*a*) their seizures are not under control despite adequate trials of medications confirmed by AED-level monitoring; (*b*) current medications cause unacceptable side effects, such as incapacitating drowsiness and personality changes; (*c*) most seizures arise from a single cortical focus, as confirmed clinically and electroencephalographically; (*d*) the cortical focus is in an area that can be destroyed surgically without causing deficit; and (*e*) the patient has no other significant clinical and EEG deficit in another area of the central nervous system. When the patient has a single, well-defined lesion, the results are quite good: more than 65% of patients either become seizure free or experience a significant decrease in their seizure frequency.

Other nondrug methods that attempt to bring intractable seizures under better control can also be used. In the child, these methods include the ketogenic diet,[24] and more recently, the use of biofeedback.[25] The latter technique is presently being investigated; little data are now available regarding its efficacy. The ketogenic diet is employed to treat children whose seizure disorder is not controlled by AEDs. Generally, these patients are mentally retarded and suffer from a mixed seizure disorder. Their EEGs are characterized by slow spike and wave or multifocal paroxysmal abnormality and a disordered background. This diet may control certain seizures even if the use of all available AEDs has failed. At the Cleveland Clinic, a combination of the ketogenic diet and medication is employed. The mechanisms of action of this high-fat, low-carbohydrate diet are unknown. Absolute compliance by the patient with the dietary regimen is necessary. Sustained ketosis appears to be an important factor in modifying the convulsive threshold. Even a small increase in the amount of carbohydrate intake can affect this ketosis and cause the diet to no longer have its effect. The patient must be watched in case hypoglycemia develops during the initiation of this diet. In some series, approx-

imately 50%–70% of patients have had a substantial reduction in their seizure frequency while remaining on this diet conscientiously.

Most recently, Snead et al[26] have advocated the use of intramuscular ACTH injections on a daily basis for weeks to months to effectively control patients with intractable seizures. Although this technique seems to be promising, follow-up data are not currently available.

The treatment of the patient with intractable seizures stresses a proper diagnosis; proper drug therapy and drug monitoring; patient and family education; avoidance of seizure stimulation; use of multiple medications; consideration of epilepsy surgery; use of the ketogenic diet; and vocational, educational, and psychological rehabilitation.

Department of Neurology
The Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland OH 44106

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