Epilepsy and Developmental Disability

Part I: Developmental Disorders in Which Epilepsy May be Comorbid

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Abstract

Epilepsy is common in patients with developmental disability. The approaches used to diagnose and treat patients with developmental delay and epilepsy may differ from those used for other patients and require additional special attention. This article reviews developmental disorders in which epilepsy is comorbid and treatment strategies that are used for patients that present with both disorders. It outlines the value of pharmacological and surgical treatments depending on the individual patient, and highlights the need for monitoring nutritional status. The importance of collaboration and cooperation from an interdisciplinary team to enhance functioning and to achieve optimal quality of care for the patient is discussed. In addition to the current knowledge and practices regarding medical treatment for patients with epilepsy and developmental disorders, this article indicates what is currently not known and what needs further research and documentation. Unusual terms used in this article are explained in a glossary.

Epilepsy is a chronic neurological condition characterized by recurrent seizures that are caused by abnormal neuronal activity. Epilepsy can be classified as either idiopathic or symptomatic. Idiopathic epilepsy has no known cause, and the patient has no other signs of neurological disease or intellectual deficiency. Symptomatic epilepsy results from a known condition, such as neoplasms, vascular anomalies, scars, stroke, genetic factors, birth trauma, brain injury, or poisoning (Engel, 1998). Epilepsy affects approximately 1% of the general population at any time. Approximately 10% of the general population will experience a seizure in their lifetime and 3% will develop epilepsy by the age of 75.

Many patients with developmental disorders present with an epilepsy comorbidity. For example, seizures appear in more than 20% of children with cerebral palsy, unspecified cognitive impairment, pervasive developmental delay, as well as in specific genetic syndromes associated with cognitive impairment. In addition, there are different types of epilepsy that may be associated with different types of developmental disability. Both the paper electroencephalogram (EEG) and the video EEG remain the most valuable tools that are used to evaluate patients with both epilepsy and a developmental disorder.

The approaches used to diagnose and treat patients with developmental delay and epilepsy may differ from other patients and require additional special attention (Mattson, 1996; Steffenburg, Hagberg & Kyllerman, 1996). While the focus of this paper is on epilepsy in people with a primary developmental disorder, the companion paper, Part II, outlines what is known about the developmental consequences of seizures in neurocognitive and neurobehavioural development.

The Molecular Basis of Epilepsy

Inhibition versus excitation hypotheses

The most predominant hypotheses of mechanisms of epileptogenesis implicate the amino acid transmitters gamma aminobutyric acid (GABA) and glutamate. GABA is thought to be the main neurotransmitter at inhibitory neurons, while glutamate is thought to be the main neurotransmitter at the excitatory synapses (Snead, 1995). Normal brain function depends upon a balance of both excitation and inhibition. If there is an imbalance of either excitation or inhibition in the brain, seizure production may result. If excitation exceeds inhibition, the brain tissue becomes hyperexcitable leading to a low seizure threshold. If the imbalance is sufficiently large, a seizure occurs and may eventually lead to epilepsy - recurring, spontaneous seizures. Research is currently being done to investigate the hypotheses that chronic low seizure threshold results either from too much activity in the excitatory glutamatergic system (the glutamate hypothesis) or from too little activity in the inhibitory GABA system (GABA hypothesis). Thus far, neither hypothesis has been conclusively proven; however, there is pharmacological evidence to support both hypotheses (Burnham, 1998).

Alternative underlying mechanisms of epileptogenesis

In addition to the inhibition and excitation hypotheses, other potential mechanisms thought to be involved in epileptogenesis include alteration of dendritic spines, abnormal ion channels, and perturbation of neurotransmitter functions (Stafstrom, 1993). Patients with both developmental disability and epilepsy may have nutritional deficiencies (such as specific nutrient intolerance and atypical dietary preferences) that aggravate their epilepsy. Efforts should be made to remedy any deficiencies. As in the general population, electrolyte imbalances (for example, deficiencies of magnesium, sodium, or calcium) and abnormal blood sugar levels (hypo- or hyperglycemia) may play a role in seizure induction in people with developmental disability, especially in neonates (Sood, Grover & Sharma, 2003). These factors should be monitored and corrected, if abnormal. Finally, treatment with antiepileptic drugs may actually cause deficiencies of folate, vitamin B12 and vitamin B6 (Apeland, Mansoor, Strandjord & Kristensen, 2000). More research is needed to determine whether these and other mechanisms are responsible for seizures in specific developmental disorders associated with epilepsy.

Animal models of epilepsy

Animal models may be useful in studying the underlying mechanisms for human epilepsies (Snead, Depaulis, Vergnes & Marescaux, 1999). Much of what is known about the epilepsies is derived directly or indirectly from animal models. There are many more models of chronically recurrent seizures than epilepsies, as such. Nevertheless, the phrase "animal model of epilepsy" is often used instead of the more precise phrase "animal model of a seizure disorder." In vitro brain slices can be used to answer certain questions pertaining to the epileptic process but there are some drawbacks that animal models may not have. For example, an in vitro preparation cannot seize, and certainly cannot suffer epilepsy, but this does not detract from the insight into the mechanisms gained from the use of these model systems (Fisher, 1989). A logical way to determine which model system to use would be to first choose the experimental question that needs to be addressed. Questions regarding the influence of anticonvulsants on membrane ion channels can be answered in tissue culture. If the researcher is asking whether surgical interruption of certain neuronal pathways can block seizure spread, then experiments must be done on intact animals (Fisher, 1989). The use of inappropriate model systems may yield irrelevant results and lead to a waste of money, time and lives of animals.

Epilepsy in Specific Developmental Disorders

Down syndrome

Down syndrome (trisomy 21) is the most common chromosomal cause of developmental delay, with a birth incidence of approximately 1/1000. Seizures occur in 5-10% of persons with Down syndrome, which is several times the expected frequency in the general population (Pueschel, Louis & McKnight, 1991; Romano et al., 1990; Tatsuno, Hayashi, Iwamoto, Suzuki & Kuroki, 1984). Ischemic-hypoxic brain damage, hypoxia from congenital heart disease, or infection, are thought to precipitate seizures in children with Down syndrome whose brains already are predisposed to hyperexcitability because of abnormal neuron development (Stafstrom, Patxot, Gilmore & Wisniewski, 1991). Seizures also are associated with brain changes that occur in Alzheimer-like dementia which occurs at high frequency in people with Down syndrome, 30 to 40 years earlier than in the general population (Prasher & Percy, 2003). Although all seizure types can occur in Down syndrome patients, tonic-clonic seizures are the most common. Infantile spasms, reflex seizures, and startle epilepsy are also common. Late onset epilepsy may take the form of myoclonus. Treatment should be chosen according to seizure type and in many cases each patient requires a unique approach to their medical care. It has been hypothesized that nutritional deficits may be responsible, at least in part, for the high frequency of epilepsy in people with Down syndrome (Thiel & Fowkes, 2004). Phenytoin should not be given for late-onset seizures in adults with Down syndrome (Tsiouris, Patti,Tipu & Raguthu, 2002).

Fragile X syndrome

Second to Down syndrome, Fragile X syndrome is the most common chromosomal disorder leading to developmental delay (Chakrabarti & Davies, 1997). Hyperkinetic behaviour, hypotonia, and macro-orchidism in males after puberty are other features of the condition (Shorvon, 2000). Approximately 10 to 25 % of patients with Fragile X syndrome have epilepsy. Seizures usually develop early on in life and remit spontaneously during adulthood. The most common form of seizures in patients with Fragile X syndrome is tonic-clonic seizures, although atypical absence and complex partial seizures can occur. The epilepsy can usually be completely controlled with conventional therapy. In general, rare isolated seizures do not require antiepileptic therapy.

Angelman syndrome

The main characteristics of Angelman syndrome include learning difficulty, lack of speech, microcephaly, hyperactive behaviour, and puppet-like movements. Other difficulties include failure to thrive and feeding problems. Epilepsy develops in 90% and is intractable in about 50%, especially in children (Matsumoto et al., 1992; Zori et al., 1992). By adult life, however, seizures are no longer a major feature of the condition. Both convulsive and non-convulsive seizure types can occur. Rhythmic limb jerking caused by cortical myoclonus is characteristic and can be mistaken for tremor. The anti-epileptic drug treatment for patients with Angelman syndrome is usually initiated with valproate, ethosuximide, and/or benzodiazepines (Shorvon, 2000). Because some cases of Angelman syndrome are associated with epilepsy and some are not, studies of genes surrounding the UBE3A gene, which is functionally deficient in people with Angelman syndrome, should provide some important clues about a cause of epilepsy in this disorder (Dan & Boyd, 2003).

Rett syndrome

Rett syndrome is a X-linked syndrome that is characterized by learning difficulty, acquired microcephaly, loss of fine motor skills, severe impairment of expressive and receptive language, gait apraxia, growth retardation, and other features, such as breathing dysfunction, scoliosis, and spasticity. Rett syndrome affects only females (it usually is lethal in males) and seizures occur in 70-80% of patients, usually starting between the ages of 3-5 years (Shorvon, 2000). The most frequent seizure types seen in patients with Rett syndrome are complex partial, atypical absence, generalized tonic-clonic, atonic, and myoclonic seizures. Other behavioural abnormalities can be mistaken for seizures including tremor, bruxism, hyperpnoea/apnoea, and episodic cyanosis. The epilepsy can become severe and intractable by school age but lessens in severity in adult life. Clinical trials of carbamazepine, clonazepam, and valproic acid have been reported without obvious superiority of any specific anti-epileptic drug (Shorvon, 2000).

Because of the high frequency of seizures in people with Rett syndrome, genetic defects resulting in this disorder also might be causing the seizures. Many cases of Rett syndrome are now known to be caused by different types of mutations in a gene called X-linked MECP2 that encodes a protein called methyl-CpG-binding protein 2 (Amir et al., 1999). The introduction of

methyl groups on the C residues of regulatory regions of DNA called CpG islands is associated with gene inactivation.

Autism Spectrum Disorders (ASD)

This category of developmental disorders consists of a number of different subtypes including autism, Asperger syndrome, pervasive developmental disorder, and childhood disintegrative disorder (Joshi, Percy & Brown, 2002).

Autism. This disorder is a complex developmental disability that typically presents during the first three years of life. It is the result of a neurological disorder that affects the functioning of the brain. Autism has been estimated to occur in as many as 1 in 500 individuals. It is approximately 4 times more likely to occur in boys as girls (Deuel, 2002). Autism impacts the typical development of the brain and is often defined by communication impairments, altered behavioural manifestations, and problems with social interaction (Myhr, 1998). Persons with autism typically have difficulty with verbal and non-verbal communication, social interactions, and leisure or play activities. Some may tend towards aggression or self-injury. Some may exhibit repeated body movements (hand flapping, rocking), unusual responses to people, unusual attachments to objects, and resistance to changes in routines.

Asperger syndrome. This disorder involves autistic, odd, and eccentric behaviour but well-developed language skills (Raja & Azzoni, 2001). Impairments are noticed in social interactions with the presence of restricted interests and activities. There is usually no clinically significant general delay in language, and testing indicates that the patients fall in the range of average to above average intelligence.

Pervasive Developmental Disorder (PDD). A diagnosis of PDD may be made when a child does not meet the criteria for a specific diagnosis, but there is a severe impairment in specific behaviours.

Child Disintegrative Disorder. This disorder is characterized by normal development for at least the first two years, followed by significant loss of previously acquired skills.

Epilepsy is common in the ASDs (Shinnar et al., 2001). Numerous investigators have documented that there is an increased frequency of seizures in ASD. Recent studies suggest that about one third of children in

the autistic spectrum develop epilepsy (Deyken & MacMahon, 1979). The seizures are observed more frequently in those patients with more severe mental retardation. Various forms of epilepsy, including complex partial seizures, generalized tonic-clonic seizures, and (more rarely) absence seizures occur in children with ASD. The frequency of seizures in persons with ASD increases when they reach puberty. To date, although there is some evidence to suggest that the use of anticonvulsants and steroids to treat epileptiform discharges thought to be producing dysfunction in selected aspects of cognition, language, and behaviour in a subgroup of children with ASD makes a positive difference, there is inadequate evidence on which to base specific recommendations (Tuchman, 2000).

Tuberous sclerosis complex

Tuberous sclerosis is the most common of the simple Mendelian inherited diseases causing epilepsy, and is inherited in an autosomal dominant fashion. It occurs with a frequency of about 1 in 10,000. Epilepsy occurs in approximately 80% of patients, and the types of seizure are strongly age related. Some patients with tuberous sclerosis experience neonatal seizures (Curatolo, Verdecchia & Bombardieri, 2002). Tuberous sclerosis is one of the most common causes of both West and Lennox Gastaut syndromes (see below and also Part II). Cognitive impairment occurs in about 50% of identified cases, and is more likely in those who develop seizures below the age of 2 years.

In the brain, the characteristic pathological findings are cortical and subependymal nodules, and other features of cortical dysgenesis may be present (Shorvon, 2000). The subependymal nodules can undergo malignant transformation in adult life. Affected individuals can show widely varying manifestations, and very occasionally no clinical features at all. At one extreme, patients can present as being entirely normal and at the other be severely disabled physically, mentally, and with severe epilepsy. The diagnosis is usually made by clinical examination, family history, brain imaging, renal ultrasound, electrocardiogram (ECG), ophthalmic examination, and scrutiny of the skin.

There is approximately a 50% chance of passing the condition to offspring. Disease determining genes for tuberous sclerosis are localized to 9q34 (tuberous sclerosis complex 1, TC1) and 16p13.3 (tuberosis sclerosis complex 2, TSC2) (Narayanan, 2003). Epilepsy in this disorder is treated on conventional lines, and the prognosis for seizure control and for other aspects of the condition is extremely variable (Hanno & Beck, 1987). The

infantile spasms respond well to vigabatrin, but there are no other known specific responses to particular antiepileptic drugs.

Neurofibromatosis

Neurofibromatosis (NF) is an autosomal dominant genetic neurodevelopmental condition affecting approximately 1 in 4,000 individuals (Kulkantrakorn & Geller, 1998). Only 50% of those affected with NF have a prior family history of NF. NF is a genetic disorder of the nervous system that causes tumours to form on the nerves anywhere in the body at any time. This progressive disorder affects all races, all ethnic groups and both sexes equally. There are two genetically distinct forms of NF, NF-1 and NF-2. The NF-1 gene is localized to chromosome 17. It primarily affects growth of Schwann and glial derived tissues, both in the central and peripheral nervous systems. Loss of the NF-1 gene leads to the development of benign glial tumours and in rare cases development of neoplastic tumours (Kulkantrakorn & Geller, 1998). NF-1 is associated with epileptic seizures in approximately 3-5% of patients. There is no known cure for either form of NF, even though the gene for both NF-1 and NF-2 have been identified.

Currently, NF has no treatment other than the surgical removal of tumours that may some times grow back. Various seizure types are found in patients with NF including febrile seizures, complex partial seizures with or without secondary generalization, and primary generalized seizures. In most cases, seizures are not a major problem and the overall prognosis for epilepsy control in NF is similar to that for seizures in the general population (Thurston, Thurston, Hixon & Keller, 1982).

West syndrome

West syndrome is an epileptic syndrome characterized by the triad of infantile spasm (generalized seizures), hypsarrhythmia (chaotic, abnormal EEG pattern), and arrest of psychomotor development at seizure onset (Wong & Trevathan, 2001). It occurs in approximately 0.7/100,000 people and accounts for 28-30% of infants with epilepsy. The age of onset is usually around 3 to 12 months with peak at 4-7 months (Dulac, 2001). Males tend to be at a greater risk of acquiring West syndrome than females. A family history of infantile spasms is reported in 3-6% of cases. Prenatal causes of West syndrome include tuberous sclerosis, intrauterine infections, brain malformations, and inborn errors of metabolism. Postnatal causes include

cerebral hypoxic events, head trauma, and infections. Cognitive impairment is found in approximately 60-70% of patients at onset of infantile spasms.

The seizure characteristics found in West syndrome include a sudden onset of a tonic seizure that is bilateral and symmetrical. The spasms may vary from massive contractions of large muscle groups to contractions of only neck and abdominal muscles. A patient may have more than one type of spasm and they tend to occur in clusters of 5-10 individual spasms. An aura or warning signal such as a cry may precede the seizure. Approximately 30% of symptomatic West syndrome patients progress to Lennox Gastaut syndrome. Treatment for West syndrome includes hormonal therapy with adrenocorticotropic hormone (ACTH) or prednisone (Snead, 1996). Total control of seizures with ACTH or prednisone is expected in about 70-75% of patients within a few weeks of therapy. Alternatively, antiepileptic medications such as clonazepam, valproate, nitrazepam, and clobazam are often prescribed to help treat seizures (Hrachovy, 2002; Mikati, Lepejian & Holmes, 2002).

Lennox Gastaut syndrome

Lennox Gastaut syndrome (LGS) is a devastating childhood epilepsy characterized and defined by several criteria: (1) static encephalopathy and learning disabilities associated with profound mental retardation; (2) multiple seizure types including atypical absence and seizures resulting in falls; and, (3) EEG demonstrating slow spike and wave (< 3 Hz) and bursts of fast rhythms at 10-12 Hz during sleep (Dulac & N'Guyen, 1993; Wheless & Constantinou, 1997). LGS represents about 5% of childhood epilepsy, and the presence of slow spike and wave on EEG among children with multiple seizure types predicts the co-existence of profound mental retardation. As children with LGS grow into adulthood, many require institutionalization in order to receive appropriate care.

Treatment is complicated by the progressive decline in IQ and progressive gait disturbances that have been reported to occur with age, and that also are associated with worsening of the epileptic encephalopathy. The risk of serious injuries from falls associated with seizures is high, and up to 10% of children with LGS die prior to 11 years of age. Many patients with LGS wear a helmet with a face guard to protect against facial injury from atonic seizures. Treatment of seizures in patients with LGS vary from individual to individual. Some therapeutic approaches include antiepileptic drugs (AEDs) (Alvarez, Besag & Iivanainen, 1998), focal cortical resection (Goldring, 1987), corpus callosotomy (Fiol, Gates, Mireles, Maxwell & Erickson,

1993), vagus nerve stimulation (Lundgren, Amark, Blennow, Stromblad & Wallstedt, 1998) and the ketogenic diet (Lefevre & Aronson, 2000).

Conditions Comorbid with Epilepsy in People with Developmental Disabilities

Depression, anxiety, attention-deficit/hyperactivity disorder (ADHD) and psychiatric disorders

Behavioural and psychiatric disorders are common in the population with developmental disabilities (Devinsky, 2002). Psychiatric comorbidity prevalence rates in patients with a developmental disorder have been estimated to range between 10 and 60% (Borthwick-Duffy, 1994). The rate of psychiatric disorders in patients with developmental disabilities and epilepsy has been found to be significantly higher among patients with persistent seizures than among patients who are seizure-free (Kanner, 2002; Lund, 1985). Various forms of psychiatric disorders may occur in patients with epilepsy or both a developmental disability and epilepsy. The occurrence of depression, anxiety, attention deficit/hyperactivity disorder (ADHD), and psychotic disorders have all been reported to occur in these patients but many of these disorders often go unrecognized because of the patients' inability to verbally communicate their symptoms (Kanner, 2002).

A depressed patient may appear withdrawn and increasingly isolated, may refuse to participate in group activities, may appear more irritable, and may be more prone to violent outbursts (Kanner & Balabanov, 2002). Anxiety disorders may be suspected when patients suddenly refuse to be left alone (e.g., sleep in their own room) and avoid participation in their usual activities. Identification of neurovegetative symptoms (i.e., changes in appetite, early night insomnia, or middle night or early morning awakening) may suggest an underlying endogenous psychiatric process. Psychosis should be suspected in the presence of bizarre behavior. Verbal patients may be able to voice paranoid delusions and acknowledge hallucinations. Insomnia also usually occurs early in a psychotic process (Kanner, 2000). ADHD is relatively frequent among pediatric patients with a developmental delay and epilepsy, and its diagnosis is usually self-evident. In autistic children, ADHD is among the earliest psychiatric disturbance (Rapin, 1995).

The identification of a family history of major or bipolar depression or panic disorders in first-degree relatives of people with a particular type of epilepsy may provide important new clues about these psychiatric disorders, because

they are thought to be mediated by genetic mechanisms. Information from such families also should help to identify the genetic basis of the epilepsy.

Despite the relatively high prevalence of psychiatric comorbidity among epileptic patients, there are only scarce data on its treatment. In particular, psychiatric illnesses diagnosed comorbid with familial epilepsies are of great clinical significance to the patient, family, and in the classroom setting, because they adversely affect the opportunity that the patient has to flourish.

To further complicate the clinical treatment of patients with comorbid psychiatric illness, they are often treated with antidepressants and neuroleptics that may lower seizure threshold. In fact, there are reports that indicate that the majority of antidepressants and neuroleptic drugs cause seizures in nonepileptic patients (Rosenstein, Nelson & Jacobs, 1993). As a result, the antidepressants of the selective serotonin reuptake inhibitor (SSRI) family should be considered as first-line treatment for depressed and anxious patients generally. They have a low seizure propensity, are well tolerated in overdose, and have a favorable adverse effect profile (Kanner, 2002).

Other conditions

There are possibilities for the occurrence of pulmonary disorders (such as aspiration), neuromuscular disorders (such as hypotonia), gastrointestinal disorders (such as oral motor dysfunction, drooling, or constipation), and nutritional deficiencies (such as specific nutrient intolerance or atypical dietary preferences, electrolyte imbalances, or hypoglycemia) in patients with both a developmental disability and epilepsy. Therefore, these patients must be monitored closely in order to assure that these adverse effects of certain antiepileptic drugs do not occur (Coulter, 1997).

Diagnosis

The coexistence of intellectual deficits and behavioural abnormalities may substantially interfere with the medical assessment of seizures in patients with developmental disorders. Some of the major problems of diagnosis include communication breakdown between patient and caregiver, difficulty in observation and interpretation of symptoms, distinguishing between epileptic and non-epileptic behaviours, EEG interpretation, and neuroleptic or other drug-induced seizure effects.

Patients with developmental disorders belong to some of the most drug-exposed groups in society. Adverse drug reactions may remain unrecognized and may be more harmful than the seizures themselves. Particular care should be taken to avoid over treatment in this group. Unfortunately, to date, the treatment end point in many cases is not a complete seizure-free state, but rather an improvement in seizure control, alertness, mood, and behaviour. The diagnosis of specific types of seizures in the developmentally disabled population is, in principle, no different from diagnosing any other population. However, since people with developmental disabilities may be limited in describing the experience of their seizures, information about seizure onset may not be available or reliable. Furthermore, it may be more difficult to distinguish between self-stimulatory behaviours, tics, automatisms, and other paroxysmal attacks from genuine epileptic seizures.

The evaluation of an individual with developmental delay who is suspected to have seizures or epilepsy begins with a determination of whether the behavioural events in question were really seizures. Scalp EEG recording may not always detect ictal changes during seizures that do not affect consciousness (partial simple seizures), but ictal changes are usually detectable during seizures that do affect consciousness (partial complex and generalized seizures). EEG recording during behavioural events believed to be seizures in individuals with developmental disorders has shown that approximately 40% of such behavioural events do not meet the definition and are not really seizures (Donat & Wright, 1990; Holmes, McKeever & Russman, 1983; Neill & Alvarez, 1986). Other causes for these seizure-like behaviours include psychiatric disorders, muscle spasms, paroxysmal movement disorders, cardiac syncope, sleep disorders, and migraines. A diagnosis of seizures is based primarily on a careful description of the behavioural events and exclusion of these other possible causes for the behaviour.

Treatment of Seizures

Principles of drug treatment

Treatment of epilepsy in people with developmental disabilities, as in the general population, is of utmost importance because there is increasing evidence that every seizure a person has is likely to result in some brain damage. Epilepsy that occurs along with learning difficulty is often severe and resistant to drug therapy. In addition, seizure identification, particularly

partial seizures without motor components, may be difficult (Rutecki & Gidal, 2002). Nevertheless, the usual principles of antiepileptic drug (AED) therapy apply. Single drug therapy should be used where possible and, if seizures continue, alternative drug options should be given as treatment trials. Some points need specific emphasis.

Antiepileptics. Prescription of AEDs should follow certain well-accepted principles of therapy. Selection of an AED is based on the relative efficacy of the drug against a particular type of seizure, the relative risks for mild and potentially life threatening adverse effects, and the relative cost of treatment. Phenytoin and carbamazepine are preferred for individuals with partial seizures (including partial simple, partial complex, and secondarily generalized tonic-clonic seizures). Valproate, gabapentin, lamotrigine, and topiramate are also effective. Ethosuximide is preferred for individuals with generalized absence seizures, although valproate, lamotrigine, and clonazepam are also effective. Valproate is preferred for individuals with generalized myoclonic, tonic, and atonic seizures. Lamotrigine, felbamate, and topiramate are also sometimes effective for these seizures as part of the Lennox Gastaut syndrome. Patients with primarily generalized tonic-clonic seizures can be treated with phenytoin, carbamazepine, or valproate. Barbiturates such as phenobarbital, mephobarbital, and primidone are usually not preferred because of the relatively high frequency of adverse effects of these drugs on alertness, mood, and behaviour (Coulter, 1997).

AED monotherapy is preferred. The increased availability of newer AEDs and the emphasis on single drug treatment (monotherapy) have influenced the prescription of AEDs for patients with epilepsy and developmental disabilities. Various studies have documented the usefulness and effectiveness of the newer AEDs (Mattson, 1996). In addition, a study looking at the treatment of patients with epilepsy revealed that a reduction of the number of prescribed AEDs and increased prescription of a single AED did not result in any significant deterioration in seizure control (Coulter, 1997). Furthermore, a reduction in the prescription of barbiturates was often accompanied by significant improvement in behaviour. These results confirm the findings of several smaller studies (Coulter, 1988, 1997). This research demonstrates that the vast majority of individuals with epilepsy and developmental disorders should be treated with no more than one or two AEDs, and that these AEDs should not include barbiturates if possible.

Side effects and complications. Side effects caused by AEDs can be more devastating in patients with both epilepsy and a developmental

disability compared to those with epilepsy alone. These patients display adverse effect profiles that differ from other patients because of coexistent central nervous system or systemic abnormalities (Pellock & Morton, 2000). For example, in the presence of cerebral damage, drug side effects tend to be more frequent, to occur at lower serum levels, and to take unusual forms. The increasing knowledge of how protein structure and function is disrupted in many disorders will allow the design of AEDs that have fewer severe side effects. This subject is reviewed in more depth in Part II.

Adverse drug effects that occur in these patients include confusion, behavioural changes, mental deterioration, encephalopathy, weight gain which may be attributed to neuroleptics or inactivity, hypersensitivity to the muscle relaxing effects of benzodiazepines in hypotonic children, and dystonia or ataxia in patients with pre-existent motor deficits. The individual with learning difficulty may not be able to clearly communicate the adverse consequences of drug therapy. It is an essential duty of the prescribing physician to maintain extreme vigilance for side effects, to prevent distress or harm (Tsiouris, Patti, Tipu & Raguthu, 2002).

Clusters of seizures and episodes of status are common in patients with severe epilepsy and learning difficulty. These episodes can be precipitated by minor problems, such as infections or trivial environmental changes. Emergency therapy is often needed earlier and more frequently with these patients. Drug doses may need to be modified as handicapped individuals often show special sensitivities to the usual drugs. Tailored regimens for emergency intervention need to be defined for each individual based on previous, often unfortunate, experiences. It is helpful to document these in writing, and to have these available to all those involved in the medical care team.

Overmedication, especially in patients that have intractable epilepsy, is a particular problem in patients with developmental delay. Some reasons for this include the need for a third party to decide upon treatment on behalf of the patient and the difficulty in communicating side effects. In many instances, benefits, without loss of seizure control, are often gained by reducing the overall AED load.

Seizure control in developmental and psychiatric disorders. Not much attention has been given to the study of AEDs in people with epilepsy and developmental disorders. One group documented that virtually all of their community-based subjects with epilepsy and mental retardation could be managed successfully with only one or two AEDs (Singh & Towle, 1993).

They noted that many other such patients living in the community might still be overmedicated with excessive and unnecessary amounts of AEDs. Another group found no support for the commonly held idea that seizure control is related to IQ (worse seizure control in those with lower IQ) (Marcus, 1993). The study excluded primary epilepsies, including the PMEs, for which neuodegeneration and cognitive decline is always the major concern, and the familial idiopathic epilepsies, for which neuropsychiatric and learning disabilities are usually the major concern. In the community based study, however, seizure control was not related to IQ, neurologic status, or degree of EEG abnormality in patients with a primary developmental disability. Similarly, Singh and Towle (1993) found no relationship between IQ and seizure control in adult developmental disability subjects living in the community.

Both studies suggested that seizure control was related to the number of types of seizures present, with generally less control in those with mixed seizure types. Importantly, however, these community-based studies did not include subjects with epileptic syndromes (such as the Lennox Gastaut syndrome), often associated with multiple seizure types that are known to be difficult to control (Mariani, Ferini-Strambi, Sala, Erminio & Smirne, 1993), the PME neurodegenerative disorders, or the familial idiopathic epilepsies such as JAE. These disorder are reviewed in more detail in the companion article to this one.

These findings have three significant implications subject to the reservation that these may not apply to people with epileptic syndromes, PME, or JAE, as noted above. One is the importance of accurate classification of the seizure type, which predicts AED selection and response, and of the classification of the type of epilepsy or epileptic syndrome, which may predict long-term seizure control. The second implication is that, currently, the principles of AED treatment are the same for patients with epilepsy and developmental disability (and/or psychiatric comorbidity) as they are for those with epilepsy alone, and do not depend on the level of IQ. The third implication is that the optimal management of epilepsy with AEDs requires monitoring of the effects of therapy (Alvarez et al., 1998). This includes periodic interval recording of the occurrence of seizures, the dosage of AEDs prescribed and the serum levels of these AEDs, adverse effects observed (including clinical observations and laboratory results), and any interventions made in response to these findings. Therapeutic drug monitoring is usually facilitated by the use of a flow sheet that tracks these findings over time.

Treatment of refractory seizures

Some individuals with epilepsy will not achieve satisfactory seizure control despite the adherence to these principles, and are therefore said to have refractory epilepsy. These patients may benefit from application of additional strategies to improve seizure control. Individuals may be enrolled in clinical trials of new AEDs. Careful attention to control and reduction of seizure-inducing factors, such as reduced alertness, altered sleep patterns, excessive or insufficient physical activity, intense or prolonged emotional stress, specific sensory stimuli (such as flashing light), hormonal or metabolic imbalance, excessive water intake, hypoxia, fever, and toxic states, was crucial in achieving seizure control in 17% and helpful in another 26% of children and adults with refractory epilepsy (Aird, 1983). Individuals with a developmental delay who have refractory epilepsy may benefit from similar strategies to identify and control possible seizure-inducing factors.

Surgery. Surgical therapy can benefit a small number of individuals with epilepsy (Goldring, 1987; Goldring & Gregorie, 1984). The presence of a handicap does not rule out this possibility. However, assessment should be carried out in experienced health care centres. The prediction of quality of life after surgery and informed consent are often problematic topics for patients with developmental delay. A professional heath care team is required to sort out these issues. Although epilepsy surgery has generally excluded patients with mental retardation, it may be worth considering in appropriate situations. For example, in some cases, a focal cortical resection of the brain (e.g., vascular lesion, tumor) can improve seizure control in patients with developmental delay.

Subdural grids are used to locate precisely what area of the brain should be removed (Rosenbaum, Laxer, Vessely & Smith, 1986; Wyler, Ojemann, Lettich & Ward, 1984). The subdural grid consists of electrodes that are surgically placed inside the skull, directly on the surface of the brain, during a 2 to 4 hour surgery. The grid is used to localize the site of seizure onset and to determine certain critical areas of brain involved in seizure progression (e.g., language and motor areas). Another surgical approach that is used to control seizures in rare cases is called the corpus callosotomy or "split brain surgery." This operation interrupts the spread of seizures by cutting the nerve fibers connecting one side of the brain to the other via the corpus callosum. In LGS patients, the corpus callosotomy is effective in reducing drop attacks but typically is not helpful for other seizure types. It is considered palliative rather than curative and complete seizure freedom following a corpus callosotomy is rare but can occur (Fiol et al., 1993).

Vagal nerve stimulation. Another approach to controlling otherwise intractable seizures in patients with developmental disorders is vagal nerve stimulation. This therapy includes a pulse generator similar to a heart pacemaker that is used to abort seizure. The generator is inserted in chest and linked to an electrode inserted into an opening at the side of the neck. The electrode is fitted around the vagal or vagus nerve. Clinicians program the generator to stimulate the nerve at varying frequencies, typically at 30 seconds for every 5 minutes, using a laptop computer and wand. Additionally, patients who experience an aura or warning before a seizure can use a special magnet to manually activate the generator. One study estimated that approximately 75% of patients with LGS experience a > 50% reduction in seizure frequency using the vagus nerve stimulator (Lundgren et al., 1998). Other studies found vagal nerve stimulation to be effective in idiopathic, cryptogenic, and symptomatic generalized epilepsies (Devinsky, 2002).

The ketogenic diet. Frequently a treatment of last resort, the ketogenic diet can also be used in patients with developmental delays and epilepsy. It is composed of a 2:1, 3:1, 4:1, or higher ratio of fats (ketogenic foods) to proteins and carbohydrates. In general, its benefits include fewer seizures, less drowsiness, better behaviour, and fewer AEDs needed. The ketogenic diet is more effective for generalized epilepsies than for partial epilepsies. The efficacy of the ketogenic diet appears best for atonic, myoclonic, and atypical absence seizures, but other seizure types also respond. Seizures often decrease shortly after initiation of the diet, but some patients may not respond for months. Unfortunately, the ketogenic diet is not always successful (Lefevre & Aronson, 2000) even in patients refractory to AEDs.

Safety Considerations

Although epilepsy is one of the most important medical conditions that may jeopardize an individual's safety and predispose to seizure-related injury, it has received little attention in the literature on developmental and psychiatric disabilities. Mortality is increased two- to threefold among persons with epilepsy (particularly those with tonic-clonic, myoclonic, and atonic seizures) compared to the general population. Causes of death include seizure-related accidents (e.g., trauma, drowning), pulmonary aspiration, status epilepticus, suicide (untreated psychiatric comorbidity), and adverse effects of AEDs. Sudden, unexpected, and unexplained death in patients with epilepsy may be due to autonomic instability, cardiac arrhythmias, or abrupt drug withdrawal (Coulter, 1997). The nonfatal injuries that also occur in these patients may reflect many of the same causes.

Unfortunately, very few published studies have reported systematic data regarding these safety concerns. The types and frequencies of injury (seizure-related or not), the settings in which injuries occur (e.g., residential facility, community home, school, work, leisure activity), the antecedents and causes of injuries, and the severity and complications of injuries in persons with mental retardation have rarely been the subjects of systematic study in epilepsy comorbid with developmental and/or psychiatric disability. Clearly, these data are needed to develop rational procedures to ensure safety and prevent injury.

Until such data become available, each patient should be treated as a unique case. The likelihood of injury on the basis of those risk factors that may be present in an individual situation should be evaluated and appropriate safe guards should be taken. Strategies may include avoidance of identified risk factors, AED changes to improve seizure control and reduce adverse effects of AEDs, environmental changes or modifications to reduce threats to personal safety, enhanced staff supervision, and better staff training in emergency response, first aid, and resuscitation. Agencies need to clearly define policies for individualizing safety assessment and assurance, monitoring the occurrence of injuries, and responding promptly and appropriately when emergencies occur. Excessive reliance on the use of passive restraints (such as wheelchairs for otherwise ambulatory persons) or mechanical devices (such as helmets) to prevent seizure-related injuries should be discouraged because many anecdotal experiences have shown that injuries often continue to occur even when these restraints and devices are used (Coulter, 1997).

The presence of epilepsy and the attendant risks of injuries are often cited as critical factors that prevent individuals with developmental disorders from leaving an institution and entering a community based setting. Litzinger, Duvall and Little (1993) showed that institutionalized individuals with severe or profound mental retardation, virtually all of whom had experienced at least one seizure per week despite prescription of multiple AEDs, could be safely moved to a community based setting. Their subjects experienced fewer emergency room visits or hospitalizations for seizures or adverse effects of AEDs, no increase in seizure-related injuries, better seizure control, and more independent behaviour in the community based setting.

Team Management and Institutional Care

Comprehensive management of epilepsy and developmental (and/or psychiatric) disorders requires the involvement, collaboration, and

cooperation of an interdisciplinary team to enhance functioning and achieve optimal quality of care (Devinsky, 2002; O'Neill, Ladon, Harris, Riley & Dreifuss, 1977). Ideally, the team should consist of the individual with epilepsy, the family, the primary care physician, neurologist, nurse, pharmacist, social worker, psychologist, physical and occupational therapists, nutritionist, educator, and others as needed. The primary care physician and neurologist are principally responsible for the diagnosis and classification and the prescription of AEDs, but the rest of the team will have important input into these aspects of management. The registered professional nurse assesses, plans, coordinates, implements, and assesses the effectiveness of interventions and educates the staff as well as the recipients of services. The entire team works together to ensure safety and protection from injury and to optimize psychosocial functioning. Experience indicates that no single person or profession can do it all and that the patient with epilepsy and developmental (and/or psychiatric) disability does best when the entire team is present and communicates well. To assess and improve the interdisciplinary team process, the patient and family members must cooperate and become active participants in all treatment decisions (Devinsky, 2002).

The needs of individuals with multiple handicaps are often complex, and care is difficult to organize. In patients with severe epilepsy, the seizures usually pose major problems but in others the problems of epilepsy are less pressing than those of other handicaps including psychiatric and learning disorders. Epilepsy adds a dimension that the caregivers often find difficult to deal with. The responsibility of dealing with potentially life-threatening seizures is felt to be too great by many otherwise competent persons. It is therefore often difficult to find suitable residential or daytime placements for patients with a developmental disorder and epilepsy. There are specialized institutions that provide expert epilepsy care and, although these provide a secure environment from the epilepsy point of view, they may be geographically distant from the family home, adding additional stress to the overall scenario.

Teamwork is needed, with facilities for outpatient and inpatient treatment and good communication between the different professional groups and also the family (Devinsky, 2002). Care can be shared between an institution and the family, and in both settings a balance has to be set between overprotection and neglect. This balance can be very difficult to define or achieve. Individuals deserve an individually tailored solution, and the issues involved and the risks taken should be explicitly agreed with the individual, the family, and the professional caregivers.

Conclusions

There has been significant progress in the comprehensive management of epilepsy in persons with developmental disorders. Recent advances in the treatment of epilepsy need to be extended to people with both epilepsy and a developmental disability. In several developmental disorders with a known genetic basis, such as Rett syndrome and Angelman syndrome, the mutations causing the developmental disability may also be causing the epilepsy. This raises the possibility that various novel therapies that target a particular developmental disorder may in fact alleviate the epileptic comorbidity in some patients. Implementing the current knowledge about AED treatment, community living, and psychiatric treatment will enable patients with epilepsy and developmental disorders to benefit from inclusion in the mainstream of best practices in the field. Overall, continuing attention to this important subject is needed to ensure optimal patient management and the best possible quality of medical care.

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Glossary

absence seizures: During an absence seizure (also called petit mal), epileptic activity occurs throughout the entire brain. It is a milder type of activity, which causes unconsciousness without causing convulsions. After the seizure, there is no memory of it. An absence seizure begins abruptly and without warning, consists of a period of unconsciousness with a blank stare, and ends abruptly. There is no confusion after the seizure, and the person can usually resume full activity immediately. An absence seizure may be accompanied by chewing movements, rapid breathing, or rhythmic blinking. Absence seizures are short, usually lasting only 2-10 seconds.

apnoea: Transient cessation of respiration whether normal (as in hibernating animals) or abnormal (as that caused by certain drugs).

apraxia: A disorder of the nervous system characterized by an inability to perform purposeful movements but not necessarily by a loss of sensory function or paralysis.

ataxia: An inability to coordinate voluntary muscular movements that is symptomatic of some nervous disorders.

atonic seizures: Atonic seizures (drop attacks) are not seen in many children. Without warning, a child abruptly loses consciousness, collapses and falls to the floor. There is no convulsion, but children may injure their head as they fall. Recovery occurs after a few seconds. The child regains consciousness, and can again stand and walk. Atonic seizures may occur with Lennox Gastaut Syndrome. They sometimes resist anticonvulsant medication. If so, the child may have to wear a helmet to prevent head injuries.

atypical absence seizures: Atypical absence seizures are similar to typical absence seizures, but usually have more pronounced jerking or automatic movements, a duration of longer than 20 seconds, incomplete loss of awareness during the seizure, and are associated with other types of seizures and a damaged nervous system. Atypical absence seizures are more likely to occur in children who have developmental delay.

autosomal dominant inheritance: Inheritance pattern for a trait that is inherited when a child receives one gene for the trait from one parent who is affected by the trait.

autosomal recessive inheritance: Inheritance pattern for a trait that is inherited when a child receives two genes for the trait, one from each parent, both of whom must carry the gene for that trait although they are not necessarily affected by it.

bruxism: The habit of unconsciously gritting or grinding the teeth especially in situations of stress or during sleep.

cerebral hypoxic events: A deficiency of oxygen reaching areas of the brain.

corpus callosotomy: An operation that interrupts the spread of seizures by cutting. The nerve fibers connecting one side of the brain to the other. The nerve bridge is called the corpus callosum.

comorbid: Existing simultaneously with and usually independently (though not necessarily) of another medical condition.

cortex: Also known as grey matter, a term that describes the brain's outer layer. The cerebral cortex is involved in complex brain function such as language and information processing.

cortical dysgenesis: Defective development of the cortex.

cortical nodules: Small tumours of the cerebral cortex consisting of clusters of small oligo-like cells and a myxoid pattern rich in mucopolysaccharides. Most are associated with small benign tumours composed of multiple cell types, called microhamartias, in the adjacent brain and pharmacoresistant epilepsies.

CpG islands: Regions of DNA that are rich in the CpG pattern. When such regions are not methylated, genes are frequently turned on. Clusters of the CpG pattern often are associated with the promoter region of genes.

dystonia: A neurologic movement disorder characterized by sustained muscle contractions, resulting in repetitive, involuntary, twisting or writhing movements, and unusual postures or positioning. Dystonia may be limited to specific muscle groups (focal dystonia), such as dystonia affecting muscles of the neck (cervical dystonia or spasmodic torticollis) or the eyes, resulting in closure of the eyelids (blepharospasm).

electroencephalography (EEG): A diagnostic technique that records the electrical impulses produced by brain cell activity. An EEG reveals characteristic brain wave patterns that may assist in the diagnosis of particular neurologic conditions, such as seizure disorders, impaired consciousness, and brain lesions or tumors.

encephalopathy: A disease of the brain, especially one involving alterations of brain structure.

epilepsy: A disorder of the nervous system, usually characterized by fits of convulsions that end with loss of consciousness.

epileptogenesis: The production of epileptic attacks.

episodes of status: A state in epilepsy in which the attacks occur in rapid succession without recovery of consciousness.

episodic cyanosis: A state that presents as a bluish or purplish discoloration (as of skin) due to deficient oxygenation of the blood.

failure to thrive: A presenting symptom (not a diagnosis) in which a child under 2 years of age (and usually under 1 year of age) exhibits some degree of growth failure in the absence of an obvious cause.

focal cortical resection: A surgical procedure that involves excising out part of the brain (e.g. vascular lesion, tumor) in order to improve seizures in some epileptic patients.

gait apraxia: Loss or impairment of the ability to execute complex coordinated foot movements without impairment of the muscles or senses.

gamma aminobutyric acid (GABA): An amino acid that serves as the principal inhibitory neurotransmitter in the brain.

generalized seizures: Occur when the excessive electrical activity in the brain encompasses the entire organ. The two most common forms are generalized absence seizures and tonic-clonic seizures.

glial cells: Cells in the central nervous system consisting of three different types: astrocytes and oligodendrocytes (collectively, macroglia which are of ectodermal origin) and microglia (which are of mesodermal origin). The first group appears to play a role in myelin formation, transport of material to neurons, and maintenance of the ionic environment of neurons.

glutamate: A non-essential amino acid occurring in proteins. It also serves as an excitatory neurotransmitter in all regions of the central nervous system.

hyperkinetic behaviour: Diminished movement and decreased motor function.

hyperpnoea: Abnormally rapid or deep breathing.

hypsarrhythmia: An abnormal EEG that is characterized by slow waves of high voltage and a disorganized arrangement of spikes, occurs especially in infants, and is indicative of a condition that leads to severe mental retardation if left untreated.

ictal changes: Alterations during a seizure episode.

infantile spasms: Clusters of seizures that usually begin before the age of 6 months. During these seizures the infant may bend and cry out.

intractable: Resistant to cure, relief or control.

ischemic-hypoxic brain damage: Localized brain tissue injury due to anemia and obstruction of the inflow of arterial blood and a deficiency of oxygen.

ketogenic diet: The ketogenic diet is composed of a 2:1, 3:1, 4:1, or higher

ratio of fats (ketogenic foods) to proteins and carbohydrates. It is used to help reduce seizure occurrence. This diet's efficacy appears best for atonic, myoclonic, and atypical absence seizures, but other seizure types also respond.

macro-orchidism: The condition (as in fragile X syndrome) of having large testicles.

microcephaly: A condition of abnormal smallness of the head usually associated with mental retardation.

myoclonus: A neurologic movement disorder characterized by brief, involuntary, twitching, or "shock-like" contractions of a muscle or muscle group.

neonatal: Pertaining to the first four weeks after birth.

neuroleptics: Antipsychotics that work by acting on the nervous system.

paroxysmal movement disorders: Neurologic movement disorders characterized by abrupt, transient episodes of abnormal involuntary movement or impaired coordination of voluntary actions and other associated findings (i.e., paroxysmal ataxias).

partial complex: Complex partial seizures occur when epileptic activity spreads to both temporal lobes in the brain. A complex partial seizure often occurs after a simple partial seizure of temporal lobe origin. Complex partial seizures are experienced most by children. In some children, they lead to tonic-clonic seizures. A complex partial seizure does not involve convulsions, but consciousness is impaired. Someone experiencing one will no longer respond to questions after the seizure starts. The seizure usually lasts about 2 to 4 minutes and may be followed by a state of confusion lasting longer. Once the pattern of seizures is established, it will usually be repeated with each subsequent seizure. Complex partial seizures sometimes resist anticonvulsant medication.

partial seizures: Occur when the excessive electrical activity in the brain is limited to one area. The two most common forms are simple partial seizures and complex partial seizures.

partial simple: Simple partial seizures result from epileptic activity which is localized in one part of the brain, usually the cortex or limbic system. Consciousness is not impaired, people experiencing a simple partial seizure can talk and answer questions. They will remember what went on during the seizure. Simple partial seizures usually last just a few seconds, although they may be longer. If there are no convulsions, they may not be obvious to the onlooker. In some children, simple partial seizures lead to complex partial seizures, or to tonic-clonic convulsions.

refractory: Resistant to or not readily yielding to treatment.

reflex seizures: Seizures (most commonly tonic-clonic or partial) that are initiated by a distinct sensory stimulus such as a strobe light, the glare of a television, or vertical lines.

Schwann cells: Any of the large nucleated cells whose cell membrane spirally enwraps the axons of myelinated peripheral neurons and is the source of myelin.

scoliosis: A lateral curvature of the spine.

secondarily generalized seizures: Seizures are usually partial seizures evolving into generalized seizures, most often with tonic-clonic convulsions. The partial seizures that were once limited to one hemisphere of the brain progress to encompass the entire brain bilaterally, causing a generalized seizure. The clinical nature of a secondarily generalized seizure usually does not differ from that of the initial, originating seizure.

seizure threshold: The amount of stimulation required to cause a seizure.

seizures: Episodes of uncontrolled electrical activity in the brain. These abnormal electrical disturbances may lead to involuntary jerking, spasms, or rhythmic contraction and relaxation of certain muscle groups and impaired control of involuntary functions such as breathing or bladder or bowel control. There may also be loss of consciousness or sensory or behavioral abnormalities.

spasticity: Feelings of stiffness and a wide range of involuntary muscle spasms-sustained muscle contractions or sudden movements.

startle epilepsy: Characterized by seizures induced by sudden and unexpected stimuli, usually a sudden sound. The seizures are frequent, usually lasting less than 30 seconds and consisting of a startle response followed by a brief but characteristic tonic phase, which is usually asymmetric. Many subjects fall, and clonic jerks may occur.

status epilepticus: A series of rapidly repeated epileptic convulsions without any periods of consciousness between them.

subependymal nodule: Small abnormal tumorous growth or calcification found under the epithelial membrane lining the ventricles of the brain and the canal of the spinal cord.

symptomatic epilepsy: Epilepsy that results from a known condition, such as stroke, head injury or poisoning.

syncope: Loss of consciousness resulting from insufficient blood flow to the brain.

tics: Involuntary, compulsive, stereotypic muscle movements or vocalizations that abruptly interrupt normal motor activities. These repetitive, purposeless motions (motor tics) or utterances (vocal tics) may be simple or complex in nature; may be temporarily suppressed; and are often preceded by a "foreboding" sensation or urge that is temporarily relieved following their execution. Simple tics include abrupt, isolated movements, such as repeated facial twitching, blinking, or shoulder shrugging, and simple sounds, including grunting, throat clearing, or sighing. Complex tics may involve more sustained, complex movements, such as deep knee bending, leg kicking or complex vocalizations.

tonic-clonic seizures: Involve a mixture of symptoms, including stiffening of the body and repeated jerks of the arms and/or legs as well as loss of consciousness. Tonic-clonic seizures are sometimes referred to as grand mal seizures.

ultrasound: A diagnostic or therapeutic noninvasive technique involving the formation of a two-dimensional image used for the examination and measurement of internal body structures and the detection of bodily abnormalities.

vagus nerve stimulation: A technique that uses a pulse generator, similar to a heart pacemaker, to abort seizures. The stimulator is inserted in the chest and linked to an electrode inserted into an opening at the side of the neck. The electrode is fitted around the vagal or vagus nerve and is programmed to stimulate the nerve at varying frequencies.

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