The 2010 Revised Classification of Seizures and Epilepsy


Abstract

Purpose of Review:

Classifications of epilepsies (1989) and seizures (1981) took a central role in epilepsy care and research. Based on nearly century-old concepts, they were abandoned in 2010, and recommendations for new concepts and terminology were made in accordance with a vision of what a future classification would entail. This review outlines the major changes, the ways these changes relate to the earlier systems, the implications for the practicing health care provider, and some of the recommendations for future classification systems.

Recent Findings:

New terminology for underlying causes (genetic, structural-metabolic, and unknown) was introduced to replace the old (idiopathic, symptomatic, and cryptogenic) in 2010. The use of generalized and focal to refer to the underlying epilepsy was largely abandoned, but the terms were retained in reference to mode of seizure initiation and presentation. The terms “complex” and “simple partial” for focal seizures were abandoned in favor of more descriptive terms. Electroclinical syndromes were highlighted as specific epilepsy diagnoses and distinguished from nonsyndromic-nonspecific diagnoses. The importance of diagnosis (a clinical goal focused on the individual patient) over classification (an intellectual system for organizing information) was emphasized.

Summary:

Accurate description and diagnosis of the seizures, causes, and specific type of epilepsy remain the goal in clinical epilepsy care. While terminology and concepts are being revised, the implications for patient care currently are minimal; however, the gains in the future of clear, accurate terminology and a multidomain classification system could potentially be considerable.

Key Points

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The goals of the original international classifications of the epilepsies and of seizures, published in 1970, were to introduce some standardization of terminology to improve communication, provide some organization to the knowledge concerning epilepsy at the time, and facilitate research.

A classification is a system for organizing knowledge about the similarities among and differences between items that are part of some overarching group.

In epilepsy, the term “classification” is also often used to refer to the list of the different forms of epilepsy organized within the classification system and to an individual diagnosis itself.

While diagnoses can be organized within a classification structure, the classification structure is not essential to diagnosis.

Although the classification structure has been formally abandoned, the individual diagnoses for epilepsy have not, even if some of the names have been modified. This is a crucial point, as the recommended changes in 2010 entail little or no change in what health care providers do in daily practice (that is, diagnose and treat individual patients).

To refer to groups of causes, the terms “genetic,” “structural-metabolic,” and “unknown” were recommended in 2010.

The revised terminology separates cause from consequences and reflects the changing knowledge of the nature of many genetic disorders.

Currently, the best exemplars of genetic epilepsies are the channelopathies. Perhaps channelopathies could be a category of their own, although recent work on the role of neuroinflammation in epilepsy has also demonstrated the potential for acquired channelopathies.

Other factors such as immune-mediated/inflammatory processes are not explicitly recognized in the 2010 report, but their importance as a precipitating cause of epilepsy and as part of a process induced by frequent seizures and exacerbating the tendency to have more seizures is increasingly recognized.

Previous thinking in the field of epilepsy often mixed seizure types (ie, the manifestations) with the epilepsy itself (ie, the underlying disorder affecting the brain).

The current emphasis is to separate the manifestations from the underlying cause.

“Generalized” seizures may arise from discrete, focal lesions, and “focal” manifestations are not necessarily inconsistent with a diffuse (generalized) epileptic process. The implications for clinical care are profound, as many forms of epilepsy, especially in infants and toddlers, do not clearly fit meaningfully into the generalized or focal categories.

The 2010 report recommends that seizures be clearly described according to their motor, cognitive, autonomic, and sensory-experiential manifestations. When these occur in sequence, that sequence can be described as well.

Epileptic spasms, which were not recognized in the 1981 document, represent a unique seizure type with distinct semiology and electrographic and electromyographic correlates.

Electroclinical syndromes are the most specific form of epilepsy diagnosis. These are clinical entities defined on the basis of age at onset, seizure types, specific electroclinical patterns, and to a varying extent, the underlying cause.

Diagnosable electroclinical syndromes are still important for adult neurologists to recognize and treat appropriately, as many adults have epilepsy of childhood onset.

Although the remaining nonsyndromic epilepsies were previously labeled as cryptogenic, the current recommendations refer to these as epilepsies of unknown cause, with the caveat that unknown depends on the extent of the investigations.
EEG and Epilepsy Monitoring


Abstract

Purpose of Review:

This article reviews the utility of EEG and prolonged video-EEG telemetry in the diagnosis and management of a patient with epilepsy.

Recent Findings:

The EEG can be the most helpful test to determine a diagnosis of epilepsy; it can also distinguish focal and generalized neurophysiologic correlates of epilepsy. Furthermore, when paired with video monitoring, EEG can not only define epileptic and nonepileptic events but also aid in localization of seizures in patients with epilepsy. Finally, when history and other imaging modalities are considered with the EEG, the epileptic syndrome can usually be defined and the treatment can be focused. In critically ill patients, continuous EEG monitoring can define subclinical seizures, although a variety of periodic patterns may also be identified.

Summary:

EEG is an invaluable tool in the diagnosis and management of a patient with epilepsy, and continuous EEG monitoring is useful in identifying subclinical seizures and nonconvulsive status epilepticus in critically ill patients.

Key Points

- Yield of an outpatient EEG may be low even in patients with known epilepsy.
- Repeat EEGs over time or sleep deprivation may increase the yield.
- With an epileptiform abnormality on EEG, chances of recurrence of seizures are high, and treatment decisions may be made even after first-time seizures.
- Several nonspecific patterns may be seen in patients with epilepsy.
- Abnormal epileptic patterns can be syndrome-specific and if seen on an EEG can readily provide syndromic diagnosis.
- Many normal variants can lead to erroneous diagnosis of epilepsy, such as wicket spikes, small sharp spikes, and 14 and 6 positive spikes.
- EEG in status epilepticus can show progressive changes.
- Several periodic EEG patterns are seen in comatose patients in the intensive care unit, many of which are indicative of status epilepticus, although some are controversial (such as triphasic waves).
- Continuous EEG monitoring should be considered in any critically ill patient with unexplained mental status changes, especially those with acute neurologic injury, as nonconvulsive seizures may be underrecognized.
- Ambulatory EEG may be useful in diagnosing spells or in classifying seizures in some cases.

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Video telemetry in the epilepsy monitoring unit should be readily considered in classifying spells as well as in localizing seizures among those with intractable epilepsy. Gelastic seizures and frontal lobe seizures may have a poor or no scalp EEG correlate that may lead to an erroneous diagnosis of nonepileptic events.

Neuroimaging in Investigation of Patients With Epilepsy


Abstract

Purpose of Review:

This review discusses the MRI and functional imaging findings in patients with focal seizures, practical ways to improve the detection of subtle lesions, and limitations and pitfalls of the various imaging techniques in this context.

Recent Findings:

A proper MRI investigation of patients with focal epilepsy requires the use of specific protocols, selected based on identification of the region of onset by clinical and EEG information. For practical purposes, the focal epilepsies are divided here into mesial temporal lobe epilepsies and neocortical epilepsies. The majority of patients with mesial temporal lobe epilepsies associated with hippocampal sclerosis undergoing presurgical evaluation will have a clear-cut unilateral atrophic hippocampus with increased T2 signal and a normal-appearing contralateral hippocampus. Among the several types of neocortical lesions, focal cortical dysplasias deserve special attention because these lesions are often missed on routine MRIs. The focal cortical dysplasias include a gradient of morphologic changes from dysplastic lesions that can be easily identified by conventional MRI techniques to minor structural abnormalities with small areas of discrete cortical thickening and blurring of the gray/white matter interface that often go unrecognized.

Summary:

The use of MRI protocols targeted for the study of patients with epilepsy allows the diagnosis of the etiology of epilepsy in most patients with focal seizures. However, in a considerable number of patients with epilepsy, MRI results are considered normal. Although the etiology remains unclear in these cases, the malformations of cortical development (mainly focal cortical dysplasias) have been identified as most likely pathologic substrates. The effort involved in trying to increase the detection of these "invisible" lesions involves the improvement of structural imaging techniques and the combination of metabolic and functional studies, including 18F-fluorodeoxyglucose–positron emission tomography (18F FDG-PET), ictal single-photon emission computed tomography (SPECT), diffusion MRI, and magnetic resonance spectroscopy (MRS). The methods used to enhance the detection of subtle cortical abnormalities by improving

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the structural images have addressed two basic aspects of the examination by MRI: signal acquisition and imaging postprocessing.

Key Points

- CT scans are indicated in emergent situations but are of limited usefulness for limited or small lesions, particularly in regions of orbitofrontal or medial temporal cortex. Focal lesions are only seen in 30%.
- A proper MRI investigation of patients with focal epilepsies requires the use of specific protocols selected based on identification of the region of onset by clinical and EEG findings.
- MRI epilepsy protocols should include a three-dimensional, T1-weighted volumetric acquisition with isotropic voxel size of 1 or 1.5 mm in order to enable the reconstruction of images in any plane.
- Methods of image reconstruction from three-dimensional acquisitions allow a better evaluation of patients with discrete structural lesions, in particular focal cortical dysplasia where the main findings are cortical thickening, abnormal gyri, and poor delineation of the transition between white and gray matter.
- The hippocampal MRI abnormalities in patients with hippocampal sclerosis can be bilateral and sometimes symmetric, but usually are unilateral or with clear asymmetry. MRI also shows atrophy and signal changes in structures outside of the hippocampus, usually ipsilateral to the side of hippocampal sclerosis.
- MRI sequences should include T1- and T2-weighted images covering the entire brain in the three orthogonal planes, with minimum slice thickness allowed by the scanner. The injection of contrast is usually unnecessary; however, it may be important in situations when the images without contrast are not sufficient for diagnosis or when a tumoral or inflammatory lesion is suspected.
- The use of appropriate MRI protocols targeted for the study of patients with epilepsy allows the diagnosis of the majority of patients with lesional epilepsies. However, in a considerable number of patients with epilepsy, the MRI is considered normal. Although the etiology remains unclear in these cases, the disorders of cortical development, mainly focal cortical dysplasia, have been identified as the most likely pathologic substrates.
- Focal cortical dysplasia may be observed in MRI examinations as areas of cortical thickening, loss of the interface between white and gray matter, focal atrophy, and hyperintense signal in T2/fluid-attenuated inversion recovery (FLAIR) sequences.
- Gangliogliomas, oligodendrogliomas, and dysembryoplastic neuroepithelial tumors are frequently located in the temporal lobe and may be associated with focal cortical dysplasia, and their most common clinical manifestation is epilepsy.
- $N$-acetylaspartate appears to be a dynamic marker of epileptogenic activity as well as a marker of neuronal density; therefore, $N$-acetylaspartate abnormalities should be interpreted with caution.
- The major limitation of magnetic resonance spectroscopy is its limited coverage area, which in current practice undermines the evaluation of patients with neocortical epilepsy without a strong suspicion of the location of the epileptogenic focus or lesion on MRI.
- PET images using 18F-fluorodeoxyglucose may demonstrate a focal or regional hypometabolism within the epileptogenic area, especially in mesial temporal lobe epilepsy. This hypometabolic area can extend beyond the epileptogenic zone defined by EEG, or beyond the area of structural damage.
- In clinical practice, the additional yield of fluorodeoxyglucose-PET in patients with mesial temporal lobe epilepsy and clear video-EEG and MRI findings is modest, and in
most of these cases it may be considered unnecessary. However, for patients with inconclusive video-EEG and MRI results, 18F-fluorodeoxyglucose-PET is extremely helpful.

- SPECT examinations for the study of interictal cerebral blood flow have low accuracy and are of little utility. By contrast, SPECT studies during a seizure using the radiotracer HMPAO-99mTc or ECD-99mTc can identify both temporal and extratemporal epileptogenic foci, as long as the radiopharmaceutical is injected as soon as possible after the onset of the seizure during video-EEG monitoring.
- To improve the spatial resolution, functional images can be subtracted (eg, ictal SPECT minus interictal SPECT) and coregistered (eg, the subtracted ictal-interictal SPECT, or a PET image) with a high-resolution anatomical MRI. All functional images must be interpreted in the context of all clinical and laboratory data.

**Antiepileptic Drug Treatment: New Drugs and New Strategies**


**Abstract**

**Purpose of Review:**

Selection of the ideal antiepileptic drug (AED) for an individual patient can be a daunting process. Choice of treatment should be based on several factors, including but not limited to epilepsy classification, AED mechanism of action, AED side-effect profile, and drug interactions. Special consideration must be given to populations such as women, older adults, patients with other medical comorbidities, and patients who are newly diagnosed.

**Recent Findings:**

Head-to-head trials between AEDs in newly diagnosed patients rarely demonstrate that one AED is more or less effective. The second-generation drugs, lamotrigine, topiramate, oxcarbazepine, zonisamide, and levetiracetam, have undergone head-to-head trials confirming similar efficacy and equal or better tolerability than standard drugs in focal epilepsy.

**Summary:**

A thoughtful approach to the AED selection process must factor in data from clinical AED trials as well as a variety of patient characteristics and confounding factors. When neurologists apply an individualized approach to AED drug selection for their patients, they can find an effective and well-tolerated drug for most patients.

**Key Points**

- Antiepileptic drugs that are narrow spectrum are much more effective at controlling seizures associated with select syndromes or within a specific category (partial versus
generalized). Other antiepileptic drugs are broad-spectrum agents able to treat both partial and generalized epilepsy.

- Studies indicate that, at the time of diagnosis, classification of partial or generalized seizures can only be made about half of the time. If a clear diagnosis cannot be made, it is wise to choose a broad-spectrum antiepileptic drug.
- The choice of initial therapy can be crucial because many patients will remain on the initial therapy long term.
- The first antiepileptic drug should be one that is expected to be well tolerated and reasonably safe.
- When using drugs in polytherapy, pharmacokinetic interactions must be considered and doses should be altered as appropriate.
- Avoiding combinations of antiepileptic drugs with similar side-effect profiles can be helpful but is often impossible. For example, multiple antiepileptic drugs can cause dizziness, imbalance, and diplopia. The following combinations, which are commonly employed, are notorious for exacerbating these symptoms: (1) carbamazepine and lamotrigine, (2) carbamazepine and lacosamide, (3) oxcarbazepine and lacosamide, (4) lamotrigine and lacosamide.
- Elimination of drugs that have been deemed ineffective is optimal.
- The reduction of any medication, even those deemed ineffective, can trigger a withdrawal response and seizure clusters or status epilepticus.
- Complex polypharmacy is one of the most challenging aspects of managing patients with epilepsy, as both physicians and patients continue to search for the “Goldilocks” combination of antiepileptic drugs that is “just right.”
- Drugs such as levetiracetam, gabapentin, pregabalin, and valproate have a low risk of hypersensitivity and may be good choices in patients with a history of rash or hypersensitivity to antiepileptic drugs or other agents.
- It is preferable to avoid enzyme-inducing antiepileptic drugs (eg, phenytoin, carbamazepine, phenobarbital, and primidone) in patients with chronic medical conditions other than epilepsy since two-thirds of drugs will undergo increased clearance as a result of enzyme induction.
- Older patients tend to have lower thresholds for developing side effects.
- Planning for pregnancy in women with epilepsy is crucial not only to construct a treatment approach, but also to predetermine a baseline, or minimal drug level, required to maintain seizure freedom.

Management of Childhood Epilepsy


Abstract

Purpose of Review:

This article outlines a diagnostic and management approach to pediatric seizures and epilepsy syndromes, and delineates pharmacologic and nonpharmacologic treatment options.

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Recent Findings:

Progress in tracking of seizures, identifying and addressing medication nonadherence, treatment with novel devices, and clinical decision support algorithms will provide additional management options in the future.

Summary:

The management of pediatric seizures and epilepsies presents multiple challenges to the clinician because of nonepileptic imitators, evolving classification approaches, clinical presentations, limited clinical trial data for medications, and the toxicities of therapies. While certain pediatric seizures and epilepsy syndromes respond best to certain medications, early identification of pharmacologically resistant patients who may be candidates for epilepsy surgery is important. Alternative treatment options may include ketogenic diet or vagus nerve stimulation.

Key Points

- The first step in approaching a child with suspected epilepsy is to confirm that the reported spells are actually seizures rather than another condition such as syncope, migraines, tics, or behavioral events.
- Seizure classification uses the International League Against Epilepsy’s 1981 Clinical and Electrographic Classification of Epileptic Seizures. This classification approach used clinical seizure symptoms and interictal/ictal EEG expressions to divide seizures into three categories: partial (focal, local), generalized (convulsive or nonconvulsive), and unclassified.
- After a first unprovoked seizure, the chances of a second seizure range from 30% to 55% over the next 2 to 5 years. Seizure recurrence is higher in patients with a known etiology for seizures, with abnormal examination findings, occurrence during sleep and abnormal EEGs with interictal epileptiform discharges.
- After a second unprovoked seizure, the chances of a third unprovoked seizure are 80% to 90% within 2 years if treatment is not initiated. Therefore, treatment after the second (rather than the first) unprovoked seizure is recommended.
- Ideally, the three goals of epilepsy therapy are complete seizure control, no adverse events, and the best quality of life. Realistically, many children can reach seizure freedom with a good to excellent quality of life but may do so at the cost of some adverse events.
- In children with treatment-resistant epilepsy, defined as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom,” the goals of therapy shift to be fewest seizures, fewest adverse events, and best quality of life.
- The selection of the first (or subsequent) antiepileptic medication is affected by a combination of patient-specific and drug-specific factors. Patient-specific factors include the child’s disease characteristics (e.g., seizure type, epilepsy type, and epilepsy syndrome) along with their comorbidities, comedications, age, gender, and ability to swallow pills. Drug-specific factors include the drug’s effectiveness and/or efficacy for a specific seizure type or epilepsy syndrome, its pharmacokinetic characteristics, dose-dependent adverse effects, idiosyncratic reactions, chronic toxicities, teratogenicity, and carcinogenicity.
- Matching the patient to the best potential antiepileptic drug for them requires attention to both these side effects and the patient’s comorbidities and concomitant medications.
- In order to assess response to treatment, information on baseline seizure frequency and intervals between initial seizures is crucial. Tracking response to seizures is important, either with paper diaries or with online seizure-tracking tools.

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A trial of epilepsy medication discontinuation is usually recommended after 2 seizure-free years. Medications should be discontinued over at least a 6-week period, and if the patient is on polytherapy, only one medication should be weaned at a given time. Children with pharmacologically resistant epilepsy are potential candidates for epilepsy surgery. The surgical workup algorithm aims to identify the area of cortex that needs to be resected in order to make the child seizure free (ie, epileptogenic zone) while leaving eloquent cortical areas intact.

Epilepsy and Neuropsychological Comorbidities


Abstract

Purpose of Review:

Epilepsy is a chronic disorder with several associated comorbidities requiring timely recognition and treatment. This article discusses aspects of cognitive impairment; psychiatric disorders including depression, anxiety, and psychosis; and health-related quality-of-life issues pertaining to patients with epilepsy.

Recent Findings:

Cognitive problems in epilepsy may be present early in the disease course. Advances in imaging techniques are allowing correlation of structure and function as they relate to cognitive impairment in epilepsy. The relationship between epilepsy, depression, and anxiety is increasingly recognized, and these psychiatric comorbidities may affect suicide risk, patient-reported adverse antiepileptic drug effects, and quality of life. Psychiatric disorders are underrecognized and undertreated in patients with epilepsy.

Summary:

Physicians who treat patients with epilepsy should be aware of the major impact that cognitive impairment and psychiatric comorbidities have on these patients. Identifying and treating these comorbidities in epilepsy patients is just as important as seizure treatment.

Key Points

- Multiple factors can affect cognition in epilepsy patients, including pathologic substrates of epilepsy, seizures, prior status epilepticus, interictal discharges, treatments, and psychosocial factors.
- Asking epilepsy patients about their subjective cognitive functioning may be inadequate. Baseline brief objective measures of cognition could detect dysfunction and track progression over time.

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Some antiepileptic drugs have more cognitive side effects than others. Gabapentin, lamotrigine, levetiracetam, and tiagabine affect cognition the least, while benzodiazepines, phenobarbital, topiramate, and zonisamide affect it most. Carbamazepine, oxcarbazepine, phenytoin, and valproate pose an intermediate risk.

Antiepileptic drug titration rate, final dose, blood levels, the specific antiepileptic drug used, and polytherapy can affect cognition in individual epilepsy patients.

Cognitive abilities most affected by antiepileptic drugs are processing speed, sustained attention, dual processing, verbal learning, verbal fluency, and memory.

Patients may not recognize cognitive effects of antiepileptic drugs until after a drug is discontinued.

Fetal exposure to valproate is associated with reduced cognitive outcomes in childhood. The effect is dose related and includes a range of cognitive abilities.

A nonlesional brain MRI and unimpaired memory at baseline are risk factors for postoperative memory decline after temporal lobe epilepsy surgery.

Neurostimulation in epilepsy patients does not appear to adversely affect cognition.

Subjective patient cognitive complaints should raise a red flag to the clinician that a possible mood disorder is present.

A bidirectional relationship exists between epilepsy and depression, likely due to dysfunction in overlapping brain systems.

Depression is underdiagnosed and undertreated in epilepsy patients.

Most antiepileptic drugs can produce negative behavioral effects. However, some antiepileptic drugs are used in a variety of psychiatric disorders (eg, carbamazepine, lamotrigine, and valproate are used in bipolar disorder).

A history of a mood disorder or depression is a significant risk factor for developing suicidality in patients with epilepsy.

Since suicidal ideation is common in outpatient epilepsy clinic settings, physicians should ask about suicidal thoughts during routine visits in order to identify patients for interventions to decrease the risk of suicide in this population.

Patients with epilepsy frequently experience depression, which should be treated aggressively to improve their quality of life even if they have subsyndromic depressive episodes that do not meet Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria for major depressive disorder.

First-line treatment of depression in epilepsy patients can include psychological therapies or selective serotonin reuptake inhibitors followed by a serotonin and norepinephrine reuptake inhibitor for treatment failures. Tricyclic antidepressants are second-line, and monoamine oxidase inhibitors are third-line.

The risk for suicidality is increased after surgery.

The US Food and Drug Administration issued a class warning for suicidal ideation and behaviors for antiepileptic drugs used for any purpose. Methodologic concerns have been raised for this conclusion.

Coexisting depression and anxiety disorders in patients with epilepsy decrease quality of life and are associated with the frequency of reported antiepileptic drug–related adverse events.

Epilepsy surgery can improve quality of life, but patients who do not become seizure free and have a verbal memory decline after surgery have decreased quality of life.

Psychiatric disorders in epilepsy are common and should be diagnosed and treated to improve patients’ quality of life.

Identifying and treating depression and adverse effects of antiepileptic drugs can have a major positive impact on the lives of epilepsy patients.

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Abstract

Purpose of Review:
Optimal treatment of women with epilepsy includes consideration of the complex interactions of sex steroid hormones with epilepsy and antiepileptic drugs, and of the potential risks of any antiepileptic drug prescribed during a pregnancy.

Recent Findings:
Clinical studies in women with epilepsy have provided a better foundation of knowledge about the complex relationships between cycling sex steroid hormones, seizure frequency, antiepileptic drugs, contraception, and neuroendocrine abnormalities. Pregnancy registries and observational studies have provided key data that allow for a better estimation of risks to the developing fetus.

Summary:
Understanding these key factors should enable informed treatment recommendations that can reduce adverse health effects in women with epilepsy and improve both seizure control and maternal and fetal outcomes.

Key Points

• Criteria for catamenial epilepsy have become more consistent and formalized.
• For patients having a threefold or greater increase in seizure frequency in a C1 pattern, cyclic progesterone lozenges are an adjunctive treatment option.
• Long-acting reversible contraceptives (including the progestin implant) and intrauterine devices are excellent choices for women with epilepsy receiving enzyme-inducing antiepileptic drugs.
• Determining the individual target concentration of an antiepileptic drug in a woman with epilepsy before conception can be a valuable tool for therapeutic drug monitoring during pregnancy.
• Recent data support the concern that the amount of fetal exposure to an antiepileptic drug is important, as well as the type of antiepileptic drug. Therefore, reduction of the dose before conception while maintaining seizure control may reduce the risk of structural teratogenicity.
• Children born to women with epilepsy receiving valproate during pregnancy are at a fivefold higher risk of having a major congenital malformation, lower IQ, and possibly autism spectrum disorder.
• Therapeutic drug monitoring of antiepileptic drug concentrations during pregnancy is recommended. Establishing the individualized ideal antiepileptic drug concentration is important as a target to maintain during pregnancy. Dosages of the antiepileptic drug will need to be readjusted in the postpartum period.
• Although more research is needed to understand underlying mechanisms for bone density loss associated with antiepileptic drugs, awareness of risk for osteopenia or osteoporosis should be a consideration in antiepileptic drug selection and maintenance.

Nonepileptic Behavioral Disorders: Diagnosis and Treatment


Abstract

Purpose of Review:

This article will review the important steps in making an accurate diagnosis of psychogenic nonepileptic events or episodes (PNEE), and recent developments in diagnosis and treatment.

Recent Findings:

Several clues can be obtained from the history to help the clinician suspect the diagnosis of PNEE. While none of these clues are diagnostic on their own, each is valuable, and there are often multiple clues in a given patient. Clinical clues have limitations, and once PNEE is suspected, video-EEG monitoring remains the gold standard and the only way to make a definite diagnosis of PNEE. Like most tests, video EEG has its limitations, but in most cases the diagnosis can be made and is not difficult. Regarding treatment, growing evidence exists that psychotherapy, especially cognitive behavior therapy, is effective, and a recent finding is that pharmacotherapy may have a role.

Summary:

The diagnosis of PNEE can be made reliably, but the management of PNEE remains problematic, in large part because of the insufficient involvement of mental health professionals.

Key Points

• Psychogenic nonepileptic events or episodes are very commonly seen at epilepsy centers, where patients with psychogenic nonepileptic events or episodes represent about 30% of those referred for refractory seizures. In addition to being common, psychogenic nonepileptic events or episodes may represent a challenge in diagnosis and management, and many health care professionals are uncomfortable dealing with them.
• Despite the ability to make a diagnosis of psychogenic nonepileptic events or episodes with near certainty, the average delay in diagnosis remains long at about 7 to 10 years.
• The presence of certain symptoms argues in favor of epileptic seizures, including significant postictal confusion, incontinence, occurrence in sleep, and significant injury. In particular, tongue biting is highly specific to generalized tonic-clonic seizures.
• A diagnosis of psychogenic nonepileptic events or episodes should always be confirmed by video-EEG monitoring.
• Video-EEG monitoring is the gold standard for diagnosis of psychogenic nonepileptic events or episodes.

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Many patients with psychogenic nonepileptic events or episodes seen at epilepsy centers have had previous EEGs, and often at least one of these was interpreted as epileptiform. When reviewed, the vast majority of EEGs interpreted as epileptiform in patients with psychogenic nonepileptic events or episodes will turn out to show overinterpreted normal variants. In treatment of psychogenic nonepileptic events or episodes, the evidence for the efficacy of cognitive behavior therapy is growing, and pharmacologic treatment with a selective serotonin reuptake inhibitor antidepressant may be similarly helpful.

**Surgical Treatment of Epilepsy**


**Abstract**

**Purpose of Review:**

This article outlines indications for neurosurgical treatment of epilepsy, describes the presurgical workup, summarizes surgical approaches, and details expected risks and benefits.

**Recent Findings:**

There is class I evidence for the efficacy of temporal lobectomy in treating intractable seizures, and accumulating documentation that successful surgical treatment reverses much of the disability, morbidity, and excess mortality of chronic epilepsy.

**Summary:**

Chronic, uncontrolled focal epilepsy causes progressive disability and increased mortality, but these can be reversed with seizure control. Vigorous efforts to stop seizures are warranted. If two well-chosen and tolerated medication trials do not achieve seizure control, an early workup for epilepsy surgery should be arranged. If this workup definitively identifies the brain region from which the seizures arise, and this region can be removed with a low risk of disabling neurologic deficits, neurosurgery will have a much better chance of stopping seizures than further medication trials.

**Key Points**

- About one-third of patients with epilepsy have seizures that cannot be controlled with medication.
- Uncontrolled epilepsy causes progressive disability and increased mortality risk.
- Resective epilepsy surgery requires definite demonstration that the seizures originate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction.
- Epilepsy is termed drug-resistant when two appropriate, tolerated medications fail to control seizures.

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• Epilepsy surgery should be considered in drug-resistant cases before the vagus nerve stimulator.
• Lesional epilepsy has a poorer response to medications than cryptogenic/idiopathic epilepsy but a better chance of seizure freedom with epilepsy surgery.
• The effectiveness of temporal lobectomy for mesial temporal epilepsy has been demonstrated in a randomized controlled trial.
• Current evidence and practice guidelines indicate that epilepsy surgery should be considered more often and earlier in the course of chronic uncontrolled epilepsy.

Neurostimulation for Drug-Resistant Epilepsy


Abstract

Purpose of Review:

The purpose of this review is to provide an evidence-based update on the neurostimulation options available for patients with drug-resistant epilepsy in the United States and in European countries.

Recent Findings:

The field of neurostimulation for epilepsy has grown dramatically since 1997, when vagus nerve stimulation became the first device to be approved for epilepsy by the US Food and Drug Administration (FDA). New data from recently completed randomized controlled trials are available for deep brain stimulation of the anterior thalamus, responsive neurostimulation, and trigeminal nerve stimulation. Although vagus nerve stimulation is the only device currently approved in the United States, deep brain stimulation and responsive neurostimulation devices are awaiting FDA approval. Deep brain stimulation, trigeminal nerve stimulation, and transcutaneous vagus nerve stimulation are now approved for epilepsy in the European Union. In this article, the mechanisms of action, safety, and efficacy of new neurostimulation devices are reviewed, and the key advantages and disadvantages of each are discussed.

Summary:

The exponential growth of the field of neuromodulation for epilepsy is an exciting development; these new devices provide physicians with new options for patients with drug-resistant epilepsy.

Key Points

• Failure of the first or second antiepileptic drug in a patient is a predictor of drug-resistant epilepsy.

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Physicians can go to www.epilepsycases.com to help them determine whether the patient is a candidate for epilepsy surgery.

Deep brain stimulation of the anterior thalamus is approved in the European Union for epilepsy. It is not yet approved in the United States.

Deep brain stimulation of the anterior thalamus and responsive neurostimulation are awaiting approval by the US Food and Drug Administration.

Vagus nerve stimulation is the first device for epilepsy approved by the US Food and Drug Administration; it is also approved by the European Union.

Vagus nerve stimulation is generally well tolerated. Serious side effects (eg, vocal cord paralysis, device infection) occur in 1% to 1.5% of patients.

Vagus nerve stimulation is associated with a long-term responder rate of approximately 35%.

Side effects of deep brain stimulation of the anterior thalamus include depression (14.8%), memory problems (13%), hemorrhage (4.5%), and infection (12.7%).

No deaths due to hemorrhage or infection occurred in the pivotal trial of deep brain stimulation of the anterior thalamus.

In a phase III randomized controlled trial of deep brain stimulation of the anterior thalamus, the active-treatment group experienced a 38.8% reduction in seizures versus 22.8% in the control group.

In the phase III randomized controlled trial of responsive neurostimulation, the treatment group had a 37.9% reduction in seizures versus 17.3% seizure reduction in controls.

External trigeminal nerve stimulation is approved in the European Union for adults and children aged 9 and older with epilepsy and depression.

External trigeminal nerve stimulation is not approved and is investigational in the United States.

Side effects of external trigeminal nerve stimulation include skin irritation, headache, and anxiety.

In a phase II randomized controlled trial of external trigeminal nerve stimulation, the responder rate was 30.2% overall.

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Dietary Treatment of Intractable Epilepsy


Abstract

Purpose of Review:

Dietary therapies for seizure management date back further than pharmacologic interventions, but many neurologists are not familiar with these treatment options. This introduction to dietary therapies will discuss administration of ketogenic diets, comparisons between diet types, evidence-based efficacy of diet therapies in epilepsy treatment, and management of side effects. This review will provide the general neurologist with the skills to identify appropriate candidates for these treatments and to offer comprehensive ongoing care.

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Recent Findings:
In adults and children with medically resistant epilepsy, studies have consistently shown a greater than 50% reduction in seizure frequency in approximately one-half of patients within days to months after starting dietary therapy.

Summary:
Dietary treatment options for epilepsy include the classic ketogenic diet, the medium-chain triglyceride diet, the modified Atkins diet, and the low glycemic index treatment. These were first used to control seizures in children with intractable epilepsy, but in recent years have also been demonstrated to be safe and effective in children and adults with a broad range of seizure types and are being used with increased frequency worldwide.

Key Points
- The traditional or classic ketogenic diet is a high-fat, carbohydrate-restricted diet with the primary goal of producing urinary ketosis and mimicking a starvation state without depriving the body of necessary calories to sustain growth and development.
- The classic ketogenic diet is traditionally started as a 3:1 or 4:1 ratio of fat to carbohydrates and protein in grams, of which 90% of the patient’s caloric intake is obtained from consumption of fat. Patients are typically admitted to the hospital for initiation of the ketogenic diet, which includes a 24-hour fast followed by gradual introduction of the diet over 2 days.
- Medium-chain triglycerides can be substituted for long-chain fatty acids with the potential advantages that they produce more ketones per kilocalorie of energy and are more readily absorbed. Therefore, medium-chain triglycerides used with the ketogenic diet may require reduced overall fat intake compared to a ketogenic diet using long-chain fatty acids to produce urinary ketosis.
- With the modified Atkins diet, patients limit their daily intake of net carbohydrates to 10 to 20 g/d indefinitely.
- The low glycemic index treatment offers another, less restrictive alternative to the ketogenic diet by limiting consumption of foods with a high glycemic index.
- Seizure reduction that results from starvation or treatment with ketogenic diets has not been shown to directly correlate with the degree of either acidosis or ketosis achieved.
- Dietary therapies, most often the classic ketogenic diet, have been shown to be effective in treating a variety of epilepsy syndromes in children with frequent, medically resistant seizures.
- Randomized controlled studies and meta-analyses have shown that approximately 50% of children with pharmacoresistant epilepsy have a greater than 50% reduction in seizures on the ketogenic diet.
- Ketogenic diets are contraindicated in patients with pancreatitis, hepatic failure, primary carnitine deficiency, carnitine palmitoyl transferase I and II deficiencies, carnitine translocase deficiency, beta-oxidation defects, pyruvate carboxylase deficiency, and porphyria.
- Appropriate monitoring and follow-up with a neurologist and a dietitian or nutritionist is critical to the success of dietary therapies and to preventing, detecting, and treating side effects.
- Animal studies are ongoing to understand the underlying mechanisms of the ketogenic diet and other dietary therapies.

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Status Epilepticus


Abstract

Purpose of Review:
This review presents the state of the art in the diagnosis and management of status epilepticus.

Recent Findings:
In addition to general background, this article presents the most recent findings regarding the diagnosis and treatment of status epilepticus, including the results of the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) and the available data on the use of newer antiepileptic and anesthetic drugs in the treatment of refractory status epilepticus. It also presents available guidelines such as those from the Neurocritical Care Society.

Summary:
Despite recent advances, the management of status epilepticus remains a challenge. Rapid treatment, a written treatment protocol, early consideration of nonconvulsive seizures, and avoiding overtreatment and medical complications are the keys to successful management. This article summarizes the current evidence and guidelines.

Key Points

- Status epilepticus in adults and in children over 5 years old is defined as at least 5 minutes of ictal activity or two or more seizures between which there is incomplete recovery of consciousness.
- Nonconvulsive status epilepticus is the form of status epilepticus most commonly encountered in critically ill patients. It usually cannot be identified without an EEG.
- More than one-half of episodes of status epilepticus in adults occur in patients without prior seizures.
- If the patient’s level of consciousness is not improving by 20 to 30 minutes after cessation of movements, or mental status remains abnormal 30 to 60 minutes after convulsive activity ceases, ongoing nonconvulsive status epilepticus must be considered.
- Prolonged generalized convulsive status epilepticus may lead to cardiorespiratory collapse, multiple organ failure, and neuronal injury.
- Some patients, especially young adults with normal or near-normal results of brain imaging and an encephalitislike illness, make a meaningful or even full cognitive recovery even after very prolonged refractory status epilepticus that lasted months.
- The diagnosis of nonconvulsive status epilepticus in critically ill patients is sometimes difficult because of the presence of equivocal EEG patterns. A trial of a rapidly acting IV antiepileptic drug can be helpful if there is improvement in both the EEG and clinical examination, but results should be interpreted with caution and are often equivocal. Small incremental doses or use of a nonsedating antiepileptic drug are preferable as they may allow observation of a clinical improvement without marked sedation.

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• In the intensive care unit, most seizures are nonconvulsive and would be missed in the absence of EEG monitoring. Twenty-four hours of continuous EEG is a reasonable screen for nonconvulsive seizures in noncomatose patients, but 48 hours or more may be needed in comatose patients.
• Early recognition of status epilepticus allows for prompt treatment and increases the likelihood of treatment success and prevention of further neuronal damage.
• Results from randomized controlled trials indicate that the first-line treatment of choice in generalized convulsive status epilepticus is a benzodiazepine: IV lorazepam if IV access is established, or IM, nasal, or buccal midazolam or rectal diazepam if IV access is not established.
• Pruritis during fosphenytoin infusion is not an allergic reaction; it is most likely due to the phosphate load. Slowing the rate of infusion may reduce itching.
• Evidence from small randomized controlled trials suggests that IV valproate is not inferior and is perhaps superior to phenytoin.
• Continuous IV propofol may be a poor option in children with status epilepticus because of the risk of the propofol infusion syndrome, although proper dosing may allow safe use.
• Seizures can arise from suppression-burst and even from suppressed background.
• Uncertainty exists regarding the agent to be used and the depth and duration of anesthesia required for the treatment of refractory status epilepticus.
• The treatment of nonconvulsive status epilepticus has not yet been specifically studied in a prospective, randomized trial. It is recommended by experts and in the European Federation of Neurological Societies’ published set of guidelines to adopt a similar but less aggressive course than for the treatment of generalized convulsive status epilepticus. In particular, recommendations emphasize to postpone anesthesia.

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