Clinical Presentation, epileptic syndromes, and goals in workup.

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The management of seizures and epilepsy begins with forming a differential diagnosis, making the diagnosis, and then classifying seizure type and epileptic syndrome. Classification guides treatment, including ancillary testing, management, prognosis, and if needed, selection of the appropriate antiepileptic drug (AED). Many AEDs are available, and certain seizure types or epilepsy syndromes respond to specific AEDs. The identification of the genetics, molecular basis, and pathophysiologic mechanisms of epilepsy has resulted from classification of specific epileptic syndromes. The classification system used by the International League Against Epilepsy is periodically revised. The proposed revision of the classification (Engel J. Epilepsia 2001;42:796) emphasis the correlation from the anatomic origin of seizures (focal vs generalized) to seizure semiology (i.e., the signs or clinical manifestations). See Table 1. Modified systems have been developed for specific circumstances (e.g., neonatal seizures, infantile seizures, status epilepticus, and epilepsy surgery).

TABLE 1. Proposed diagnostic scheme for people with epileptic seizures and with epilepsy

<table>
<thead>
<tr>
<th>Axis 1</th>
<th>Ictal phenomenology, from the Glossary of Descriptive Ictal Terminology, can be used to describe ictal events with any degree of detail needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axis 2</td>
<td>Seizure type, from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.</td>
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<tr>
<td>Axis 3</td>
<td>Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.</td>
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<tr>
<td>Axis 4</td>
<td>Etiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.</td>
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<tr>
<td>Axis 5</td>
<td>Impairment, this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from the WHO ICIDH-2.</td>
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The semiological classification proposed by Lüders et al (Epilepsia 1998;39:1006) devides the epileptic seizures into 5 groups (aura, autonomic, dialeptic, motor and special seizures). This classification gives information about the symptomatogenic zone, independently from the epileptogenic, ictogenic and irritative zone importantly for epilepsy surgery investigations.

The epilepsies and epileptic syndromes

In 1989, the international League Against Epilepsy (ILAE) revised the classification of epilepsy in an attempt to simplify the classification. The epilepsies and epileptic syndromes are devided into generalized, localization-related (partial) epilepsies, epilepsies undetermined as to whether focal or generalized, and special syndromes.
Idiopathic generalized epilepsy

**Childhood absence epilepsy (CAE).** Childhood absence epilepsy is the epileptic syndrome of typical absence seizures with onset usually before the age of 10 years and a peak at 5-6 years. Absences are frequent (tens or hundreds each day) manifesting with sudden, severe, and brief impairment of consciousness. Commonly absences are the only type of seizure. Interictal EEG shows generalized polyspike-and-wave discharges that translate into a clinical seizure, if the duration outlasts 3-4 seconds. They usually respond well to ethosuximide, sodium valproate or lamotrigine and remit within 2-5 years from onset.

**Juvenile absence epilepsy (JAE).** Juvenile absence epilepsy (JAE) has its onset around puberty and is characterized by rare typical absence seizures which cluster upon awakening. In 80% of patients GTCS are also present. Ictal EEG can show either a typical # Hz or a faster, 4-5 Hz, spike-and-wave discharges. Valproic acid is effective.

**Juvenile myoclonic epilepsy (JME).** JME (Janz's syndrome) is thought to represent 5–10% of all epilepsies. It is characterized by bilateral, single or repeated, arrhythmic, irregular myoclonic jerks, predominantly in the arms and often occurring shortly after awakening. Consciousness is usually not impaired, and sudden falls are unusual. Generalized tonic–clonic seizures (GTCS) and absences may also occur. Intelligence is normal in these patients. The onset is around puberty, and the EEG shows rapid, generalized, often irregular 3–6 Hz spike-waves and polyspike-waves. Seizures in JME usually persist through adult life, but can be controlled in most patients with valproic acid monotherapy.

**Epilepsy with grand mal seizure on awakening (GMA).** GMA develops during adolescents and is more frequent in females. GTCS take place within two hours of awakening or during evening relaxation. Sleep deprivation, high alcohol intake and induced arousals from sleep are all triggering factors. Ictal EEG can be normal or can show generalized spike/poly-spike wave activity.

**General epilepsy with febrile seizures plus (GEFS+).** GEFS+ has its onset during childhood and is characterized by febrile convulsions that, in contrast with typical febrile convulsions, do not remit before the age of 6 years. In addition, afebrile generalized seizures, such as myoclonic and atonic seizures and absences, or focal seizures may occur. Seizure phenotypes vary widely, even among relatives who carry the same mutation: patients may have febrile seizures only, febrile seizures followed by afebrile seizures, or they even may have a very severe phenotype with refractory seizures and developmental delay. Due to the variability of the epilepsy phenotype within families, the diagnosis GEFS+ is hard to make. Seizures usually remit at the age of 11 years.

Idiopathic localization-related (partial) epilepsy

**Benign familial infantile convulsions (BFIC).** BFIC is a focal epilepsy syndrome of early childhood, characterized by brief seizures with motor arrest, deviation of the head and eyes to one side, generalized hypertonia, cyanosis, and limb jerks. The age at onset is usually between 3 and 12 months and seizures may occur in clusters of 2–4 days. Patients with low seizure frequency do not necessarily have to be treated. Ictal EEGs show variable abnormalities; most
interictal EEGs show no abnormalities, but occasional slow spike-waves can be observed. Subsequent psychomotor development is normal.

**Benign Childhood Epilepsy (BECTS).** Benign epilepsy of childhood with centrotemporal spikes (BECTS) is the most common partial epilepsy syndrome in the pediatric age group, with an onset between age 3 and 13 years. The typical presentation is a partial seizure with parasthesias and tonic or clonic activity of the lower face associated with drooling and dysarthria. Seizures commonly occur at night and may become secondarily generalized. The EEG shows characteristic high-voltage sharp waves in the centrotemporal regions, which are activated with drowsiness and sleep. In this typical form, BECT is easily recognized. BECTS may not require antiepileptic drugs but, if treated, it tends to be easily controlled with essentially all children entering long-term remission by mid-adolescence. Children with BECT are neurologically and cognitively normal. However, atypical cases are common and the definition of BECT can become blurred. Some research has found language disruption in children with BECTS during the active phase, affecting in particular reading, spelling, and expressive grammar. These results question the benign nature of this epilepsy, and suggested a direct link between paroxysmal anomalies and cognitive functions. Some studies support this hypothesis and have shown that interictal discharges could lead to transient cognitive impairment, dependant on the nature of the task (verbal vs visuospatial), according to the localization (left vs right) of the epileptic focus (Binnie).

Panayiotopoulos syndrome (PS) is a type of benign childhood partial epilepsy with mainly autonomic seizures, which has a good prognosis despite the fact that it is frequently associated with abundant multifocal spikes on the electroencephalography (EEG).

**Gastaut-type childhood occipital epilepsy** is a rare syndrome with an age-dependant onset from 3 to 15 years. Seizures mainly manifest with elementary visual hallucinations, blindness or both. Patients suffer from frequent seizures and medical treatment (carbamazepine) is probably mandatory.

**Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).** ADNFLE is characterized by clusters of brief tonic and hyperkinetic motor seizures occurring mostly during sleep. Onset is usually in childhood but may range from 1 to 50 years. Carbamazepine monotherapy is generally effective. Seizures are often misdiagnosed as nocturnal parasomnias such as somnambulism and pavor nocturnus. The predominant finding of the ictal EEG is bilaterally sharp wave. However, ictal EEG recordings mainly show movement artefacts and, unless combined with a video recording, are not of help for the final diagnosis. Interictal EEG is commonly normal.

**Cryptogenic or symptomatic generalized epilepsies**

**West syndrome (Infantile Spasms).** West syndrome is the classical denomination of a form of epilepsy occurring in early infancy, including the classic triad of infantile spasms, psychomotor regression, and a specific chaotic EEG pattern, combining almost continuous polyspike and spike discharge, called hypsarrhythmia. West syndrome is caused by multiple causes. (e.g., Miller-Dieker lissencephaly, tuberous sclerosis, biotinidase deficiency). One of the most interesting causes of West syndrome is an X-linked condition mapped to Xp11.4-Xpter, where the ARX gene has been recently identified. The ARX gene is responsible for a
large neurological spectrum, from X-linked lissencephaly with corpus collosum agenesis to isolated X-linked mental. The etiology is divided into symptomatic forms, 80%, and cryptogenic forms, 20%, the latter with variable prognosis. Major AEDs are of little help. Vigabatrin is very effective besides ACTH and steroids.

**Lennox-Gastaut syndrome (LGS).** LGS is a childhood epileptic encephalopathy characterized by an electroclinical triad of generalized slow spike wave (SSW) activity in the EEG, multiple types of epileptic seizures, and slow mental development. It is usually subdivided into symptomatic and cryptogenic types, the latter accounting for at least one fourth of all patients. Symptomatic cases are due to diverse cerebral conditions, which are usually bilateral, diffuse, or multifocal, involving cerebral gray matter. Twenty percent of all patients with LGS have prior infantile spasms with hypsarrhythmia. Tonic seizures are the most characteristic type of seizures. Atonic seizures with head nodding and atypical absences are not uncommon. The characteristic interictal EEG pattern of LGS is 1.5 to 2.5 Hz SSW activity, which is bilaterally synchronous, dominant over the frontocentral regions, and usually symmetric. There are varying degrees of slowing of the background. Sleep discloses paroxysms of generalized fast (10 to 25 Hz) rhythmic activity. Prognosis is usually poor both in term of seizure control and cognitive outcome.

**Myoclonic-astatic epilepsy (MAE).** MAE is perhaps more a conceptual category of idiopathic myoclonic epilepsy than a discrete syndrome. Childhood-onset myoclonic-astatic attacks are the characteristic seizures associated in most with episodes of nonconvulsive status and generalized tonic-clonic seizures. The onset is typically preceded by febrile convulsions. EEG is early often normal but within years bilateral spike-wave discharges appear. Treatment with antiepileptic drugs and outcome are unpredictable. Either remission within a few years with normal cognition or long-lasting intractability with cognitive impairment is possible. Ketogenic diet seems beneficial.

**Epilepsies undetermined as to whether focal or generalized**

**Severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome).** SMEI was first described by Dravet in 1978. It is a rare disorder (1:40,000 children) characterized by generalized or unilateral tonic, clonic, and tonic–clonic seizures beginning before the age of 1 year in infants with normal development at that stage. Initially, seizures are induced by fever. Typically febrile status epilepticus appears. Later, patients also manifest other seizure types. The EEG shows generalized spike-waves and polyspike-waves, photosensitivity and focal spikes. In the second year of life, slowing or even an arrest of psychomotor development becomes obvious and ataxia appears. Seizures are often resistant.

**The Landau-Kleffner syndrome (LKS) and electrical status epilepticus in slow wave sleep (ESES)** are rare childhood-onset epileptic encephalopathies in which loss of language skills occurs in the context of an epileptiform EEG activated in sleep. Although in LKS the loss of function is limited to language, in ESES there is a wider spectrum of cognitive impairment. The two syndromes are distinct but have some overlap. The relationship between the epileptiform EEG abnormalities and the loss of cognitive function remains controversial,
Epilepsy surgery.

Refractory (therapy-resistant, intractable) epilepsy is defined as the persistence of unacceptable seizures during 2 years or more, despite correct drug treatment, or control of seizures at the cost of excessive side effects. About 30% of partial seizures are resistant to treatment; many of them are potentially a candidate for surgical treatment (Wyllie et al., Ann. Neurol 1998;44:740). Selection of patients is based fundamentally on precise identification of the epileptogenic area and on the evaluation that possible removal of that area will not be followed by serious neurological or neuropsychological deficits, or by onset of seizures in another part of the brain. To this end, careful clinical, neurophysiological and functional studies are conducted. Compared with adults, video-electroencephalographic (EEG) study of seizures in childhood is more difficult because of the lack of patient cooperation and, therefore, the lack of every subjective element in the seizures. Furthermore, the criteria for defining drug resistance in childhood are more difficult, as many epilepsies are age dependent and seizures stop with growth. Despite this, the age at time of surgery has been steadily decreasing, in the conviction that the persistence of intractable partial epilepsy is detrimental to cognitive development and can damage brain areas that are apparently healthy. The clinical and EEG criteria for epilepsies that are secondary to some specific disorders have been defined, e.g. hemimegalencephalia and focal cortical dysplasias often produce epilepsy with onset in the first days of life, EEG record of focal or hemispheric burst suppression and drug resistance that can be defined within the first months of life. These catastrophic epilepsies are defined as having persistent daily focal or generalized seizures, resistant to drug treatment, during at least 3 months and running a catastrophic course with developmental delay, cognitive impairments and negative social outcome (Ishii et al., 2002. Ped Neurol:369).

Non-pharmacological treatment. New therapies.

The refractory and catastrophic epilepsy syndromes of childhood are initially treated with a pharmacologic intervention in most cases. Resective surgery offers the best chance of seizure control with 50-80% of appropriately selected children becoming seizure-free, but many patients are not suitable candidates, or epilepsy surgery may be unsuccessful. However, nonpharmacologic treatment options are an important part of a comprehensive treatment plan for this group of children to offer a method to minimize associated morbidity and mortality. The ketogenic diet (Mackay et al. 2005. Journal of Paediatrics and Child Health 41;353) and vagus nerve stimulation (Wheless and Baumgartne 2004.Drugs Today;40:501). are important in the treatment of patients with refractory epilepsies like Lennox-Gastaut syndrome and progressive myoclonic epilepsy. Efficacy of the nonpharmacologic treatment options, as measured by reduction in seizure frequency, as well as by developmental progress or behavioral improvement, varies according to the specific epilepsy disorder and the treatment option.