Management of Epilepsy in Children

Surachai Likasitwattanakul, M.D.

Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Siriraj Med J 2008;60:161-166
E-journal: http://www.sirirajmedj.com

Epileptic seizures are paroxysmal events that result from abnormal excessive or synchronous neuronal activity in the brain.[1] Seizure is among the most common neurological diseases in children. The cumulative incidence of children less than 15 years who have at least one first unprovoked seizure is 1.0-1.7% and 0.7-0.8% for repeated seizures.[2] When epileptic seizures result from acute brain injury (head trauma, central nervous system infection, hypoxic-ischemic encephalopathy, electrolyte imbalance, or other metabolic disturbances), they are referred to as acute symptomatic seizures or provoked seizures. These seizures occur in close temporal relationship to neurological insult or metabolic disturbances and usually resolve after correction of the underlying causes. If seizures occur in the setting where there is no evidence of acute brain injury or systemic disturbances, these epileptic seizures are called unprovoked seizure.

Epilepsy is a chronic brain disorder and is diagnosed when there is a recurrence of unprovoked seizure.[3] In this special issue, the author will review the evolution and current seizure, epilepsy, and epileptic syndrome classifications, how to make a diagnosis of epileptic seizure, the rationale for investigations, and treatment options in childhood epilepsy.

Seizure and Epilepsy classification

The classifications of seizure and epilepsy are essential in the management of childhood epilepsy. A correct diagnosis leads to appropriate investigations and treatment since management is different for each seizure type. Classification is an active process and changes constantly upon new information regarding seizure and epilepsy.

Classification of epileptic seizure by the International League Against Epilepsy (ILAE) in 1981 is a standard system that has been accepted worldwide. This classification is based on the clinical description of seizure events, and electroencephalographic (EEG) data.[4] Under this classification, there are two main seizure types: a. partial seizures (seizures that begin focally in the brain) and b. generalized seizures (seizures that begin bilaterally symmetric and without focal onset). (Table 1)

In 1989, the ILAE published the international classification of epilepsies and epileptic syndromes.[5] This classification is based on two methods of categorization. This begins by dividing epilepsies according to the overall seizure type: generalized or localization-related. Epilepsies are then divided according to the underlying causes of epilepsy: idiopathic (epilepsy with no underlying cause other than possible hereditary), symptomatic (epilepsy caused by known underlying causes) and cryptogenic (epilepsy with presumed symptomatic but not identified causes). In this classification, a term epileptic syndrome was introduced. Epileptic syndrome is characterized by a cluster of signs and symptoms customarily occurring together. The signs and symptoms are derived from seizure types, age at the onset, etiology, precipitating factors, severity, interical

TABLE 1. International classification of epileptic seizures (1981)

I. Partial seizures
A. Simple focal seizures (consciousness not impaired)
1. With motor signs
2. With somatosensory or special sensory signs
3. With autonomic signs
4. With psychic signs
B. Complex focal seizures (with impairment of consciousness)
1. Simple partial onset followed by impairment of consciousness
2. With impairment of consciousness at onset
C. Partial seizures evolving to secondarily generalized seizures
1. Simple partial seizure evolving to generalized seizures
2. Complex partial seizure evolving to generalized seizures
3. Simple partial seizure evolving to complex partial seizures evolving to generalized seizure
II. Generalized Seizures (convulsive or nonconvulsive)
A. Absence seizures
B. Myoclonic seizures
C. Clonic seizures
D. Tonic seizures
E. Tonic-clonic seizures
F. Atonic seizures
III. Unclassified Epileptic Seizures

Modified from Commission on Classification and Terminology of the International League Against Epilepsy.[4]

TABLE 2. Proposed classification of epileptic seizures (2006)

Self-limited epileptic seizures
I. Generalized onset
A. Seizures with tonic and/or clonic manifestations
1. Tonic-clonic seizures
2. Clonic seizures
3. Tonic seizures
B. Absences
1. Typical absences
2. Atypical absences
3. Myoclonic absences
C. Myoclonic seizure types
1. Myoclonic seizures
2. Myoclonic astatic seizures
3. Eyelid myoclonia
D. Epileptic spasms
E. Atonic seizures
II. Focal onset (partial)
A. Local
1. Neocortical
a. Without local spread
b. With local spread
2. Hippocampal and parahippocampal
B. With ipsilateral propagation to:
1. Neocortical areas
2. Limbic areas
C. With contralateral spread to:
1. Neocortical areas
2. Limbic areas
D. Secondarily generalized
1. Tonic-clonic seizures
2. Absence seizures
3. Epileptic spasms
III. Neonatal seizures

Modified from Engle et al.[6]

and ictal EEG, duration of epilepsy, associated clinical features, and occasionally prognosis.

The latest version of the ILAE classification of epileptic seizure was published in 2006. This classification divided seizure types into those that are self-limited and status epilepticus. It further divides the self-limited seizures into those that are generalized at onset and those that are focal at onset.[6] (Table 2)

How to make a diagnosis of epilepsy

Most seizures last for 1-2 minutes and are only rarely witnessed by physician. Thus, the most important part of diagnosis of epileptic seizure is a detailed clinical history. Seizure history should include the child's behaviors before, during, and after the seizure. Patients with partial seizure may begin with motor, sensory, autonomic, or psychic symptoms. While generalized seizure may begin with bilaterally synchronous tonic, clonic movements, or bilateral myoclonic jerks. Other history should include past medical history, family history, developmental status, history of head trauma, exposure to toxins, and health during the seizure to determine the possible cause of the seizure.[7]

Physical examinations should include both general and neurological examinations. The aims are to look for signs that may be the cause or associated with seizures such as dysmorphic features, head trauma, neurocutaneous syndrome (hypopigmented macule suggests Tuberous Sclerosis Complex or port-wine stain in Sturge-Weber syndrome), focal or diffuse neurological a bnormalities. Hyperventilation for at least 3 minutes should be done in patients suspected of absence seizure since this procedure usually elicits a typical absence attack.

Investigations

Laboratory tests and neuroimaging studies should be individually selected to find the cause of a new onset seizure.[7] Selection of the studies should be based on clinical suspicion. EEG studies should be obtained whenever possible.[7] EEG is used to confirm a diagnosis of epilepsy. More over, it gives information about the location of seizure focus, seizure types, or epileptic syndrome. However, EEG may be normal in up to 50% in the first EEG study. A repeat EEG with sleep deprivation or with special electrodes may have a higher yield of EEG abnormalities. Up to 10% of patients with epilepsy may not reveal any abnormality after several EEG studies.

Other laboratories tests and neuroimaging studies should be obtained when clinically indicated.[7] Complete blood count and electrolytes may not be necessary in otherwise healthy children. However, when central nervous system infection is suspected, these laboratory tests and lumbar puncture should be performed. Emergent neuroimaging studies should be done when clinically indicated such as postictal focal neurological deficits or suspected head trauma. Nonurgent neuroimaging studies, preferably magnetic resonance imaging, may be performed in those with significant cognitive or motor impairment or abnormal neurological deficits of unknown etiologies, non-benign focal seizure or in children under 1 year of age.[7]

Diagnosis of epilepsy

Diagnosis of epileptic seizure is made mainly by clinical history and is supported by physical examination, EEG and other investigations. If the nature of the paroxysmal events could not be made, further information of the events (by another witness or video recording) or repeated EEG should be obtained. If the diagnosis is uncertain, a close follow up without medication should be offered. A therapeutic diagnosis with antiepileptic drug (AED) is not recommended.

Once the diagnosis of seizure is made, the next step is to determine the seizure type and, whenever possible, epileptic syndrome. If a specific syndrome could be identified, the guiding of investigation, the prognosis regarding recurrence, response to AED, and cognitive outcome could be determined.

The recent ILAE classification of epileptic syndrome was published in 2006.[6,8] (Table 3) The important childhood epileptic syndromes are West syndrome, Lennox-Gastaut syndrome, Childhood and Juvenile absence epilepsy, Benign Rolandic epilepsy, and Juvenile

TABLE 3. Proposed Classification of Epilepsies and Epileptic Syndromes (2006)

Neonatal period
Benign familial neonatal seizures (BFNS)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Migrating partial seizures of infancy
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile seizures
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Childhood
Early onset benign childhood occipital epilepsy (Panayiotopoulos type)
Epilepsy with myoclonic astatic seizures
Benign childhood epilepsy with centrotemporal spikes (BCECTS)
Late onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome (LGS)
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) including Landau-Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)
Adolescence
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Progressive myoclonus epilepsies (PME)

Modified from Engle et al.[8]

myoclonic epilepsy. The characteristics of each epileptic syndrome are briefly reviewed.

West syndrome (WS)[9]

WS consists of infantile spasm, mental retardation or developmental regression, and hypsarrhythmia on interictal EEG. The most common age at onset is between 4-7 months. Infantile spasm is characterized by sudden contraction of neck, trunks and limbs and followed by a tonic contraction that is less intense but more sustained, lasting 2-10 seconds. Seizures usually occur in clusters. Interictal EEG shows a very high voltage of randomized slow waves and multifocal spikes and sharp waves which characterize the hypsarrhythmia EEG pattern. West syndrome is associated with multiple etiologies: hypoxic-ischemic encephalopathy, central nervous system infection, congenital brain anomaly, chromosome disorders, inborn error of metabolism, and tuberous sclerosis complex. No specific etiology is found in 30% of the patients. Prednisolone, adrenocorticotropic hormone (ACTH), and vigabatrin are the most commonly used AEDs in the treatment of WS.[10] Prognosis in terms of seizure control and neurobehavioral outcome is generally poor.

Lennox-Gastaut syndrome (LGS)[9]

LGS consists of mixed seizure types, interictal EEG shows slow spike-wave during awake and rhythmic fast activity during sleep, and mental retardation. Most common seizure types are generalized tonic, atonic, myoclonic, and atypical absence. The peak incidence is between 1-7 years. LGS is associated with the similar brain insults that produce infantile spasm. It may follow infantile spasm in some cases. LGS is one the most severe forms of childhood epileptic syndrome. Seizures are rarely completely controlled with AEDs, and most patients need AED combinations. Thus, the treatment goal in this syndrome may not be complete seizure control but to reach a balance between severity/frequency of seizure and side effects of AEDs. A broad spectrum AED should be used because most patients have mixed seizure types. Valproic acid, topiramate, lamotrigine, benzodiazepine have been used frequently in this condition. Prognosis is generally poor in this syndrome.

Benign Rolandic epilepsy (BRE)[11]

BRE or Benign childhood epilepsy with centrotemporal spikes is a benign focal childhood epileptic syndrome. The peak onset is 5-10 years. Seizures occur during sleep in 75% of the patients. The most common seizure type is focal motor seizure involving one side of the face, oropharyngeal muscle and may be followed by generalized tonic-clonic seizure. If seizures occur while awake, it is almost exclusively simple partial seizure involving the face and tongue. EEG shows spikes over the midtemporal (T3, T4) and central (Rolandic, C3, C4) region. Prognosis in these children are excellent, most children are in remission by the midteenage years (15-16 years). Treatment with AED may not be indicated in patients with only a few seizures. For those who need treatment, AED used for partial seizures are effective.

Childhood and Juvenile absence epilepsy (CAE/JAE)[11]

CAE and JAE are classified as generalized seizure. The onset is between 6-7 years in CAE and 10-12 years in JAE. Absence seizures are the predominating seizure type in both syndromes. Absence seizure is characterized by sudden onset of a decreased level of awareness and responsiveness and frequently associated with automatism such as eye lid fluttering, lips smacking. There are no aura or postictal symptoms. The duration of seizures are short, and usually last less than 15 seconds. Another seizure type is generalized tonic-clonic seizure which is more common in JAE than CAE. Seizures can be precipitated by hyperventilation. Ictal EEG shows generalized synchrounous and symmetrical 3-Hz spike-waves on a normal background activity. Valproic acid and lamotrigine are the AEDs of choice.

Juvenile myoclonic epilepsy (JME)[12]

JME is classified as generalized seizure. The main seizure type in JME is myoclonic seizure characterized by irregular myoclonic jerks of shoulders or arms that occur shortly after awakening. No impairment of consciousness is noted. Generalized tonic-clonic seizure is seen in 90% of the patients. Interictal EEG shows generalized synchronous and symmetrical of spike-wave or polyspike-wave complexes with a frequency of 4-6 Hz. Valproic acid, lamotrigine, and topiramate are the AEDs of choice. The seizures are usually completely controlled with AEDs. Unfortunately, the patients need

lifelong treatment since seizure recurrence is almost universal after AEDs withdrawal.

Management of patients with a first unprovoked seizure

In a patient with a first unprovoked seizure, the overall risk of seizure recurrence ranges from 40-50%.[13] The etiology of seizure and the EEG findings are the strongest predictors of seizure recurrence. The risk of seizure recurrence is as low as 24% in the idiopathic group with normal EEG and as high as 65% in the symptomatic group with abnormal EEG.[14]

Most seizure recurrences occur early, with approximately 50% of recurrences occurring within 6 months and over 80% within 2 years after the first seizure.[15] In patients who have two or more seizures, the risk of a second seizure recurrence was 57% and 63%, and 72% at 1, 2, and 5 years after the first seizure recurrences.[15]

The decision of whether to administer AED in a patient with epileptic seizure is to balance between the risks and benefits of treatment in each case.[16] Treatment with AED in children with a first unprovoked seizure have been show to decrease the risk of recurrence after 2 years, although it does not alter the long term remission or prognosis.[17] Thus it is generally recommended that treatment by AED should only be administered to the patient after the patient has had two or more seizures.[2,18] In selected cases that the patient may have a higher risk of recurrence such as CNS anomaly and/or EEG abnormalities and considerable psychosocial issues, AED may be started after the first unprovoked seizure.[18]

Principles of treatment

Epilepsy is not a single entity. Treatment of epileptic seizure should be individual and based on seizure types, risk of seizure recurrences, and epileptic syndrome. For example, patient with BRE may not be treated with AED because of its excellent prognosis.

Treatment with AED should only be started when the diagnosis of epileptic seizure is confirmed. AED is generally started in patients who have 2 or more unprovoked seizures. In clinical practice, the selection of AED should be matched to seizure type, age, sex, weight, concomitant medication, and economic status. Furthermore, certain neuro-psychiatric co-morbidities in children with epilepsy such as attention deficit/hyperactivity disorders, depression and anxiety may be exacerbated or ameliorated by specific AEDs.[19] All of these factors should be considered in selecting an appropriate AED for each child.

The treatment goal should be individually set for each patients. As mentioned, epilepsy is not a single entity, but a diverse condition with different causes, responses to AED, and prognoses. The ideal goal is to have complete seizure control with no or minimal AED side effects and good quality of life.

In the past, epilepsy treatment relied only on monotherapy or combination of older AEDs: phenobarbital (PHB), phenytoin (PHT), carbamazepine (CBZ), and valproic acid (VPA). However, over the past 10 years, there are several newer AEDs (gabapentin (GBP), lamotrigine (LTG), topiramate (TPM), oxcar-bamazepine (OXC), and levetiracetam (LEV)) which are proved to be safe and effective in epilepsy treatment.[20,21] These AEDs are currently available in Thailand.

Monotherapy is the gold standard treatment in patients with epilepsy. This approach is preferred since monotherapy can achieve seizure control in 70% of patients and avoid unnecessary risks of drug interactions or side effects from combination therapy. Table 4 shows the efficacy of the major AEDs according to the seizure types and epileptic syndromes. The usual starting and maintenance dosage and adverse side effects of commonly used AEDs are summarized in table 5.

A recent ILAE treatment guideline showed that there was a paucity of randomized controlled trail support for particular AEDs as initial monotherapy for children with epilepsy. There is only one class I study which showed that oxcarbamazepine and Class III study which showed that CBZ, PHB, PHT, VPA, and TPM appear to be effective as initial monotherapy for children with newly diagnosed partial-onset seizures.[22]

For generalized tonic-clonic epilepsy, there is no Class I and II study. Only class III studies are available and show that CBZ, PHB, PHT, TPM, and VPA are possibly effective for children with GTC.[22] For patients with absence seizure, a class III study shows that VPA and LTG may be considered as initial monotherapy.

AED should be started in an average dosage and gradually titrated until the seizure is completely controlled.[18] If the first drug is pushed to the maximum dose and lack of efficacy or the patients develop intolerant side effects, a second line AED should be tried. The success of a second AED depends on the reason for discontinuation. Seizure free with a second AED is less when treatment failure with the first AED is due to lack of efficacy than when it is due to intolerable side effects or idiosyncratic reaction.[23] It is generally recommended that the first AED should only be tapered after a therapeutic dose of the new AED is obtained.[24]

For patients with refractory epilepsy, AED polytherapy is generally used. However, these patients are more prone to have side effects and drug interactions which can be worse than the seizures. Thus, the main goal treatment in these patients may not to complete seizure elimination, but a balance between maximum seizure control with minimal adverse effects.[18]

TABLE 4. Appropriate AED used according to seizure type and epileptic syndrome

Seizure type	First Line AED	Second Line AED
Partial seizure with or without generalized	PHB, PHT, CBZ, VPA LTG, TPM, OXC	GBP, LEV
Primary generalized tonic-clonic	PHB,PHT, CBZ, VPA LTG,TPM	LEV
Absence	VPA, LTG	TPM
Myoclonic. Atonic	VPA	LTG, TPM
Epileptic syndrome		
West syndrome	VGB, Hormonal therapy	VPA, TPM
Lennox-Gastaut syndrome	VPA, LTG	TPM, LEV
Childhood/ Juvenile Absence Epilepsy	VPA, LTG	TPM
Benign Rolandic Epilepsy	PB, PHT, CBZ, VPA	TPM
Juvenile Myoclonic Epilepsy	VPA, LTG	TPM

TABLE 5. Usual initial and maintenance dosage and adverse side effects of commonly used AED

Drug	Initial dose (mg/kg/day)	Dosing regimen	Escalation	Maintenance doge (mg/kg/day)	Time to steady state (day)	Therapeutic range (μg/ml)	Common side effects	Potential severe side effect
Carbamazepine	10-15	bid-tid	5 mg/kg/wk	10-30	3-4	4-12	Nausea, vomiting, ataxia, diplopia, sedation, dizziness	Rash and hypersensitivity reaction, hepatitis, leukopenia, hyponatremia
Gabapentin	10	tid-qid	10 mg/kg/d	30-100	1-2	-	Sedation, dizziness, ataxia	-
Lamotrigine	*	bid	**	***	3-10	-	Sedation, dizziness, ataxia, diplopia,	Rash and hypersensitivity reaction
Levetiracetam	10	bid	10 mg/kg/wk	20-80	2	-	Sedation, dizziness	
Sodium valproate	15-20 (10)	bid-tid	5-10 mg/kg/wk	30-80	2	50-150	Nausea, vomiting, abdominal pain, tremor, weight gain, hair loss	Hepatitis (especially in age < 2 year), pancreatitis, hyperammonemia
Oxcarbaxepine	10	bid	10 mg/kg/wk	20-50	2	-	Sedation, dizziness, ataxia	Rash and hypersensitivity reaction, hyponatremia, leukopenia
Phenobarbital	3-5(4)	qd-bid	1-2 mg/kg/2wk	3-5	15-20	10-40	Sedation, hyperactivity, aggressive behaviors, cognitive concerns	Rash and hypersensitivity reaction
Phenytoin	5	qd-bid	1-2 mg/kg/2wk	5-8	15-20	10-20	Nausea, vomiting, nystagmus, gum hypertrophy, hersutism	Rash and hypersensitivity reaction, hepatitis, Systemic lupus erythematosus
Topiramate	1	bid	1 mg/kg/wk	5-9	3-5	-	Sedation, dizziness, Mental slowness, weight loss	Renal stone, glaucoma, oligohydrosis
Vigabatrin	40-50	bid	10-20 mg/kg/wk	100-150	2	-	Sedation, dizziness	Visual field abnormalities

* 0.5 mg/kg/day monotherapy, 0.1-0.3 mg/kg/day with VPA, 1 mg/kg/day with inducer (PHB, PHT, CBZ)
** 0.5 mg/kd/2 wk monotherpy, 0.1-0.3 mg/kg/2 wk with VPA, 1 mg/kg/d with inducer (PHB, PHT, CBZ)
*** 10 mg/kg/day monotherapy, 5mg/kg/day with VPA, 15 mg/kg/day with inducer (PHB, PHT, CBZ)

Treatment monitoring

Epilepsy is a chronic brain disorder that needs a long term follow up. Patients should have a follow up 4-6 weeks after initiation of treatment and then on a regular basic to assess for seizure control, AEDs side effects, and overall quality of life. A regular blood test is not routinely recommended, but it may be done to assess compliance, drug toxicity, and drug interactions. Drug level may be monitored in phenytoin where the therapeutic level is narrow and its non-linear pharmacokinetics.

The patients should be instructed to avoid certain situations that can precipitate seizures: fevers, infection, sleep deprivation, stress, and alcohol consumption.

Discontinuation of medication

After 2 years of AED therapy and the patient remains seizure free, withdrawal of AED should be considered. Decision of withdrawal should be individualized. More than 60 percent of the patients remain seizure free after AED withdrawal.[25] The risk of seizure recurrence is higher in patients with symptomatic epilepsy, a known structural lesion, EEG abnormalities, the seizure onset during adolescence, neurological abnormalities, and history of difficult to control epilepsy.[25] Epileptic syndrome is also a significant factor that predicts the outcome. For example, the seizure recurrence in patients with BRE is low but the risk is high in patients with JME.

If decision of AED withdrawal is made, the AED should be withdrawn slowly over a period of at least 6 weeks to avoid the risk of withdrawal associated seizures. A longer period may be appropriate for phenobarbital and benzodiazepines.[2,18] Approximately 80-90% of recurrences occur within the first year after discontinuation.[25]

Other treatment modalities in childhood epilepsy

In general, AED is the first line treatment in childhood epilepsy. However, in patients with refractory epilepsies, seizures are difficult to control and most patients need multiple AED combinations which lead to more side effects and drug interactions. Now there are other treatment modalities in treatment for these difficult to treat epilepsies. These are ketogenic diet, vagus nerve stimulation, surgery, and brain stimulation.

Ketogenic diet (KD) has been used in difficult-to-control seizures and numerous severe childhood epileptic syndromes.[26] Its efficacy is at least comparable to AED. KD has been used successfully in Thailand.[27] Complication from KD include hypoglycemia, metabolic derangements, dehydration, hyperlipidemia and renal stones.

Vagus nerve stimulation (VNS) is used for refractory epilepsy. VNS has efficacy comparable to new AEDs for refractory partial seizure. Complications from VNS include vocal cord paralysis, hoarseness of voice and shortness of breath.[28]

Surgery is an option for children with refractory epilepsy.[29] The evaluations before surgery are extensive

which include video-EEG monitoring, structural and functional neuro-imaging studies, and appropriate neuropsychological testing. MRI with epilepsy protocols is recommended as a tool to detect structural abnormalities. In some patients ictal or interictal single photon emission computed tomography (SPECT), or positron emission tomography (PET) may be needed to identify the epileptic zone. If a specific lesion can be found, a resective surgery could be performed with good seizure control. In certain catastrophic epileptic syndromes such as LGS, a palliative surgery, corpus callosotomy, may be performed. This procedure is to inhibit inter-hemispheric spreading of the seizure activity which causes seizure with fall (atonic seizure) or generalized tonic seizure. Other types of epileptic surgery are hemispherectomy, and multiple subplial resections.

There are several ongoing treatment options in the treatment of refractory surgery such as transcranial magnetic stimulation (TMS), deep brain structures (DBS) (thalamic or hippocampus) or direct stimulation of the epileptic area.[30]

SUMMARY

In this review, the author summarized the essential knowledge about the management of childhood epilepsy. In addition to the treatment, the patients and their family should be counseled about the nature and prognosis of epilepsy, the need for long-term treatment, the importance of compliance, and avoiding of any seizure precipitants. The goal of treatment should not only be focused on complete seizure control, but also on good quality of life.

REFERENCES

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470-2.
2. Guerrini R. Epilepsy in children. Lancet 2006;367:499-524.
3. ILAE Commission Report. The epidemiology of the epilepsies: future directions. International League Against Epilepsy. Epilepsia 1997;38: 614-8.
4. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1981; 22:489-501.
5. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389-99.
6. Engel J, Jr. Report of the ILAE classification core group. Epilepsia 2006;47:1558-68.
7. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. Neurology 2000;55 :616-23.
8. Engel J, Jr. ILAE classification of epilepsy syndromes. Epilepsy Res 2006;70 (Suppl 1):S5-10.
9. Nabbout R, Dulac O. Epileptic encephalopathies: a brief overview. J Clin Neurophysiol 2003;20:393-7.
10. Hancock E, Osborne J, Milner P. Treatment of infantile spasms. Cochrane Database Syst Rev 2003:CD001770.
11. Camfield P, Camfield C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. Epilepsia 2002;43(Suppl 3):27-32.
12. Beghi M, Beghi E, Cornaggia CM, Gobbi G. Idiopathic generalized epilepsies of adolescence. Epilepsia 2006;47(Suppl 2):107-10.
13. Berg AT. Risk of recurrence after a first unprovoked seizure. Epilepsia 2008;49 Suppl 1:13-8.
14. Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology 1991;41:965-72.
15. Shinnar S, Berg AT, O'Dell C, Newstein D, Moshe SL, Hauser WA. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. Ann Neurol 2000;48:140-7.
16. Hirtz D, Berg A, Bettis D, et al. Practice parameter: treatment of the child with a first unprovoked seizure: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2003;60: 166-75.
17. Camfield P, Camfield C. Special considerations for a first seizure in childhood and adolescence. Epilepsia 2008;49(Suppl 1):40-4.
18. Raspall-Chaure M, Neville BG, Scott RC. The medical management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol 2008;7:57-69.
19. Wilfong AA. Monotherapy in children and infants. Neurology 2007;69 (Suppl 3):S17-22.
20. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004;62:1261-73.
21. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004;62:1252-60.
22. Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094-120.
23. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314-9.
24. St Louis EK, Gidal BE, Henry TR, et al. Conversions between monotherapies in epilepsy: expert consensus. Epilepsy Behav 2007;11: 222-34.
25. Shinnar S, Berg AT, Moshe SL, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. Ann Neurol 1994;35: 534-45.
26. Keene DL. A systematic review of the use of the ketogenic diet in childhood epilepsy. Pediatr Neurol 2006;35:1-5.
27. Kankirawatana P, Jirapinyo P, Kankirawatana S, Wongarn R, Thamanasiri N. Ketogenic diet: an alternative treatment for refractory epilepsy in children. J Med Assoc Thai 2001;84:1027-32.
28. Majoie HJ, Berfelo MW, Aldenkamp AP, Renier WO, Kessels AG. Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. Seizure 2005;14:10-8.
29. Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006;47: 952-9.
30. Theodore WH, Fisher R. Brain stimulation for epilepsy. Acta Neurochir 2007;97(Suppl Pt 2):261-72.