Chapter 4
Epilepsies in Children and Adolescents and Their Treatment

CQ 4-1

Which epilepsy syndromes with childhood or adolescent onset have high prevalence?

Summary

According to epidemiological studies, partial epilepsy syndrome constitutes 60–70% of all childhood epilepsies, generalized epilepsy syndrome 20–30%, and undetermined epilepsy around 1–10%. In childhood epilepsies, many epilepsy syndromes have good prognosis, such as childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes. Childhood epilepsy covers the onset age range of one month after birth to around 18 years of age.

Comment

In a prospective community-based study, Berg et al.[1] attempted to classify 613 patients with childhood epilepsy into epilepsies, epilepsy syndromes and related seizure disorders. They found partial epilepsy in 58.6% of the cases, generalized epilepsy in 29.0%, and undetermined epilepsy in 12.4%. Regarding the proportions of epilepsy syndromes, they reported 74 cases (12.1%) of childhood absence epilepsy, 59 cases (9.6%) of benign childhood epilepsy with centrotemporal spikes, 15 cases (2.4%) of juvenile absence epilepsy, 12 cases (2.0%) of juvenile myoclonic epilepsy, 24 cases (3.9%) of West syndrome, 10 cases (1.6%) of Doose syndrome, and 4 cases (0.7%) of Lennox-Gastaut syndrome. In an epidemiological study conducted in Japan, Oka et al.[2] analyzed 1,337 patients younger than 13 years with strictly defined epilepsies (excluding those with a first unprovoked convulsion or febrile seizure), and classified 907 (75.8%) patients as partial epilepsy, 268 (22.4%) patients as generalized epilepsy, 21 (1.8%) patients as undetermined epilepsy, with the remaining 141 (10.5%) patients as unclassifiable. In addition, Wirrell et al.[3] studied all 359 patients diagnosed with new-onset childhood epilepsy (0–17 years of age) in Olmsted County, Minnesota in 1980–2004, and classified the epilepsy of each patient based on the 2010 ILAE classification (see Chapter 1, CQ1-3 on page 6). As for the classification of seizure type, focal seizure accounted for 68%, generalized or bilateral seizures 23%, spasms 3%, and undetermined 5%. For the classification of epilepsy syndrome, 105 cases (29.2%) could be classified, and they comprised benign childhood epilepsy with centrotemporal spikes in 26 cases (7.2%), childhood absence epilepsy in 17 cases (4.7%), juvenile absence epilepsy in 11 cases (3.1%), juvenile myoclonic epilepsy in 11 cases (3%), West syndrome in 9 cases (2.5%), Doose syndrome in 2 cases (0.6%), Lennox-Gastaut syndrome in 1 case (0.3%), and mesial temporal lobe epilepsy with hippocampal sclerosis in 8 cases (2.2%).

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■ Search formula and secondary reference sources

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#5 classification/TH or classification/AL 126,662

#6 #2 or #3 or #4 or #5 399,286

#7 #1 and #6 2,059

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CQ 4-2

What examinations are recommended for the first unprovoked seizure in children and adolescents?

Summary

The examinations are basically the same as those in adults (see also Chapter 2 "Examinations for Clinical Practice of Epilepsy"). They include electroencephalogram (EEG), neuroimaging studies, and routine blood tests. Of these, EEG can detect epileptiform activities at a higher rate than in adults, and it is the most useful examination. MRI is recommended among the neuroimaging modalities.

Comment

1. EEG

Previous studies reported that epileptiform EEG abnormalities are detected in 18–56% of children after new-onset seizures (compared with 13–35% in adults)[1]. In addition, an epidemiological study including children and adults shows that we rarely detect an epileptiform abnormality after the third negative EEG examination[2]. The patients with epileptiform discharges have epilepsy approximately two times more frequently than those with normal EEGs[1]. In a prospective study in children with a first unprovoked seizure conducted by Shinnar et al.[3], EEG abnormalities were found in 135 (42%) of 321 children studied. The EEG abnormalities comprised focal spikes in 77 cases, generalized spike-and-wave complexes in 28 cases, slowing in 43 cases, and nonspecific abnormalities in 7 cases. The detection rate was higher in partial seizures than in generalized seizures, higher in children aged 3 years or older than in younger children, and higher in symptomatic epilepsies than in idiopathic epilepsies. In the symptomatic epilepsy group, seizure recurrence was observed in 54% of 103 cases with EEG abnormalities, but in only 25% of 165 cases without any EEG abnormalities. EEG abnormalities, especially epileptiform discharges and localized slow waves, are useful for predicting seizure recurrence. When used in combination with other clinical findings, EEG may play an important role in the diagnosis of epilepsy syndrome even in patients with only a single seizure. For example, when a child with a convulsion attack during sleep for the first time shows spikes in the centrotemporal region, a diagnosis of childhood benign epilepsy with centrotemporal spike is strongly suggested, and the prognosis can be predicted.

2. Neuroimaging examinations

There is no sufficient evidence on whether neuroimaging examination should be performed routinely after the first unprovoked seizure in children. If symptomatic epilepsy is suggested, neuroimaging studies are recommended, especially MRI. Shinnar et al.[4] performed imaging examinations in 411 children with a first unprovoked seizure, and found brain tumor and neurocysticercosis in two children each. They enrolled the remaining 407 children in a prospective study. Among them, 58 children underwent MRI examination, and abnormalities were found in 19 children (33%), including cortical dysplasia in six children with normal imaging findings at the initial examination. In a prospective study conducted by Tanabe et al.[5] in Japan, MRI examination was performed in children having a first seizure, and abnormal findings were detected in 10 of 41 children (24.4%), including cortical dysplasia in 4 children. Even with these results, the clinical significance of the lesions shown by imaging studies should be evaluated carefully, especially for their epileptogenicity.

3. Routine blood tests

In children, routine blood tests have clinical significance because the first seizure may also occur under conditions of hypoglycemia or electrolyte abnormalities.

References

1) Wirrell EC. Prognostic significance of interictal epileptiform discharges in newly diagnosed seizure disorders. J Clin Neurophysiol. 2010; 27(4): 239-248.
2) Baldin E, Hauser WA, Buchhalter JR, et al. Yield of epileptiform electroencephalogram abnormalities in incident unprovoked seizures: a population-based study. Epilepsia. 2014; 55(9): 1389-1398.
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4) Shinnar S, O'Dell C, Mitnick R, et al. Neuroimaging abnormalities in children with an apparent first unprovoked seizure. Epilepsy Res. 2001; 43(3): 261-269.
5) Tanabe T, Hara K, Kashiwaki M, et al. Prospective study of first unprovoked seizure. No To Hattatsu. 2005; 37(6): 461-466 (in Japanese with English abstract).

Search formula and secondary reference sources

PubMed search: December 31, 2015
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CQ 4-3

For unprovoked seizures in children and adolescents, is the long-term prognosis worse if treatment would start after the second seizure?

Summary

For unprovoked seizures in children and adolescents, the long-term seizure outcome is not affected even if treatment is started after the second seizure, as in the case of adults (see CQ3-1 on page 21).

Comment

There have been debates on whether there is any difference in the long-term outcome between patients who start antiepileptic drug therapy promptly after the first epileptic seizure and those who start later. According to a large-scale, prospective, randomized, controlled trial reported from the UK, immediate treatment after onset was superior to delayed treatment in terms of prompt seizure control, but there was no significant difference in the long-term outcome (remission)[1]. There was also no significant difference in QOL such as employment status. The natural courses of the epilepsies were not affected by the number of epileptic seizures. Apart from controlling seizures, it is an unsolved issue in clinical epileptology of whether antiepileptic drug treatment also changes the natural course of epilepsy. To date, there is no clear evidence that antiepileptic drugs affect the natural course of epilepsy.

On the other hand, there is evidence that even when patients with unprovoked seizures are followed without any treatment, seizures do not recur in one-half of them. Therefore, if treatment is started after the first seizure, one-half of the patients would be treated unnecessarily. Most clinicians start treatment with antiepileptic drugs when seizures are repeated three or four times, but there are only a few studies on the short-term and long-term outcome of this policy.

■ References

1) Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet. 2005; 365(9476): 2007-2013.

■ Search formula and secondary reference sources

PubMed search: December 31, 2015
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CQ 4-4

How to make a diagnosis of juvenile myoclonic epilepsy?

Summary

Juvenile myoclonic epilepsy is a disease with major symptoms of myoclonic seizures and generalized tonic-clonic seizures. Medical history, onset age, triggers of seizures, and electroencephalographic findings are important for diagnosis.

Comment

Myoclonic seizures are sudden, brief, shock-like muscle jerks affecting muscles of the face, trunk and extremities. The jerks occur in a single muscle or several muscles together[1]. Usually, no loss of consciousness is associated with the seizures. Although the seizures may occur alone, they may also develop into generalized tonic-clonic seizures. Myoclonic seizures are readily induced by external stimuli, especially by photic stimuli.

Juvenile myoclonic epilepsy (JME) accounts for 26% of idiopathic generalized epilepsy and 5–10% of all epilepsies[2]. Symptoms suggestive of this epilepsy are (1) childhood to adolescent onset, (2) induced by sleep deprivation and alcohol, (3) tonic-clonic seizure or myoclonic seizure in the early morning, (4) brief absence seizure, (5) photoparoxysmal EEG response with generalized 3-Hz spike-and-wave complexes or polyspike-and-wave complexes[3].

■ References

1) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission of Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981; 22(4): 489-501.
2) Grünewald RA, Panayiotopoulos CP. Juvenile myoclonic epilepsy. A review. Arch Neurol. 1993; 50(6): 594-598.
3) Zifkin B, Andermann E, Andermann F. Mechanisms, genetics, and pathogenesis of juvenile myoclonic epilepsy. Curr Opin Neurol. 2005; 18(2): 147-153.

■ Search formula and secondary reference sources

PubMed search: December 31, 2015
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CQ 4-5

What are the first-line drugs for childhood- or adolescence-onset epilepsy with undetermined seizure type (partial or generalized)?

Summary

Valproate, carbamazepine, zonisamide, levetiracetam, and lamotrigine are the candidate drugs, and physicians should select one of them taking into consideration various factors including the antiepileptic spectrum, age, sex, and adverse effect profile. Carbamazepine has been reported to exacerbate generalized seizures other than generalized tonic-clonic seizure. For lamotrigine, physicians should strictly follow the package insert for the dosage and administration, and it therefore takes a long time to up-titrate to the effective dosage. For child-bearing aged women, see Chapter 13 (page 113).

Comment

When 260 children with newly diagnosed idiopathic generalized epilepsy and partial epilepsy were randomly allocated to treatment with valproate or carbamazepine, the efficacy did not differ significantly between the two drugs[1]. Valproate was more effective than carbamazepine for generalized seizures (all ages)[2]. Carbamazepine may exacerbate idiopathic and symptomatic generalized epilepsies manifesting absence and myoclonic seizures[3]. Zonisamide is effective for partial seizures and secondarily generalized seizures, but physicians should pay attention to some adverse effects including hypohidrosis and impaired cognitive function in children[4]. Levetiracetam is also effective for partial seizures and secondarily generalized seizures, with only few adverse effects including teratogenicity. Lamotrigine has broad spectrum antiepileptic activities for partial seizures, generalized seizures, and absence seizures, with generally few adverse effects including teratogenicity; but note that the prescribed dosage and administration processes have to be strictly followed.

■ References

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2) Cowling BJ, Shaw JE, Hutton JL, et al. New statistical method for analyzing time to first seizure: example using data comparing carbamazepine and valproate monotherapy. Epilepsia. 2007; 48(6): 1173-1178.
3) Guerrini R, Belmonte A, Genton P. Antiepileptic drug-induced worsening of seizures in children. Epilepsia. 1998; 39(Suppl 3): S2-10.
4) Ohtahara S. Zonisamide in the management of epilepsy. Japanese experience. Epilepsy Res. 2006; 68(Suppl 2): S25-33.

■ Search formula and secondary reference sources

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#2 Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years = 207

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CQ 4-6

If seizures recur in those treated with valproate for childhood/adolescent generalized seizure or carbamazepine for childhood/adolescent partial seizures, even when their drug concentrations are in the therapeutic ranges, which drugs should be the next candidates?

Summary

1. In the case of recurrence when valproate is used for generalized seizures

a. Generalized tonic-clonic seizure (GTCS)

Select lamotrigine, carbamazepine, oxcarbazepine†, clobazam, levetiracetam, or topiramate†, considering their adverse effect profiles. However, when absence seizures and myoclonic seizures coexist, we should consider the fact that carbamazepine and oxcarbazepine† have a risk of aggravating these seizures.

b. Absence seizures

Ethosuximide is recommended. If ethosuximide cannot be used, lamotrigine is recommended, although it is considered less effective than ethosuximide.

c. Myoclonic seizure

For juvenile myoclonic epilepsy, levetiracetam†, lamotrigine and topiramate† are recommended. For myoclonic seizure complicating other epilepsies, clonazepam and clobazam are selected although the evidence is low.

2. In the case of recurrence when carbamazepine is used for partial seizures

Select zonisamide, lamotrigine, levetiracetam, clobazam, topiramate, valproate, or gabapentin, considering their adverse effect profiles.

Comment

1) There was no significant difference in effectiveness between valproate and carbamazepine in children with new-onset generalized tonic-clonic seizures or partial seizures[1]. In children with new-onset generalized tonic-clonic seizures and partial seizures, there were also no significant differences in efficacy among phenobarbital, phenytoin, carbamazepine, and valproate[2]. In adults and children with generalized epilepsy or unclassified epilepsy randomly allocated to treatment with valproate, lamotrigine or topiramate, valproate was the best in both tolerability and efficacy. As the initial treatment for generalized tonic-clonic seizures, NICE guideline 2012 recommends valproate followed by lamotrigine, and then carbamazepine and oxcarbazepine†, or adjunctive therapy using clobazam, levetiracetam or topiramate†[3].
2) In randomized controlled trials comparing valproate, ethosuximide, and lamotrigine for childhood absence epilepsy, valproate and ethosuximide were superior in efficacy to lamotrigine, but there was no difference between the two former drugs[4, 5]. However, since ethosuximide has less adverse effects compared to valproate, ethosuximide is recommended as the first-line drug for childhood absence epilepsy.
3) In a study comparing valproate and lamotrigine for juvenile myoclonic epilepsy, no significant difference in seizure control rate was observed between the two drugs, while the rate of discontinuation due to adverse effects was lower with lamotrigine[6]. In an randomized controlled trial (RCT) for idiopathic generalized epilepsy with myoclonic seizures, levetiracetam reduced myoclonic seizures at a significantly higher rate compared to placebo[7]. In addition, expert consensus studies recommended the following drugs for myoclonic seizure, in the order of: valproate, clonazepam, and clobazam in one paper, and valproate and lamotrigine in another paper[8, 9]. Based on all these studies, valproate followed by levetiracetam, lamotrigine, clonazepam, and clobazam are recommended. However, it should be noted that lamotrigine has a risk of deteriorating myoclonic seizures in patients with Dravet syndrome (severe myoclonic epilepsy in infancy) and in some patients with juvenile myoclonic epilepsy.

4) In children aged 2–16 years with partial epilepsy and in some children with generalized epilepsy, there was no significant difference in efficacy among clobazam, carbamazepine and phenytoin when used as monotherapy[10]. However, in Japan, clobazam is currently not approved for monotherapy.

5)Lamotrigine and carbamazepine were equivalent in efficacy for partial seizures with or without generalized tonic-clonic seizures[11]. When the effects and efficacy of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate were compared in 1,721 adults and children with partial epilepsy, lamotrigine was more useful than carbamazepine, gabapentin or topiramate in terms of lower discontinuation rate and fewer adverse effects, and was not significantly different from oxcarbazepine.

6) NICE guideline 2012 recommends adjunctive use of clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topiramate[12].

*For the use of perampanel in patients aged 12 years and above, and lacosamide in patients aged 16 years and above, see Chapter 3 “Drug Therapy for Adult Epilepsy”.

■ References

1) Verity CM, Hosking G, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. The Paediatric EPITEG Collaborative Group. Dev Med Child Neurol. 1995; 37(2): 97-108.
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■ Search formula and secondary reference sources

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Table 1. Drug options by seizure type in revised NICE guideline (2012).

Seizure type	First-line drugs	Adjunctive drugs	Other drugs that may be considered	Do not offer drugs
Generalized tonic–clonic seizure	oxcarbazepine[†] carbamazepine valproate lamotrigine	clobazam topiramate[†] valproate lamotrigine levetiracetam		oxcarbazepine[†a] carbamazepine[a] gabapentin[†a] vigabatrin[†a] phenytoin[a]
Tonic seizure or atonic seizure	valproate	lamotrigine	topiramate[†] rufinamide	oxcarbazepine[†] carbamazepine gabapentin[†] vigabatrin[†]
Absence seizure	ethosuximide valproate lamotrigine	ethosuximide valproate lamotrigine	clobazam clonazepam[†] zonisamide topiramate[†] levetiracetam[†]	oxcarbazepine[†] carbamazepine gabapentin[†] phenytoin vigabatrin[†]
Myoclonic seizure	topiramate[†] valproate levetiracetam[†]	topiramate[†] valproate levetiracetam[†]	clobazam clonazepam zonisamide piracetam	oxcarbazepine[†] carbamazepine gabapentin[†] phenytoin vigabatrin[†]
Partial seizure (including secondarily generalized)	oxcarbazepine[†] carbamazepine valproate lamotrigine levetiracetam	oxcarbazepine carbamazepine gabapentin clobazam topiramate valproate lamotrigine levetiracetam	zonisamide vigabatrin[†] phenobarbital phenytoin lacosamide	

[a]: in the case of complication by absence seizure or myoclonic seizure, in the case of juvenile myoclonic epilepsy
[†]: not covered by medical insurance in Japan (as of December 6, 2017)
(Modified from NICE guideline 2012)

Table 2. Drug options by epileptic syndrome in revised NICE guideline (2012).

Epilepsy syndrome	First-line drugs	Adjunctive drugs	Other drugs that may be considered	Do not offer drugs
Idiopathic epilepsy				
Childhood absence epilepsy Juvenile absence epilepsy	ethosuximide valproate lamotrigine	ethosuximide valproate lamotrigine	clonazepam clobazam† zonisamide topiramate† levetiracetam†	oxcarbazepine† carbamazepine gabapentin† vigabatrin† phenytoin
Juvenile myoclonic epilepsy	topiramate† valproate lamotrigine levetiracetam	topiramate† valproate lamotrigine levetiracetam	clonazepam clobazam zonisamide	oxcarbazepine† carbamazepine gabapentin† vigabatrin† phenytoin
Epilepsy with generalized tonic–clonic seizures alone (grand mal epilepsy on awakening	oxcarbazepine† carbamazepine valproate lamotrigine	clobazam topiramate† valproate lamotrigine levetiracetam		
Idiopathic generalized epilepsy	topiramate† valproate lamotrigine	topiramate† valproate lamotrigine levetiracetam	clonazepam clobazam zonisamide	oxcarbazepine† carbamazepine gabapentin vigabatrin phenytoin
Benign epilepsy with centrotemporal spikes Panayiotopoulos syndrome Late-onset childhood occipital epilepsy (Gastaut type)	oxcarbazepine† carbamazepine valproate lamotrigine levetiracetam	oxcarbazepine carbamazepine gabapentin clobazam topiramate valproate lamotrigine levetiracetam	zonisamide vigabatrin† phenobarbital phenytoin lacosamide	
Epileptic encephalopathy				
Infantile spasm (West syndrome) not due to tuberous sclerosis Infantile spasm (West syndrome) due to tuberous sclerosis	Discuss with or refer to specialist facility ACTH steroid vigabatrin			
Dravet syndrome (severe myoclonic epilepsy in infancy)	Discuss with or refer to specialist facility topiramate valproate	clobazam stiripentol		oxcarbazepine† gabapentin carbamazepine vigabatrin phenytoin lamotrigine
Epilepsy with continuous spike and wave during slow sleep	Discuss with or refer to specialist facility			
Lennox–Gastaut syndrome	Discuss with or refer to specialist facility valproate	lamotrigine	topiramate rufinamide	oxcarbazepine† gabapentin carbamazepine vigabatrin†
Landau–Kleffner syndrome	Discuss with or refer to specialist facility			
Myoclonic-astatic epilepsy	Discuss with or refer to specialist facility			

Only those drugs that are available for use in Japan
†: not covered by medical insurance in Japan (as of December 6, 2017)
(Modified from NICE guideline 2012)