Chapter 5
Drug-Resistant Epilepsy

CQ 5-1

What is the definition of drug-resistant epilepsy?

Summary

Clinically, drug-resistant epilepsy is defined as the epilepsy which cannot be controlled for a certain period (at least 1 year or 3 times the longest interval between seizures) by using two appropriately selected antiepileptic drugs (whether as monotherapy or combination therapy), with sufficiently high blood concentrations but without adverse events.

Comment

Since not all the epilepsies that cannot be controlled by antiepileptic drugs are intractable epilepsies (only some are intractable), "intractable epilepsy" that was used in the previous edition is replaced by "drug-resistant epilepsy" in the 2018 edition. Some subtle seizures that do not impede daily life and recur several times a year are drug resistant, but not intractable. Even when antiepileptic drugs fail to control seizures, if the seizure frequency is 1–2 times a year, the patient is not indicated for surgery. However, if seizure frequency is 1–2 times a month, the patient has an intractable epilepsy in whom surgical treatment should be considered.

The definition of drug-resistant epilepsy depends on the use situation and we have no universal definition. The ILAE proposed the above definition so that it can be applied to various situations[1]. This definition is intended not only for clinical settings but also for purposes such as designing clinical trials, clinical research, and facilitating referral of the patients to specialized facilities. Referral to specialized facilities is recommended if seizures are not controlled by two appropriately selected drugs at adequately high doses.

The evidence for two drug regimens was provided by a study of 1,098 adolescent or adult patients with untreated epilepsy. The seizure-free rate was 50% after the first drug regimen, 13% after the second regimen of monotherapy or combination therapy, but only 5% after the third to ninth regimen of monotherapy or combination therapy. Since there is very low possibility of achieving seizure-free status by continued drug therapy after failure of 2 regimens of antileptic drugs as monotherapy or combination therapy, epilepsy uncontrollable by 2 appropriate drugs as monotherapy or combination therapy can be regarded as drug resistant[2].

The evidence of at least one year is based on community-based studies showing that one or more seizures in the past two years have various impact such as psychological symptoms or disadvantages in daily life. In addition, being seizure-free for at least one year is a requirement for acquiring a driver's license in many countries. However, in a long-term follow-up (2-22 years, median 6.1 years) study of 780 adolescent-adult patients with untreated epilepsies, out of 462 patients whose seizures were controlled for more than 1 year at the time of the final observation, 74% had seizures controlled within one year, and 11% within two years after the treatment started. In another definition, drug resistance was defined as seizures persisting after at least two years of treatment, in addition to control failure with two drugs. This is because the possibility of drug resistance is high if seizures are not controlled after two years of treatment[3].

However, these definitions do not always apply to children, and there are many pediatric patients in whom seizures are well controlled by three or more drug regimens. In a cohort of 613 children with epilepsy prospectively followed for 13 years at the longest (median 9.7 years), 128 children who did not respond favorably to two drugs were treated with the third or more drugs (median 3 drugs). After treatment for 1-14 (median 10.1) years, seizures were controlled for at least 1 year during this period in 57% of the patients, and seizures were controlled for more than 1 year at the final observation in 38%[4]. Therefore, for children, drug resistance must not be defined only by seizures not controlled by two drug regimens, or not controlled after 1–2 years of treatment.

According to the guideline of the Japan Epilepsy Society for the purpose of considering surgical indication, the criterion

of drug-resistant epilepsy is seizures not controlled after more than 2 years of treatment even with 2–3 kinds of appropriate drugs[5].

It should be noted that there are many patients with pseudo-drug-resistant epilepsy due to misdiagnosis (see CQ5-3 on page 47).

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Search formula and secondary reference sources

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No references that could serve as evidence were found in Ichushi Web.

CQ 5-2

What are the true drug-resistant epilepsies in adults?

Summary

Drug-resistant epilepsies in adults include symptomatic partial epilepsies with intracranial lesions (including cerebrovascular disorder, cerebral dysplasia, brain tumor, hippocampal sclerosis, encephalitis or encephalopathy, and systemic diseases) on MRI and other imaging studies; cryptogenic partial epilepsies including temporal lobe epilepsy; symptomatic generalized epilepsies with degenerative disorders such as dentatorubral pallidoluysian atrophy (DRPLA) or metabolic disorders; various childhood onset epilepsies uncontrolled even in adulthood such as Lennox-Gastaut syndrome; and epilepsies associated with autoimmune encephalitis.

Comment

In one study, out of a total of 2,200 outpatients (partial epilepsy 1,369 cases, generalized epilepsy 473 cases, and undetermined epilepsy 358 cases) aged 16 years and above, 1,696 patients were treated and followed for 1–7 years. Among them, 45% were seizure-free for one year or longer. By epilepsy classification, the seizure-free rate was 27% in symptomatic (with a definitive cause of epilepsy) or cryptogenic (cause of epilepsy suspected but not definite) generalized epilepsy, 82% in idiopathic generalized epilepsy, 35% in symptomatic partial epilepsy, 45% in cryptogenic partial epilepsy, and 11% in partial epilepsy with hippocampal sclerosis. Among the partial epilepsies, seizure-free rate was 20% in temporal lobe epilepsy and 36% in non-temporal lobe epilepsy. For temporal lobe epilepsy, the seizure-free rate was 10% when accompanied by hippocampal sclerosis, and was 31% when not accompanied by hippocampal sclerosis. There was no difference in the seizure-free rate between temporal lobe epilepsy without hippocampal sclerosis and non-temporal lobe epilepsy. The seizure-free rate was markedly low in hippocampal sclerosis, dual pathology (hippocampal sclerosis + other lesions), and cerebral dysgenesis (11%, 3% and 24%, respectively)[1].

In a prospective study of 550 adolescent and adult patients with partial epilepsy treated with antiepileptic drugs, 312 (57%) patients were seizure-free for at least 1 year at the last follow-up. The seizure-free rate was 42% in patients with mesial temporal sclerosis, 78% with cerebral arteriovenous malformation, 67% with cerebral infarction, 63% with brain tumor, 57% with gliosis, 55% with cerebral atrophy, and 54% with cortical dysplasia. Patients with mesial temporal sclerosis were the most intractable. There was no difference in seizure-free rate between patients with symptomatic partial epilepsy and those with cryptogenic partial epilepsy[2]. In patients with Lennox-Gastaut syndrome (mean age 28.6 years) observed for an average of 16 years, seizures were controlled in only 5% of the patients[3].

Among 780 adolescent and adult patients newly diagnosed with epilepsy and followed long-term after treatment initiation (2–22 years, median 6.1 years), 318 (41%) patients did not achieve seizure control at least for the last 12 months of follow-up. These patients frequently had (1) symptomatic or cryptogenic epilepsy; (2) more than 10 seizures before treatment initiation; (3) a family history of epilepsy, previous febrile convulsion, and traumatic brain injury; (4) nonadherence or irregular use of antiepileptic drugs; and (5) prior or current psychiatric comorbidity (especially depression)[4]. The presence of these factors may predict a high possibility of drug-resistant epilepsy.

Some autoimmune encephalitis-related epilepsies such as autoimmune limbic encephalitis and anti-NMDA receptor encephalitis are highly drug-resistant and require immunotherapy[5]. Furthermore, although not an epilepsy, psychogenic nonepileptic seizure is also highly drug resistant and is difficult to diagnose and treat.

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CQ 5-3

What are the drug-resistant epilepsies in children?

Summary

Drug-resistant epilepsies in children include epileptic encephalopathies with infant and early childhood onset, such as West syndrome; cerebral dysplasia; chromosomal abnormalities such as 4p minus syndrome; neurocutaneous syndromes including tuberous sclerosis; post-encephalitis/encephalopathy; post-hypoxic ischemic encephalopathies such as severe neonatal asphyxia; epilepsy associated with cerebral degenerative/metabolic disorders; and autoimmune encephalitis-related epilepsy.

Comment

1. Causes of drug resistance

In one 2-year follow-up study of 381 children with newly diagnosed epilepsy, 75 patients (19.7%) were found to have drug-resistant epilepsy. Neuroimaging abnormalities, some abnormalities found in clinical neurological examination, and focal seizures were associated with drug resistance. Despite treatment of these patients with appropriate drugs for an average of 11.7 years, 49% remained drug resistant, and the resistance was mostly associated with neuroimaging abnormalities[1]. In another study, among 459 patients with childhood epilepsy treated for 2–14 years (mean 7.5 years), 87 patients (19%) were drug resistant. The factors associated with the drug resistance were age younger than 4 years, developmental delay or motor deficit, brain structural abnormality, and specific epileptic syndromes[2].

2. Relation of drug resistance with epilepsy syndromes or underlying diseases[3]

In children, there are drug-resistant epilepsies specific to age of onset[4, 5]. Infantile epileptic encephalopathies (including early-stage myoclonic encephalopathy, Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, West syndrome, and Dravet syndrome) and early childhood onset epileptic encephalopathies (Lennox-Gastaut syndrome, myoclonic encephalopathy in non-progressive diseases, and myoclonic absence seizure) are extremely drug resistant. In these epilepsies, seizure control is almost impossible except for West syndrome, in which seizures could be controlled in approximately 50% of the cases.

As in adults, seizures caused by localized cortical dysplasia in children are drug resistant, but some childhood-specific epilepsies such as epilepsies associated with unilateral megalencephaly, lissencephaly, and holoprosencephaly are markedly severe and seizures cannot be controlled by antiepileptic drugs.

Among chromosomal abnormalities, seizures associated with ring chromosome 20 syndrome are intractable, and seizures associated with 4p minus syndrome (Wolf-Hirschhorn syndrome) are also highly drug resistant.

Among neurocutaneous syndromes, seizures associated with Sturge-Weber syndrome and linear nevus syndrome are not controlled by drugs. Tuberous sclerosis is accompanied by epileptic seizures at a very high rate (approximately 85%), and most cases are West syndrome. West syndrome caused by tuberous sclerosis responds well to vigabatrin, but rarely responds to other antiepileptic drugs.

Epileptic seizures associated with destructive lesions in the brain caused by hypoxic ischemic encephalopathies such as encephalitis/encephalopathy, meningitis, and severe neonate asphyxia; as well as seizures associated with neurodegenerations in the brain such as metabolic neurological diseases and neurodegenerative diseases (including DRPLA, Krabbe disease, neuronal ceroid lipofuscinosis, and GLUT-1 deficiency) are drug resistant, and seizures related to autoimmune encephalitis are also drug resistant in children.

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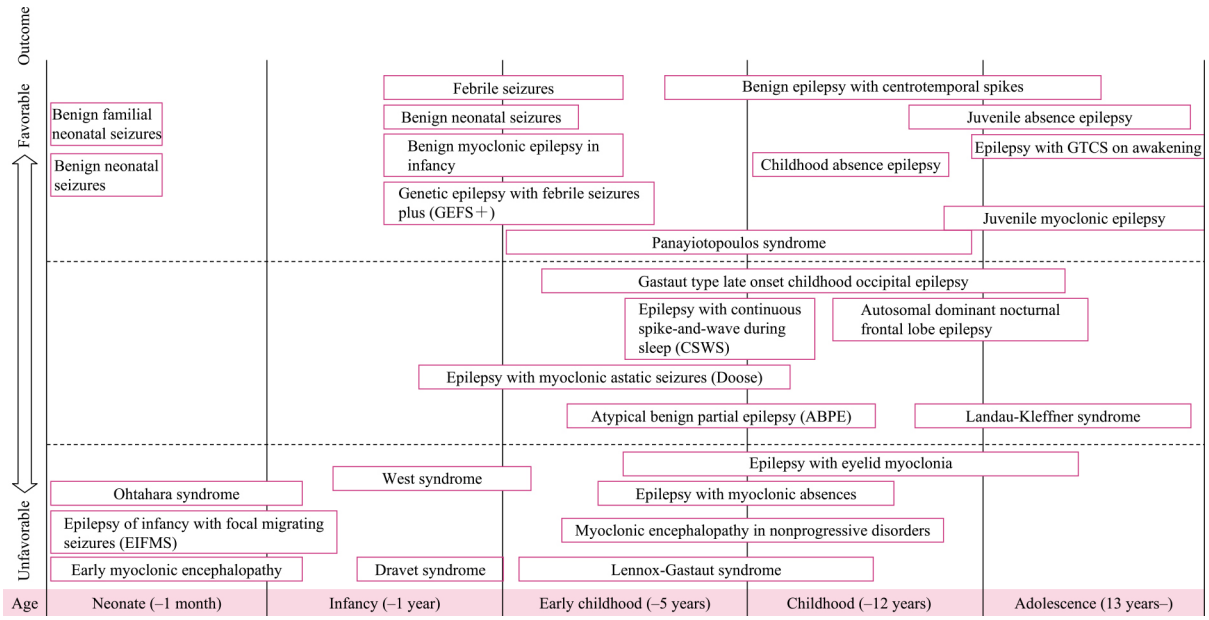

Figure 1. Ages of children and specific epilepsy syndromes.
(Modified from: Bureau M, Genton P, Dravet C, et al. eds. Epileptic syndromes in infancy, childhood and adolescence. Montrouge: John Libbey Eurotext, 2012./ Duchowny M, Cross JH, Arzimanoglou A eds. Pediatric Epilepsy. New York, McGraw Hill, 2013.)

CQ 5-4

What is pseudo-drug-resistant epilepsy?

Summary

Pseudo-drug-resistant epilepsy arises when appropriate antiepileptic drugs are not used at adequate doses, which may be due to misdiagnosis of the epilepsy or seizure type, wrong choice of antiepileptic drugs, wrong dosage, or poor adherence.

Comment

When epilepsy is found to be drug resistant, it may be truly drug resistant; that is, not responding to appropriately selected antiepileptic drugs at adequate doses, or it may be pseudo-resistant because appropriate drugs are not used at appropriate doses.

1. In the case of inappropriate choice of drugs

(1) The most common cause is misdiagnosis of non-epileptic seizures as epilepsy, such as psychogenic non-epileptic seizures (PNES), syncope, and arrhythmia. (2) Inappropriate drugs are selected due to wrong diagnosis of epilepsy syndrome or seizure type. (3) The antiepileptic drugs are inappropriate for the correct diagnosis of seizure type or epilepsy syndrome, such as using carbamazepine for myoclonic seizure leading to exacerbation[1].

In one study in which 1,590 patients underwent simultaneous EEG-video monitoring, 32.3% were found to have psychogenic seizures[2]. In another study, 46 (25%) of 184 patients treated for epilepsy did not have epilepsy, and 12 (13%) of 94 patients who were regarded as having intractable epilepsy did not have epilepsy[3].

2. In the case of drug resistance despite using appropriate drugs

The cause may be due to pharmacokinetics, such as (1) the blood concentration may be low because the dose is inadequate, or may not be much enough because not titrating the dose to the maximum tolerable level paying too much attention to the therapeutic range of blood concentration; (2) inappropriate multidrug therapy including a combination of drugs showing interactions (see **Table 1** of CQ 12-4 on page 109) that lower the blood concentration; and (3) occurrence of drug tolerance (including benzodiazepines and acetazolamide).

3. In the case of drug resistance despite prescription of appropriate antiepileptic drugs at adequate doses

The causes may include (1) poor adherence due to a lack of understanding and motivation of epilepsy treatment by the patient or the family, or excessive anxiety over antiepileptic drugs; (2) induction of seizures by alcohol or drug abuse, and poor adherence; (3) inappropriate time of drug taking or irregular time of drug taking due to irregular life rhythm such as night shift; and (4) lifestyle problem such as shift work causing disturbed circadian rhythm, sleep deprivation, and fatigue[1].

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CQ 5-5

How to manage drug-resistant epilepsies?

Summary

The first step to manage drug-resistant epilepsy is finding the cause. After reviewing the seizure symptoms, epilepsy diagnosis and etiology of epilepsy, assess whether the case is truly drug resistant or pseudo-resistant. In the case of pseudo-resistance, remove the causative factors (see CQ 5-4 on page 50). In the case of true resistance, review the drug therapy (diagnosis, choice of drugs, dose, use of antiepileptic drugs based on pharmacokinetics, rational use of multidrug combinations, etc.) and consider other treatment options such as surgery and immunotherapy.

Comment

1. Are the choices of drug and dose appropriate?

Confirm the seizure symptoms, medical history, situations when seizures occur, interictal EEG (sleep EEG essential), and brain MRI. Examine the underlying disease (family history, past history, present illness, general physical findings, and neurological findings). Based on the above, determine whether the case is truly epilepsy or not, and diagnose the seizure type and epilepsy syndrome, and investigate the etiology of epilepsy. Next, examine the type of antiepileptic drug and dose, and blood concentration. Interview, gesture mimicking seizure symptoms, and video recording by family members are useful to confirm seizure symptoms.

2. Identification of pseudo-drug resistance and management

a. Differentiation between epilepsy and confounding seizure symptoms (see CQ1-4 on page 10, and CQ1-5 on page 11)

Confirmation of seizure symptoms (from home video if possible), interview (especially the situation of seizure occurrence), interictal sleep EEG, and video-EEG monitoring are useful.

b. Review diagnosis of epilepsy, epilepsy syndrome and related seizure disorders, as well as seizure type

The procedures are similar to those described above (a). Juvenile myoclonic epilepsy is sometimes misdiagnosed as partial epilepsy and treated with carbamazepine or phenytoin, which may exacerbate the seizures[1].

c. Review the choice of drug and the dose

Examine whether the drug is appropriate for the epilepsy syndrome and seizure type (see **Table 1** in CQ4-6 on page 42 and **Table 1** in Chapter 6 on page 54), whether the drug is used sufficiently (dose and blood concentration), and whether tolerance occurs. In the case of multidrug therapy, examine whether each drug is appropriate for the seizure type, whether there is drug interaction that lowers blood concentration, and whether drugs with the same mechanism of action are used in combination.

From the above information, switch to the appropriate drug, up-titrate until the maximum tolerated dose with blood concentration exceeding the therapeutic range, and confirm the effect. Conduct rational multidrug therapy by selecting drugs appropriate for each seizure type, increase or decrease the doses considering drug interactions, and use drugs with different mechanisms of action in the combination.

d. When poor adherence is suspected

Confirm the situation of drug taking (time of drug taking, missed doses), lifestyle and rhythm, as well as time and situation at which seizures often occur. Monitoring blood concentration is useful for detecting habitual poor adherence.

To prevent lowered adherence, explain to the patient and the family about the following: (1) the nature of epilepsy from the viewpoint of epilepsy syndrome and the prognosis, (2) the necessity of treatment, (3) caution in daily life, and (4) properties of the drugs being taken (half-life, interaction with other drugs or foods, possible adverse effects and their frequency and severity). Also, adjust the time of drug taking considering the patient's lifestyle such as night shift.

3. True drug-resistant epilepsy

(1) If MRI detects an intracranial lesion, evaluate for epilepsy surgery soon.

(2) Select first-line or second-line drug that is deemed appropriate, and increase the dose up to the maximum tolerated dose. As long as adverse effects are not induced, up-titrate to blood concentrations exceeding the therapeutic range. When adverse effect appears, reduce the dose.

Despite the above procedures, if seizures remain uncontrolled, conduct rational multidrug therapy considering interactions of antiepileptic drugs (see **Table 1** of CQ12-4 on page 109) and the mechanisms of action. Add a drug that has different mechanism of action from the drug currently being used or a drug with multiple mechanisms of actions[2]. An effective combination is to use a Na^+ channel blocker and a GABAergic inhibition enhancer. Although the therapeutic effect is increased by combining two drugs that both enhance GABAergic inhibition, or combining two glutamate receptor inhibitors (such as AMPA antagonist and NMDA antagonist), tolerability is often reduced. Combination of two Na^+ channel blockers not only has limited effectiveness, but also causes adverse effects such as exacerbating dizziness[3].

(3) Consider referral to or consultation with epilepsy specialists, measurement of autoimmune antibodies, and immunotherapies (including intravenous immunoglobulin, steroids, and immunosuppressants), and consider surgical indication even though MRI shows no intracranial lesions.

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CQ 5-6

What are the intellectual prognosis and social prognosis of drug-resistant epilepsy?

Summary

Both intellectual and social prognoses are poorer than people without epilepsy, and there are major disadvantages in academic, employment, and marriage aspects. These two outcomes are especially poor when seizures are not controlled. The rate of sudden death is also higher among people with epilepsy than the general population.

Comment

1. Socioeconomic situation

For people with drug-resistant epilepsy, even when they have no intellectual problems and are in general employment, their work contents are sometimes restricted. In addition, if seizure occurs at work, they often lose their jobs. They also often have difficulty in marriage. In the United States, the total household annual income of people with epilepsy is 93% of the average annual income of the whole population, their unemployment rate is 25%, the high school graduation rate of those aged 25 years and above is 64% (82% in the United States in general), and the marriage rate of those aged 19 years and above is 51% for men and 48% for women (63% and 59%, respectively, in the United States in general)[1]. This data is for all epilepsies including treatable epilepsies, and these figures would be even worse in people with drug-resistant epilepsy.

2. Intellectual prognosis

In a study of 136 adults with various epilepsies who had uncontrolled seizures, WAIS-R was performed twice with an interval of 10 years or longer. The mean verbal IQ decreased from 90.3 to 82.3, performance IQ decreased from 91.0 to 84.5, and full scale IQ decreased from 91.0 to 84.5, and the frequency of generalized tonic-clonic seizure was most strongly related to the cognitive decline[2].

3. Social prognosis

Among 102 patients (mean age 28.6, range 15–60 years) with Lennox-Gastaut syndrome followed long-term for 10–20 (mean 16.3) years, 12 patients worked normally, 36 worked part-time or at a sheltered workshop, and the remaining 54 were under home care or institutionalization[3]. Most of the 12 patients in normal employment were seizure-free for at least 1 year or had only tonic seizures during sleep.

Ninety-nine patients with uncomplicated childhood epilepsy (onset age younger than 16 years) followed for 27–31 years were compared with controls matched for sex, age, and birthplace. The relative risk of completing primary education only was 2.1-fold, not married was 3.5-fold, no children was 3.0-fold, and unemployed was 3.8-fold[4].

4. Sudden unexpected death in epilepsy (SUDEP)

SUDEP refers to death for which no cause can be found besides suffering from epilepsy.

Patients with epilepsy have high mortality rate and high SUDEP rate. The standardized mortality rate for SUDEP was 24-fold compared to the general population, accounting for 2–17% of all-cause deaths in epilepsy patients[5].

The mortality rate of 2,689 patients with chronic epilepsy who had been followed for 20 years was 2.05 times the mortality rate of the general population in Scotland matched for sex and age[6]. The incidence of SUDEP per 1,000 person-years was 0.35–1.5 cases in a population-based incidence cohort of epilepsy, but increased to 1.2–3.8 cases in persons with chronic epilepsy and further to 3.5–9.3 cases in persons with intractable epilepsy. Seizure frequency is the strongest risk factor for SUDEP, and other risk factors are onset at an early age and long duration of disease[7]. The risk of SUDEP increases if generalized tonic-clonic seizures are not controlled.

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