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Review article

Guidelines for the diagnosis and treatment of acute encephalopathy in childhood

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Abstract

The cardinal symptom of acute encephalopathy is impairment of consciousness of acute onset during the course of an infectious disease, with duration and severity meeting defined criteria. Acute encephalopathy consists of multiple syndromes such as acute necrotizing encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion and clinically mild encephalitis/encephalopathy with reversible splenial lesion. Among these syndromes, there are both similarities and differences. In 2016, the Japanese Society of Child Neurology published 'Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood', which made recommendations and comments on the general aspects of acute encephalopathy in the first half, and on individual syndromes in the latter half. Since the guidelines were written in Japanese, this review article describes extracts from the recommendations and comments in English, in order to introduce the essence of the guidelines to international clinicians and researchers.

Keywords: Coma; Status epilepticus; Brain edema; Metabolic disorder; Cytokine storm; Excitotoxicity; Neuroimaging; Intensive care; Targeted temperature management

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1. Introduction

1.1. Background

Acute encephalopathy (AE) denotes syndromes characterized by acute onset of severe and long-lasting disturbance of consciousness, which typically occur in previously healthy children. AE is the most severe complication of common infectious diseases, such as influenza and exanthem subitum, often leading to death or severe neurological disabilities [1].

To date, many syndromes of AE have been described. Among them, Reye syndrome was originally reported in Australia [2], and hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome [3] and hemorrhagic shock and encephalopathy syndrome (HSES) [4] in Europe. During 1993–2006, child neurologists in Japan established and characterized many new syndromes, including acute necrotizing encephalopathy (ANE) [5], acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [6] and clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) [7], and achieved a general consensus upon the syndromic classification of AE by around 2007 [1]. Based on this classification, a nationwide epidemiologic study of AE was conducted in 2010, and the results were published in 2012 [8]. The time was ripe for the compilation of new guidelines.

1.2. Purpose

We aimed to provide clinicians treating acute neurologic disorders of children, such as seizures and impairment of consciousness, with guidelines that are useful for the acute stage management of AE.

Since AE is rare and many of the syndromes were recently characterized, there is only limited information about the diagnosis and treatment. On the other hand, most children with AE are critically ill, requiring prompt and intensive care; thus, there is a great need for guidelines. Until 2013, the only guidelines available for AE had been consensus guidelines specifically targeting influenza-associated AE, published in 2005 and revised in 2009 [9]. Therefore, our purpose was to publish new, evidence-based guidelines targeting AE associated with any pathogen and classified into any syndrome [10].

1.3. Formulation

In September 2013, the Japanese Society of Child Neurology (JSCN) decided to establish clinical practice guidelines for AE, and formed a working group (WG) of ten members and two advisors. From March 2014 to August 2016, the WG formulated guidelines using the methodologies recommended by the Medical Information Network Distribution System (*Minds*) with minor modifications. Briefly, clinical questions (CQs) were selected, and the system of literature search was determined. Documents in English were retrieved from the PubMed database and those in Japanese from the *Ichushi*-web were provided by the Japan Medical Abstracts Society. For each CQ, two WG members systematically reviewed the literature, and evaluated the levels of evidence. One of the two members wrote the drafts of recommendations and comments, and then the other reviewed them. For some CQs, additional specialists outside of the WG were invited to critically review the draft: a specialist of electroencephalography (EEG) for CQ 2–4, and intensivists from the Japanese Society of Intensive Care Medicine for CQs 3–2 and 3–3. At the WG meeting, the levels of recommendations (Table 1) were decided and the guidelines were further edited. In February 2016, the WG solicited public comments on the website from the other JSCN members and also asked the following organizations to review the drafts: Japanese Pediatric Society, Japanese Society for Pediatric Infectious Diseases, Japanese Society of Emergency Pediatrics and *Chiisana-inochi* (an association of families of children with influenza encephalopathy). After revision of the drafts based on the opinions and comments from members and organizations, the guidelines were published in August 2016 [10]. The guidelines were uploaded on the *Minds* homepage in February 2017.

1.4. Contents and flow chart

The guidelines consist of seven chapters, each of them including two to four CQs. The first half (three chapters) of the guidelines, corresponding to Sections 2.1–2.3 in this article, describes the general aspects of AE such as epidemiology and initial management. The second half (four chapters), corresponding to Sections 2.4–2.7, explains the diagnosis and treatment of individual syndromes. In other words, the first and second half deals with the similarities and differences, respectively, among syndromes [10].

Classification into any of the known syndromes may be difficult in some cases, in particular immediately after onset. In other cases, syndromic diagnosis may not be made at all. To facilitate the use of the guidelines in such cases, we illustrated their structure with a flow chart indicating the relevant CQs according to the patient's clinical findings [10] (Fig. 1).

2. Extract of guidelines

2.1. Entity and epidemiology

2.1.1. (CQ1-1) definition of AE

Recommendations:

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Table 1
Grading of recommendations.

Grade	Evidence and recommendation
A	There is good evidence to recommend the clinical action.
B	There is fair evidence to recommend the clinical action.
C1*	There is insufficient data to make a recommendation; however, consideration for the clinical action is acceptable.
C2*	There is insufficient data to make a recommendation; however, consideration against the clinical action is acceptable.
D	There is evidence to recommend against the clinical action.

*Given the low quality of evidence currently available, recommendations of Grade C were expected for most of the clinical questions (CQs). Therefore, we divided Grade C into two sub-grades: C1 and C2.

(1) AE is defined as impairment of consciousness of acute onset, with severity of Japan Coma Scale ≥20 or Glasgow Coma Scale (GCS) <11, and with duration of 24 h or longer [10]. (Grading not applicable)
   1) The onset usually occurs during the course of infectious diseases.
   2) Brain edema is often visualized by cranial computed tomography (CT) or magnetic resonance imaging (MRI).
   3) Distinction is made from other diseases, such as encephalitis and meningitis, and from other causes of decreased consciousness such as sleep, adverse effects of anticonvulsants, anesthetics and other drugs, and psychogenic seizures.

Comments:

AE is pathologically defined as brain dysfunction due to widespread, non-inflammatory brain edema. The clinical picture is dominated by acute disturbance of consciousness, which complicates common infections. AE may occur in any age groups, but is most frequent in infants and preschool children, during the febrile period of an acute infectious disease. The pathogens are viruses in most cases, and are *Mycoplasma* or bacteria in occasional cases [1]. The cardinal symptom is severe and long-lasting impairment of consciousness, often accompanied by convulsions or seizures. Signs of increased intracranial pressure may also be noted.

The pathologic substrate of AE is non-inflammatory brain edema, diffuse or widespread in distribution, and vascular or cellular in nature [1]. Neuroimaging techniques, such as cranial CT and MRI, are robust tools to visualize brain edema. In particular, MRI diffusion-weighted imaging (DWI) is not only sensitive but also capable of distinguishing vascular and cellular edema based on the apparent diffusion coefficient.

AE is a heterogenous condition consisting of many syndromes (Table 2).

2.1.2. (CQ1-2) epidemiology of AE

Recommendations:

(1) The annual incidence of AE in Japan is estimated to be 400–700 cases [8]. (Grading not applicable)
   1) The most common pathogen is influenza virus, followed by human herpesvirus 6 (HHV-6), rotavirus and respiratory syncytial virus (RSV).
   2) The most common syndrome is AESD, followed by MERS and ANE.
   3) Influenza virus is the most common pathogen for MERS and ANE.
   4) HHV-6 is the most common pathogen for AESD.

Comments:

In 2010, the research committee supported by the Japanese government conducted a nationwide survey of AE in Japan [8]. To date, this has been the only country-based study that specifically focused on the epidemiology of AE. Using a questionnaire, this survey collected clinical data of AE cases with onset occurring between April 2007 and June 2010. Based on the total number of cases reported (983) and the response rate (51%), the annual incidence of 400–700 cases was estimated. The common pathogens of preceding infection were influenza virus (27% of total cases), HHV-6 (17%), rotavirus (4%) and RSV (2%). Bacteria and *Mycoplasma* accounted for 2% and 1%, respectively. The common syndromes were AESD (29%), MERS (16%), ANE (4%) and HSES (1%).

2.1.3. (CQ1-3) prognosis of AE

Recommendations:

(1) The fatality of overall AE in Japan is 6% and neurologic sequelae in 36%. Prognosis varies among syndromes [8]. (Grading not applicable)
   1) In AESD, deaths are rare whereas neurologic sequelae are common.
   2) In ANE and HSES, both deaths and neurologic sequelae are common.

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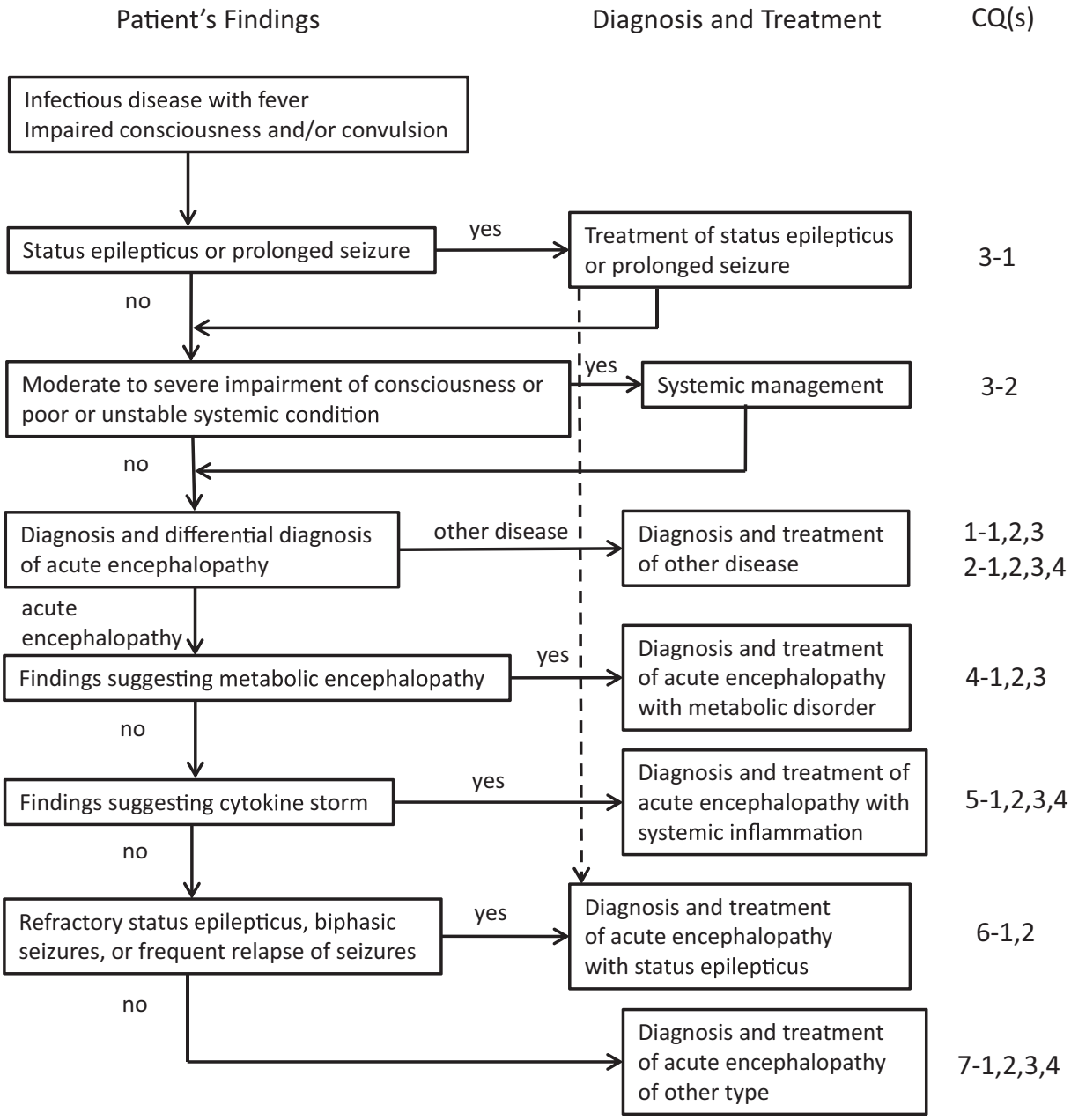

Fig. 1. Flow chart of the diagnosis and treatment of acute encephalopathy (AE).

3) In MERS, most cases recover without any sequelae.

Comments:

According to the Japanese epidemiologic study in 2010 [8], the outcome of overall AE was as follows: recovery in 56% of cases, mild to moderate sequelae in 22%, severe sequelae in 14% and death in 6%. Prognosis varied markedly among the syndromes and pathogens (Table 3). Prognosis appears to have improved recently, whereby fatality from influenza encephalopathy reportedly declined from 30% (1995–1999) to 7–8% (2005) [11].

2.2. Diagnosis and examinations

2.2.1. (CQ2-1) Physical, laboratory and radiologic examinations required for the diagnosis of AE

Recommendations:

Table 2
Classification of acute encephalopathy (AE).

A. Classification based on the pathogen of antecedent infection (microbiologic classification)
1. AE associated with viral infections
Influenza encephalopathy
Exanthem subitum (human herpesvirus [HHV]-6/7) encephalopathy
Rotavirus encephalopathy
Chickenpox (varicella-zoster virus) encephalopathy
Measles encephalopathy
Respiratory syncytial virus (RSV) encephalopathy
Other viral encephalopathy
2. AE associated with bacterial and other infections
Pertussis encephalopathy
Salmonella encephalopathy
Enterohemorrhagic *Escherichia coli* (EHEC) encephalopathy
Cat scratch fever encephalopathy
Mycoplasma encephalopathy
Other bacterial encephalopathy
3. AE associated with infection of unknown pathogen
B. Classification based on the clinicopathologic features of encephalopathy (syndromic classification)
1. AE caused by metabolic disorder
Classical Reye syndrome
Congenital metabolic disorders
2. Encephalopathy caused by cytokine storm
Acute necrotizing encephalopathy (ANE)
Hemorrhagic shock and encephalopathy syndrome (HSES)
Other cytokine storm encephalopathy
3. Encephalopathy with convulsive status epilepticus (CSE) (possibly due to excitotoxic brain damage)
Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)
Acute infantile encephalopathy predominantly affecting the frontal lobes
Hemiconvulsion-hemiplegia (HH) syndrome/Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome
Other AESD
Febrile infection-related epilepsy syndrome (FIRES)/Acute encephalitis with refractory, repetitive partial seizures (AERRPS)
4. Miscellaneous syndromes
Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)
AE associated with Dravet syndrome
AE associated with congenital adrenal hyperplasia
Other/Unclassified encephalopathy

Table 3
Epidemiology of acute encephalopathy (AE) in relation to pathogens and syndromes.

A. Comparison of two major pathogens

Pathogen	Influenza virus	HHV-6
Percentage in total cases	27%	17%
Sex (male/female)	58%/42%	43%/57%
Age (mean ± SD, median) (y)	6.3 ± 3.4, 6	0.8 ± 1.1, 1
Syndromes	MERS (20%), AESD (10%), ANE (6%)	AESD (64%), ANE (5%), MERS (2%)
Outcome	Recovery (76%), Sequelae (16%), Death (7%)	Recovery (50%), Sequelae (45%), Death (2%)

B. Comparison of three major syndromes

Syndrome	AESD	MERS	ANE
Percentage in total cases	29%	16%	4%
Sex (male/female)	41%/59%	52%/45%	58%/42%
Age (mean±SD, median) (y)	1.7±2.1, 1	3.3±3.4, 2	5.6±3.7, 5
Pathogens	HHV-6 (38%), Influenza (10%), Rotavirus (2%), RSV (2%)	Influenza (34%), Rotavirus (12%), Mumps (4%), Bacteria (3%)	Influenza (41%), HHV-6 (20%)
Outcome	Recovery (29%), Sequelae (66%), Death (1%)	Recovery (90%), Sequelae (7%), Death (0%)	Recovery (13%), Sequelae (56%), Death (28%)

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(1) When AE is suspected, clinical findings, such as disturbance of consciousness and other neurologic abnormalities, should be evaluated. Cranial imaging, EEG and blood/urine examinations should also be performed. (Grade B)
(2) When diagnosis remains indefinite, evaluation and examination should be repeated after a certain time interval. (Grade C1)
1) In AESD and other syndromes, neurologic and laboratory abnormalities are often unrecognizable at onset and become apparent after several days.
2) When it is difficult to conduct laboratory examinations due to a lack of facilities and personnel, a medical institution should consider transfer of patients to another institution where examinations are feasible.
3) Aliquots of blood/urine specimens should be stored in a freezer to be used later for specific tests for differential diagnosis.

Comments:

The diagnosis of AE is based on the following criteria:

1) Impairment of consciousness, with severity of Japan Coma Scale $\geq$20 or Glasgow Coma Scale $<$11, and with duration of 24 h or longer. (See CQ1-1)
2) Brain edema visualized by cranial CT/MRI.

Immediately after the onset of AE, however, it is often necessary to make a syndromic diagnosis of AE in a rapid and tentative way, in order to start intensive care without delay. Previous studies have elucidated the usefulness and limitation of various clinical and laboratory findings in the initial stage of AE for the purpose of (1) differentiation of AE [12–17], especially AESD, from febrile seizures, or (2) prediction of the final neurologic outcome [17,18]. Findings reportedly useful in the early diagnosis of AE include the following:

1) Neurologic examination [15,19]: Prolonged or worsening neurologic symptoms such as impairment of consciousness and seizures.
2) Cranial CT/MRI: Cerebral edema.
3) EEG: Abnormal patterns such as diffuse, high-voltage slow wave, electrical storm and absence of spindle waves.
4) Blood/urine/cerebrospinal fluid (CSF) examinations [12–17,19–21]:

(a) General examination (in-hospital; data available within minutes or hours):

Increased serum aspartate aminotransferase (AST) (>90 or 150 IU/L), lactate dehydrogenase (LDH) and alanine aminotransferase (ALT); metabolic acidosis (for 2 h or longer); increased white blood cell count, blood glucose and serum creatinine; decreased platelet count; disseminated intravascular coagulation (DIC); increased CSF protein; proteinuria.

(b) Special examination (outsourced; data available days or weeks later):

Increased serum cytochrome *c* and soluble tumor necrosis factor-alpha; increased CSF tau protein, neuron-specific enolase, interleukin-6, glial fibrillary acidic protein and visinin-like protein 1; increased urine beta2-microglobulin/creatinine ratio.

Patients with suspected AE should be evaluated by these examinations immediately after arrival. If the definite diagnosis is not initially reached, then the patients should be evaluated again several hours or days later, depending on their individual condition.

2.2.2. (CQ2-2) Differential diagnosis of AE

Recommendations:

(1) AE should be differentiated from various conditions manifesting with acute impairment of consciousness during the course of infectious diseases, including intracranial infection (e.g. viral encephalitis and bacterial meningitis), autoimmune encephalitis, cerebrovascular diseases, traumatic, metabolic and toxic disorders and effects of organ failure. (Grading not applicable)
1) During the several days immediately after onset, it is often impossible to distinguish AESD from complex febrile seizures [6].
2) ANE and other syndromes associated with cytokine storm and multiple organ damage should be differentiated from systemic inflammatory response syndrome (SIRS) due to severe infection and heat stroke [5].
3) Reye syndrome should be differentiated from congenital metabolic disorders [1]. (See CQ4-2)

Comments:

Symptoms, such as fever, convulsion and impaired consciousness, are common to all AE syndromes. Making the diagnosis of AE therefore requires differentiation from various diseases showing a combination of these symptoms [9] (Table 4). The initial diagnostic workup is typically as follows:

a. Prompt physical and neurologic examination.
b. Emergency blood examination.
c. Cranial CT (or MRI).
d. CSF examination.

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Table 4
Differential diagnosis of acute encephalopathy (AE).

1. Encephalitis
   Herpes simplex virus 1/2
   HHV-6/7
   Varicella zoster virus
   Cytomegalovirus
   Measles virus
   Mumps virus
   Adenovirus 7
   Enteroviruses
   Japanese encephalitis virus
   West Nile virus
   Bacteria/Mycoplasma
   Parasites
2. Meningitis
   a. Purulent meningitis
   b. Tuberculous meningitis
   c. Fungal meningitis
   d. Viral meningitis
3. Brain abscess
4. Subdural abscess
5. Demyelination
   Acute disseminated encephalomyelitis
   Multiple sclerosis
6. Autoimmune disorders
   Systemic lupus erythematosus

Intracranial disorders

1. Intracranial hemorrhage
   a. Subdural hematoma
   b. Epidural hematoma
   c. Intracerebral hemorrhage
   d. Subarachnoid hemorrhage
   e. Shaken baby syndrome
2. Vascular diseases
   a. Cerebrovascular diseases
   b. Cerebral arterio-venous malformation
   c. Superior sagittal sinus syndrome
   d. Moyamoya disease
3. Brain tumors

Metabolic/Toxic disorders

1. Mitochondrial encephalo-myopathy
   Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
2. Vitamin deficiency
   Wernicke encephalopathy
3. Wilson disease
4. Diabetic ketoacidosis
5. Other metabolic disorders

Organ failure

1. Liver failure
2. Kidney failure
3. Respiratory failure
4. Heart failure

Others

1. Febrile seizures
2. Myocarditis/Arrhythmia
3. Heatstroke
4. Sudden infant death syndrome
5. Hypertensive encephalopathy
6. Sleep disorders
   Hypersomnia/Periodic somnolence
   Night terror/Sleepwalking
7. Other conditions causing hypersomnia
8. Side effects of drugs
   Anticonvulsants
   Sedatives/Anesthetics
   Psychotropic drugs
   Antihistamines
9. Psychogenic seizures

After confirming the absence of findings of imminent cerebral herniation, either neurologic (e.g. deep coma, abnormal posture, pupils, respiration and/or circulation) or radiologic (marked swelling of the entire brain or brainstem), spinal tap is performed to rule out intracranial infections such as herpes simplex virus encephalitis and bacterial meningitis.

4) Microbiological examination of blood, CSF, urine, stool and/or nasopharyngeal swab.

2.2.3. (CQ2-3) imaging diagnosis of AE

Recommendations:

(1) For the diagnosis of AE, cranial CT or MRI is recommended. (Grade B)
(2) Characteristic MRI findings constitute the diagnostic criteria for ANE (Grade B), AESD (Grade B) and MERS (Grade B).

Comments:

When AE is suspected, CT is usually used as the initial neuroimaging examination because it is available in most regional centers in Japan and the time required for imaging is short. The diagnosis of AE is made based on cranial CT findings [9,11] such as:

1) Diffuse low density areas involving the entire brain or entire cerebral cortex.
2) Unclear boundary between cerebral cortex and medulla.
3) Narrowing of the subarachnoid space on the cerebral surface and of the ventricles.
4) Focal low density areas: bilateral thalamus (ANE) and unilateral cerebral hemisphere (some cases of AESD).
5) Brainstem swelling: Narrowing of the surrounding cerebral cisterns.

CT may depict the characteristic lesions in all cases of ANE and some cases of AESD, but not in the cases of MERS.

MRI visualizes the cerebral lesions characteristic of each syndrome [6,7,22–27] (Table 5). DWI is important in the diagnosis of AESD and MERS. Apparent diffusion coefficient (ADC) is useful in evaluating the status of water in lesions. Cytotoxic and intra-myelin edema show low ADC and high signal on DWI, whereas vascu-

Table 5
Diagnosis of acute encephalopathy (AE) based on cranial MRI findings.

ANE
In addition to diffuse brain edema, there are bilateral symmetric, edematous/necrotic lesions in specific brain regions, including the thalamus. Thalamic lesions are oval in shape.
On days 1–2, the lesions show low T1, high T2 and decreased diffusion.
On day 3 and thereafter, the thalamic lesions show concentric appearance due to central T1 high lesion indicating hemorrhagic changes. Diffusion weighted imaging (DWI) shows increased diffusion (necrosis and perivascular hemorrhage) in the center of thalamic lesion, restricted diffusion (edema and loosening of neuropil) in the surrounding zone, and increased diffusion (extravasation of plasma) in the periphery.
From the second week, there is progressive cerebral atrophy, and shrinkage or disappearance of thalamic lesions.
AESD
On days 1–2, CT and MRI findings are normal.
Between 3 and 14 days, DWI shows high signals in the subcortical white matter (bright tree appearance) and/or the cortex. Regions around the central sulcus are often spared.
From two weeks, CT and MRI show residual lesions or atrophy of the frontal and/or parietal lesions. Single photon emission computed tomography (SPECT) shows hypoperfusion. Peri-central regions are again often spared.
MERS
At the acute period, the splenium of corpus callosum shows high signal on DWI. T1 and T2 signal changes are only mild. The lesion(s) may involve the entire corpus callosum, and bilateral cerebral white matter symmetrically.
Within 2 months, the lesion disappears completely. There is neither residual signal changes nor atrophy.

lar edema shows high ADC and iso- or low signal intensity on DWI.

2.2.4. (CQ2-4) electroencephalographic diagnosis of AE

Recommendations:

(1) EEG is recommended because it provides information useful for the diagnosis and treatment of AE. (Grade B)
(2) Both conventional and amplitude-integrated EEG (aEEG) are useful. It is recommended to conduct either according to availability in each institution. (Grade B)
(3) The majority of AE patients have EEG abnormalities, including generalized, unilateral and localized slowing of background activity. (Grade B)

Comments:

EEG is an irreplaceable examination for evaluating function of the cerebral cortex in real time. EEG recording has recently become digitalized, and currently is easily conducted bedside. Furthermore, the recent advent of aEEG has enabled long-time, continuous monitoring.

Previous EEG findings in AE have observed abnormalities in most patients [4,28–36]. Generalized and unilateral slowing of background activity reflects dysfunction of the cerebral hemisphere. Localized slowing is often occipital dominant, and should be interpreted with caution since similar findings are also seen in fever-induced, mild alteration of consciousness [37]. Low voltage background activity may suggest poor prognosis. All these findings may be noted immediately after febrile and epileptic seizures.

Periodic lateralized epileptiform discharges (PLEDs) have been reported in various disorders of acute encephalitis/encephalopathy [29,35,36]. Electrical storm denotes the intermittent appearance of spike-waves and rhythmic activities with waning and waxing, and has been described not only in HSES but also in febrile infection-related epilepsy syndrome (FIRES)/acute encephalitis with refractory, repetitive partial seizures (AERRPS) and other syndromes [33,38]. Frontal and occipital intermittent rhythmic delta activity (FIRDA/OIRDA) have been linked to acute encephalitis/encephalopathy, but their diagnostic significance in AE remains unclear [39,40].

Since no previous studies systematically evaluated the impact of EEG on the diagnostic accuracy and outcome, the significance of EEG is yet to be established. Future multicenter, collaborative studies should elucidate the role of EEG in the early diagnosis of AE, differentiation of AE and febrile stupor, recognition of latent or subclinical seizures, and the association between EEG findings and outcome.

Continuous, multi-channel video-EEG monitoring has recently been applied to comatose children in a pediatric intensive care unit (PICU) [41–45]. Continuous monitoring enables recognition of subclinical seizures in many children, and may provide useful information not only in head trauma and cerebrovascular diseases, but also in AE. On the other hand, continuous monitoring requires a large amount of medical and human resources, making its immediate introduction unrealistic in Japan.

aEEG is a long-time, continuous recording using 1–2 channels, and is widely used in neonates to monitor neonatal encephalopathy and seizures [46–48]. To date, several groups have studied its application to AE,

demonstrating its ability to effectively recognize non-convulsive status epilepticus (intermittent, latent seizures) in AESD and FIRES/AERRPS [38,49].

2.3. Systemic management and brain hypothermia/normothermia

2.3.1. (CQ3-1) management of convulsive status epilepticus (CSE) and prolonged convulsion

Recommendations:

(1) For the treatment of CSE and prolonged convulsion, an appropriate anticonvulsant should be chosen according to the duration of convulsion, under proper management of systemic condition (Grade A). Avoiding the administration of a more than necessary dose of anticonvulsants should be considered, since the assessment of consciousness level is important for the early diagnosis of AE (Grade C1).
(2) For non-intravenous treatment of prolonged convulsion, midazolam is administered by a buccal, intranasal or intramuscular route (Grade B). On patient's arrival at the hospital, rectal administration of diazepam suppository is not recommended (Grade C2).
(3) For intravenous treatment of prolonged convulsion and CSE, first-choice drugs, such as midazolam and diazepam (Grade B), and second-choice drugs, such as fosphenytoin, phenytoin, phenobarbital and levetiracetam (Grade B), are given by rapid intravenous injection. For refractory CSE, midazolam is administered by continuous infusion, and either thiopental or thiamylal is administered by rapid or continuous intravenous infusion.

Comments:

In the guidelines, CSE is defined as either convulsion with duration of 30 min or longer, or repetitive convulsions with an interictal impairment of consciousness for 30 min or longer [50–52]. Prolonged convulsion is defined as convulsion with duration of 5 min or longer [50,51]. Prolonged convulsions are less likely to cease spontaneously, and, without adequate treatment within 15 min, often last for more than 30 min [53]. When CSE continues after the administration of second-choice intravenous antiepileptic drugs (AEDs), the diagnosis of refractory CSE is made. Super-refractory CSE, which persists or recurs despite intensive treatment for 24 h, may cause severe complications and death [54].

Prolonged convulsions require rapid intervention with AEDs adequately selected according to the duration of seizures [55,56]. If an AED fails to stop the seizures, further administration of an excessive dose may cause adverse effects. Over-dosage may also occur when postictal twilight states with an abnormal posture (e.g. dystonia) and involuntary movements (e.g. tremor and chorea) are misinterpreted as recurrent convulsions.

After initial treatment of CSE, patients should be monitored for vital signs and the level of consciousness. AEDs may make it difficult to evaluate consciousness. Since prolonged impairment of consciousness is an essential criterion for early diagnosis of AE, it is not recommended to sedate patients unnecessarily by administration of excessive AEDs.

a. Treatment of prolonged convulsion without an intravenous infusion route [57–63].

On a patient's arrival at the emergency room, administer midazolam by buccal (0.5 mg/kg), intranasal (0.5 mg/kg) or intramuscular (0.1–0.35 mg/kg) route (maximum, 10 mg). Use midazolam 0.5% solution, not 0.1% solution.

b. Treatment of prolonged convulsion and CSE with an intravenous infusion route [64–75].
   1) First line: Use either midazolam or diazepam. If unsuccessful, proceed immediately to the second line.
      i) Midazolam 0.15 mg/kg iv, at a rate of 1 mg/min. If necessary, add 0.1–0.3 mg/kg/dose, but the total dose should not exceed 0.6 mg/kg.
      ii) Diazepam 0.3–0.5 mg/kg iv.
   2) Second line: Use either fosphenytoin, phenobarbital or levetiracetam.
      i) Fosphenytoin 22.5 mg/kg (rate not exceeding 3 mg/kg/min). For maintenance, administer fosphenytoin 5–7.5 mg/kg/day, either in a single or divided dose, at a rate not exceeding 1 mg/kg/min. Alternatively, administer phenytoin 15–20 mg/kg/dose at a rate not exceeding 1 mg/kg/min (maximum 250 mg/dose).
      ii) Phenobarbital 15–20 mg/kg iv, at a rate not exceeding 1 mg/kg/dose, for more than 10 min.
      iii) Levetiracetam 20–30 mg/kg iv (for more than 15 min).

c. Treatment of refractory CSE with an intravenous infusion route.
   i) Midazolam 0.1 mg/kg/hour initially, increasing at a rate of 0.05–0.1 mg/kg/hour, up to a maximum of 0.4 mg/kg/hour.

ii) Thiopental of thiamylal 3–5 mg/kg (maximum in adults, 200 mg) iv, followed by 3–5 mg/kg/hour div.

2.3.2. (CQ3-2) systemic management of AE

Recommendations

(1) For moderate to severe cases of AE, systemic condition should be maintained or improved by using appropriate monitoring devices and conducting supportive therapies. (Grade A)
   1) Initial resuscitation based on Pediatric Advanced Life Support (PALS) 2010.
   2) Transfer to tertiary (or equivalent) emergency medical facilities [76].
   3) Admission to PICUs, if necessary.
   4) Systemic management of respiration, circulation, central nervous system, blood sugar/electrolytes and nutrition.

Comments:

The management of respiration requires monitoring devices, including a pulse oximeter, $PaCO_2$ monitor and end-tidal CO_2 monitor. To avoid secondary brain damage due to aspiration or apnea, patients with impaired consciousness (GCS $\leq$8) should be intubated and mechanically ventilated. SaO_2 should be kept >94%. With monitoring of PaO_2, concentration of oxygen and condition of ventilator should be adequately determined. Except for the case of hyperventilation therapy for refractory increased intracranial pressure (ICP), $PaCO_2$ should be kept within normal range since low $PaCO_2$ decreases cerebral perfusion blood volume. Sedation is recommended for endotracheal intubation, and administration of analgesics/sedatives for mechanical ventilation.

The management of circulation requires monitoring devices, including an electrocardiograph (ECG), blood pressure monitor and pulse oximeter. If available, monitors for central venous pressure and central venous oxygen saturation are also used. Arterial systolic pressure should be kept above (70 + 2 × age) mmHg in children aged 1 to 10 years, and above 90 mmHg in those older than 10 years. In selected cases, cerebral perfusion pressure (CPP, mean arterial pressure minus ICP) is monitored. Adequate hydration, but neither undue water restriction nor diuretics, is recommended. ECG is useful in monitoring heart rate and detecting arrhythmia, and cardiac ultrasonography is useful in evaluating cardiac function and intracardiac blood volume. Blood examination provides useful data such as arterial and venous blood gas, hemoglobin, hematocrit, glucose, electrolytes, urea nitrogen, creatinine, calcium and lactate. Hypotension may be caused by administration of AEDs, sedatives and analgesics. For sustained shock, 0.9% saline or an extracellular type solution is infused. Standard volumes for maintenance infusion are [4 × body weight (BW in kg)] mL for children with BW <10 kg, [40 + 2 × (BW-10)] mL for those 10–20 kg, and (40 + BW) mL for those >20 kg.

The management of the central nervous system (CNS) requires serial observation of the level of consciousness (GCS) and brainstem reflexes such as light, corneal and oculocephalic reflexes. Continuous monitoring of EEG may also be useful. In cases of suspected increased ICP, ICP monitoring is recommended [77–81]. ICP should be maintained below 20 mmHg; CPP above 40 mmHg in infants and young children, and above 50 mmHg in schoolchildren [80–82]. Head may be lifted by 30°. Increased ICP may be treated by intravenous infusion of either 3% sodium chloride, 6.5–10 mL/kg [83–85], or D-mannitol, 0.5–1 g/kg [86]. Barbiturates are used for children with increased ICP after head trauma, and may be attempted in children with AE [80,87]. Hyperventilation therapy with ICP monitoring is used for intractable increased ICP [88]. Continuous EEG monitoring may be useful for deciding clinical management [43].

The management of blood electrolytes includes the treatment of hyponatremia, hypocalcemia and metabolic acidosis. Blood glucose should be kept at 100–150 mg/dL.

The management of body temperature requires monitoring by thermometers. As antipyretics, either acetaminophen, 10/mg/kg/dose every 4–6 h, or ibuprofen, 10/mg/kg/dose every 6–8 h, is used. In selected cases, brain hypothermia/normothermia is attempted.

The management of nutrition lacks evidence. Either enteral or parenteral feeding is considered to avoid malnutrition in critically ill children [89].

2.3.3. (CQ3-3) brain hypothermia/normothermia: Indication and methods

Recommendations:

(1) There is no clear evidence for the efficacy of brain hypothermia/normothermia in AE. (No grade)
(2) Optimal methods of brain hypothermia/normothermia for AE have not yet been established. (No grade)

Comments:

High-quality evidence for the efficacy and safety of brain hypothermia has been documented for acute, post-resuscitation brain injury of adults [90,91] but not children [92] with out-of-hospital cardiac arrest, and for hypoxic-ischemic encephalopathy of neonates with perinatal asphyxia [93–96]. In the treatment of these conditions, brain hypothermia is recommended as a standard therapy.

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On the other hand, in children with AE, evidence for the efficacy of brain hypothermia is limited to case reports or case series. Large-scale clinical studies have not been conducted. Since AE is a wide spectrum involving various pathogenetic mechanisms, treatment should be tailored according to the condition and severity in each patient. Therefore, brain hypothermia is not listed as a routine therapy for all cases of AE.

Brain hypothermia/normothermia has already been introduced in the treatment of AE by some PICUs. For brain hypothermia, however, no standard protocols or safety guidelines are available, except for the protocols in single institutions [97]. A variety of drugs are used concomitantly, and their effects have not been evaluated separately from those of brain hypothermia alone. Based on the findings of a study on adult post-resuscitation encephalopathy showing the non-inferiority of normothermia compared to hypothermia [98], some institutions are conducting clinical trials for AE, in particular AESD, of brain normothermia or targeted temperature management [99,100], whose efficacy remains to be established [101].

Given the possibility of secondary neuronal damage in the early stage of AE, either metabolic or anoxic/ischemic, the therapeutic time window is considered to be short. At present, little information is available on the therapeutic time window and adverse effects of brain hypothermia/normothermia.

2.4. AE caused by metabolic disorders

2.4.1. (CQ4-1) characteristics of metabolic encephalopathy

Recommendations:

(1) Triggered by various factors, AE often occurs in patients with inborn errors of metabolism. Metabolic encephalopathy encompasses multiple diseases, which commonly show the following features. (Grading not applicable)
   1) Absence of precursory episodes prior to the onset of AE.
   2) Mild respiratory disturbance.
   3) Rapid progresses and/or fluctuation.
   4) Absence of localized neurological signs.

(2) When AE is accompanied by the following symptoms, inborn errors of metabolism should be suspected, and diagnostic workup should be performed. (Grade B)
   1) Rapid deterioration of general condition following an infectious disease or fasting.
   2) Abnormal facial features/cutaneous findings; body/urine odor.
   3) Tachypnea associated with metabolic acidosis; breathing disorder.
   4) Growth failure; intellectual disability.
   5) Cardiomyopathy.
   6) Splenohepatomegaly; hepatomegaly without splenomegaly; splenomegaly without portal hypertension.
   7) Symptoms of multiple organs with obscure relationship.
   8) Abnormal imaging findings suggesting mitochondrial diseases.
   9) Family history of inborn errors of metabolism.

Comments:

AE may be induced by certain inborn errors of metabolism, such as hyperammonemia (urea cycle disorders), amino-acid metabolism disorders (maple syrup urine disease, ketotic hyperglycinemia), organic acid metabolism disorders, fatty acid oxidation disorders and mitochondrial electron transport chain disorders. These disorders often show clinical features as described above [(1), 1–4]. Children presenting with characteristic signs or symptoms [(2), 1–9] must be carefully examined considering the presence of underlying, inborn errors of metabolism [102,103].

Outlines of typical disorders that may cause encephalopathy are provided below.

a. Diseases associated with hyperammonemia

Typical inborn errors of metabolism with hyperammonemia are urea cycle disorders, organic acid disorders, fatty acid oxidation disorders and mitochondrial diseases. Of these, urea cycle disorders and organic acid disorders often show hyperammonemia above 1000 μg/dL.

b. Amino-acid disorders

Maple syrup urine disease (leucine encephalopathy) [104] is a disease for which newborn mass screening programs are offered in Japan. However, AE may develop in the neonatal period before obtaining the results.

In maple syrup urine disease, impaired branched chain keto acid dehydrogenase (BCKDH) activity leads to a disturbance in the metabolism of branched chain keto acids that are derived from the branched chain amino acids—valine, leucine and isoleucine. BCKDH is a complex of enzymes coded by four genes—E1α, E1β, E2 and E3, and a defect in any of them represents an autosomal recessive genetic disorder.

c. Fatty acid oxidation disorder

AE may be induced by defects of fatty acid oxidation, and is often manifested as Reye syndrome or Reye-like syndrome. A well-known example is medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, a defect

of an enzyme that metabolizes acyl CoA with a straight medium chain (4–10 carbon atoms) fatty acid. Children aged four years or younger, who have had no characteristic findings or medical history until an acute episode, start to develop AE or Reye-like syndrome following infection or famine. If MCAD deficiency is identified by newborn mass screening, the onset of AE may be prevented by dietary instruction to avoid starvation. Moreover, patients with long-chain fatty acid oxidation disorders, such as mitochondrial trifunctional protein (TFP) deficiency and carnitine palmitoyltransferase-2 (CPT2) deficiency, may also develop as Reye or Reye-like syndrome.

Thermosensitive *CPT2* morphisms have recently been implicated in AE. Some *CPT2* polymorphisms are thermolabile, losing their activity with a rise in body temperature by 3 to 4 °C. They are relatively common in infants in East Asia and are suspected to be a predisposing factor for AE.

d. Mitochondrial diseases [105–107]

AE caused by a mitochondrial disease is often diagnosed as Leigh syndrome, Reye-like syndrome or mitochondrial encephalomyopathy with stroke-like episodes (MELAS). Leigh syndrome has bilateral and symmetrical pathological lesions mainly in the brain stem, basal ganglia and cerebellum, showing spongiform degeneration, vacuolar degeneration, demyelination and gliosis. Brain CT reveals low density areas in the basal ganglia and brain stem, whereas MRI (T2/FLAIR) reveals bilateral and symmetric high intensity areas. MELAS is characterized by headache, epilepsy and stroke-like episodes. Stroke-like episodes often give rise to headache, nausea, visual disturbances and disturbance of consciousness. Moreover, brain lesions tend to occur in the temporal and occipital lobes, giving rise to visual disturbances such as homonymous hemianopia and cortical blindness. On brain CT/MRI during the acute phase, there are edematous lesions in the cerebral cortex that do not coincide with vascular territories.

2.4.2. (CQ4-2) screening for the diagnosis of inborn errors of metabolism

Recommendations:

(1) On the suspicion of metabolic encephalopathy, a first-line screening test, including blood sugar, blood gas, ammonia, lactic and pyruvic acids, serum/urinary ketone (Grade B) and free fatty acids (Grade C1), should be initially conducted.
(2) Based on the results, a second-line screening test should be conducted (Grade B). It is also important to obtain critical samples in the second-line screening test during the hospital visit. Second line screening test includes:
1) Serum or plasma: Amino acid analysis, carnitine two fractions (free/acyl) and acyl carnitine analysis (tandem mass analysis).
2) Urine: Urinary organic acid analysis and urinary amino acid analysis (as needed).
3) Dried blood spot: Acyl carnitine analysis (tandem mass analysis).

Comments:

a. General outline [102,103,108]

If an inborn error of metabolism is suspected for cases of AE, a first-line screening test should be performed. The targets of the first-line screening test are

Table 6
Critical samples for diagnosis of metabolic encephalopathy.

A. Storage of critical samples
i) Serum or plasma: cryopreservation at −20 °C or below, 0.5 mL or greater.
Blood amino acid analysis (possible also with serum)
Serum tandem mass analysis
Blood ketone body factions/free fatty acids
ii) Urine: cryopreservation at −20 °C or below, 0.5 mL at minimum, preferably 3–10 mL.
Urinary organic acid analysis
Urinary amino-acid analysis (as needed)
iii) Dried blood spots: at least 1 spot, preferably 4 spots. Dry well and cryopreserve at −20 °C or below.
Acyl carnitine analysis
iv) Cerebrospinal fluid (optional): cryopreservation at −20 °C or below, using several tubes, 0.5 mL each.
Measurement of lactic and pyruvic acids

B. Metabolic autopsy
The following items should be preserved at autopsy:
- Collection of 5 mL of heparinized blood/Cryopreservation of leukocyte pellets at −20 °C or lower.
Enzyme activity measurement
DNA extraction and preservation/Genetic diagnosis
- Cryopreservation of bile at −20 °C or lower.
Acyl carnitine analysis
- Skin biopsy/Culture of skin fibroblast (if possible)

blood sugar, blood gas, ammonia, lactic and pyruvic acids, blood/urinary ketone bodies and free fatty acids. The results should be obtained and evaluated as quickly as possible.

Based on the abnormal results of first-line screening, an inborn error of metabolism is suspected. A clinician should move on to the second-line screening test. In this step, critical samples must be obtained (Table 6). The second-line screening test includes amino acid analysis in the blood, urinary organic acid analysis and acyl carnitine analysis.

b. Urea cycle disorders [109–111]

An amino acid analysis must be promptly undertaken for urea cycle disorders. The results determine, to some extent, the diagnosis and treatment.

1) Amino acid analysis of the blood and urine: Abnormally high or low levels of specific amino acids.
2) Urinary organic acid analysis: Abnormally high urinary orotic acid levels.
3) Enzyme assay or gene analysis.
4) Genetic analysis.

c. Amino-acid metabolism disorders

1) Maple syrup urine disease (leucine encephalopathy) [112].

For diagnosis, it is of utmost importance to promptly conduct a serum amino acid analysis. This analysis demonstrates an increase in the levels of leucine, isoleucine and valine. The development of alloisoleucine is characteristic of this condition. Urinary organic acid analysis shows an increase in the levels of branched-chain α-keto acids and branched-chain α-hydroxyl acids with this condition. Enzyme activity of the BCKDH complex may be measured using extracts from cultured cells. Genetic analysis is not used for diagnostic purpose.

d. Fatty acid oxidation disorder [108,113]

The most notable characteristic of this condition in the first-line analysis is nonketotic or hypoketotic hypoglycemia. For the diagnosis of fatty acid metabolism disorders, serum acyl carnitine analysis is conducted using dried blood spot and serum specimens in the acute phase. Urinary organic acid analysis may show nonketotic or hypoketotic dicarboxylic aciduria in an episode of hypoglycemia. Enzyme activity may be assayed using cultured skin fibroblasts in some cases. Genetic analysis may also be performed.

e. Mitochondrial diseases [114–118]

A mitochondrial disease is comprehensively evaluated by clinical/imaging findings and by the following examinations. On biochemical tests, blood levels of lactic acid are high in many cases, but normal in others. Growth and differentiation factor 15 (GDF15) is a useful biomarker for mitochondrial myopathy. An analysis of enzyme activity of the respiratory chain should be carried out using affected organs and skin fibroblasts. Pathological studies of the skeletal muscle biopsies, cultured cells or cells/tissues of affected organs show abnormalities in the mitochondria. Genetic analysis may demonstrate abnormalities in either the nuclear or mitochondrial genes, the former being more frequent in children.

2.4.3. 2.4.3. (CQ4-3) Treatment for mitochondrial rescue

Recommendations:

(1) The efficacy of mitochondrial rescue has been documented in specific metabolic conditions, but not in AE without underlying metabolic disorders. Vitamin B_1, carnitine and other drugs may be used in cases of AE when the diagnosis of metabolic disorder is suspected but not yet established (Grade shown in Table 7).

Comments:

Mitochondrial rescue drugs may be used when laboratory examination at the onset of AE shows acidosis, lactic acidemia, hypoglycemia or hyperammonemia. To prescribe them continuously, a precise diagnosis of congenital metabolic disorder as the underlying condition of AE is needed.

Vitamin B_1, a coenzyme that activates pyruvate metabolism, TCA cycle and mitochondrial electron transport system, may be effective in AE complicating Leigh encephalopathy (in particular, cases caused by Vitamin B_1-responsive deficiency of pyruvate dehydrogenase complex) and other mitochondrial disorders. Supplementation of thiamine is essential in rare disorders of thiamine metabolism and transport [119–121] and in Wernicke encephalopathy [122], a condition due to vitamin B_1 deficiency that was recently reported in children

Table 7
Treatment for mitochondrial rescue.

Mitochondrial rescue drugs in Leigh syndrome, lactic acidemia and suspected mitochondrial disorders (Grade C1)
i) Active form of vitamin B_1 (fursultiamine)
ii) Levocarnitine
iii) Coenzyme Q
Other drugs for mitochondrial treatment (No grade)
iv) Vitamin B_2 (riboflavin)
v) Vitamin C, Vitamin E, Biotin
Treatment of MELAS (Grade B)
vi) L-arginine
Other drugs for metabolic disorders (No grade)
vii) Active form of vitamin B6 (pyridoxal phosphate)

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taking an excessive amount of ionic drinking water. As an efficacy in AE, a recent study suggested that a combination of vitamin B_1, B_6 and carnitine may reduce the risk of AESD [123].

Carnitine binds to long chain acyl CoA and transports it from the cytoplasm to the mitochondria. Carnitine deficiency suppresses mitochondrial beta oxidation and impairs energy metabolism. Primary carnitine deficiency is occasionally complicated by Reye-like syndrome. Secondary carnitine deficiency due to malnutrition, drugs (valproate sodium and pivalate-conjugated antibiotics) and acyl CoA dehydrogenase deficiency may cause AE. Supplementation of carnitine is efficacious in these conditions. CPT2 deficiency is also associated with the risk of AE and requires treatment with carnitine supplementation [124]. On the other hand, in other AE cases with a *CPT2* thermolabile polymorphism, there have been no reports demonstrating the efficacy of carnitine [125,126].

Coenzyme Q, an essential factor of electron transport system with an antioxidative effect, is a drug for treating mitochondrial disorders [127,128]. However, its efficacy in the nervous system remains unclear and its transition to the brain across the blood–brain barrier is minimal [129]. Thus, evidence for the use of coenzyme Q in AE is lacking.

Vitamin B_2 (riboflavin) is a component of electron transfer complex II. A case of riboflavin-dependent, transient neonatal-onset glutaric aciduria type II reportedly had encephalopathy with hypoglycemia, acidosis and hyperammonemia.

Arginine, an amino acid synthesized from citrulline that promotes ammonia excretion, is used to treat hyperammonemic encephalopathy in urea cycle disorders, and also used for the treatment and prevention of stroke-like episodes in MELAS [130,131].

Trials with other drugs, such as sodium pyruvate, EPI-743 [132] and taurine, are in progress.

2.5. AE caused by systemic inflammation

2.5.1. (CQ5-1) markers of inflammation

Recommendations:

(1) Direct and indirect indicators have been proposed. (Grading not applicable)
1) The diagnostic items of SIRS are indirect indicators.
2) The poor prognostic factors of influenza-associated encephalopathy are indirect indicators.
3) Various cytokines and related factors have been reported.

Note: A direct indicator is a marker of the intensity of inflammatory response, whereas an indirect indicator is a marker of the degree of tissue/organ damage caused by inflammation.

Comments:

AE associated with cytokine storm (hypercytokinemia) type often exhibits SIRS. SIRS, a so-called cytokine storm, is a systemic biological response due to overproduction of inflammatory cytokines elicited in response to trauma, infection and other factors. The diagnostic items of SIRS [133] (body temperature, pulse rate, respiration rate and white blood cell count) may be markers of indirect inflammation. However, there are no data for patients with AE. Ferritin is also an indicator of the severity of SIRS, as a marker of inflammation [134], but there are no data for AE patients.

In influenza-associated AE, previous studies have pointed out poor prognostic factors: Hb 14 g/dL or more, platelets less than 100,000/μL, AST/ALT 100 IU/L or more, CK 1000 IU/L or more, blood sugar less than 50 mg/dL or less than 150 mg/dL, prothrombin time (PT) less than 70%, ammonia 80 μg/dL or more, hematuria and proteinuria [135]. These are considered indirect markers of inflammation.

Cytokines and related factors are important for the pathogenesis of cytokine storm type of AE, and have been reported to predict poor prognosis. Among them, serum interleukin-6 [21,136], serum tumor necrosis factor-α (TNF-α) [21,137,138], serum soluble TNF receptor [21,137,138] and serum interlukin-10 [137,138] are considered to be biomarkers of inflammation.

2.5.2. (CQ5-2) corticosteroid therapy: significance, indication and methods

Recommendations:

(1) Corticosteroids are recommended for AE of cytokine storm type. (Grade C1)
1) Corticosteroids are expected to improve the prognosis of ANE.
2) Corticosteroids are also recommended in other cases of cytokine storm type.
3) Methylprednisolone pulse therapy is commonly conducted.

Comments:

For anti-inflammatory therapy in children with AE, corticosteroid preparations are recommended in terms of experience and safety. The use of corticosteroids within 24 h of onset improves prognosis of influenza-associated encephalopathy and ANE [139].

The best indication of corticosteroid is for the cytokine storm type of AE. It is recommended that corticosteroids are used aggressively in cases where the presence of inflammation is suggested by the aforementioned inflammatory markers, for instance, meeting the

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definition of SIRS. The presence of hypercytokinemia is also suggested when MRI shows ANE or diffuse brain edema. Among corticosteroids, methylprednisolone pulse therapy was described in the influenza-associated encephalopathy guidelines [9], and has been widely used. Methylprednisolone 30 mg/kg/day (maximum amount, 1 g/day) is injected intravenously over 2 h. In principle, it is administered for 3 days. Heparin 100 to 150 IU/kg/-day is administered with continuous infusion until the end of pulse therapy to prevent thrombus formation due to hypercoagulation. As mentioned above, it is necessary to perform corticosteroids treatment as early as possible.

2.5.3. (CQ5-3) immunoglobulin and blood purification: significance, indication and methods

Recommendations:

(1) Theoretically, immunoglobulin and blood purification are expected to be effective for AE of cytokine storm type where inflammation is involved in the pathogenesis. However, there is no evidence for their efficacy. (No grade)
1) Gamma globulin therapy, 1 to 2 g/kg is administered intravenously.
2) Blood purification should be performed in experienced hospitals.

Comments:

The immunoglobulin preparation exerts an anti-inflammatory action by suppressing activation of immunocompetent cells and suppressing inflammatory cytokine production. The mechanism of action still remains partly unclear [140,141]. It is theoretically reasonable to use immunoglobulin in AE where inflammation is involved in the pathology such as the cytokine storm type of AE. However, sufficient evidence has not been obtained to date [139]. The method of administration is intravenous drip infusion of immunoglobulin preparation (1 to 2 g/kg). The dosage will be adjusted appropriately according to the condition of each patient. In particular, as anaphylactic shock may occur at the beginning of treatment, the infusion rate should follow the instructions in the package insert. It is also necessary to carefully observe patients and to check vital signs.

Blood purification therapy aims to control inflammation by removing inflammatory substances such as cytokines in the blood [142,143]. As with immunoglobulin, it is theoretically considered to be of use for AE in which inflammation is involved in the pathological condition. However, sufficient evidence has not been obtained. Blood purification should be considered in patients with advanced inflammatory conditions that are considered to be difficult to control with corticosteroids and immunoglobulin, and should be performed at experienced facilities because the treatment is more invasive. The main methods of blood purification therapy are continuous hemodiafiltration (CHDF) and plasma exchange (PE). Against the overproduction of inflammatory cytokines, CHDF consisting of polymethyl methacrylate (PMMA) film is considered to be excellent in mediator removal [144]. PE uses a 5% albumin solution as a substitution solution. In patients with abnormal coagulation, fresh frozen plasma is used, and anticoagulation therapy is performed with heparin or nafamostat mesilate. The daily plasma exchange volume is set as circulating blood volume = body weight (kg) × 1000/13 × (1 − Ht (%)/100). PE is carried out with one course of 3 days for total plasma replacement.

2.5.4. (CQ 5–4) diagnosis and treatment of ANE

Recommendations:

(1) The diagnosis of ANE is based on a combination of clinical symptoms, laboratory findings and neuroimaging findings. Although bilateral sympathetic thalamic lesions are characteristic, it is necessary to distinguish ANE from several diseases presenting similar imaging findings. (Grade B for neuroimaging)
(2) Early steroid pulse therapy is recommended for ANE (Grade B). The efficacy of intravenous immunoglobulin or hypothermia/target body temperature has not been established. (Grading not applicable)

Table 8
Diagnostic criteria of acute necrotizing encephalopathy (ANE).

1. Acute encephalopathy related to a febrile viral infection: rapid reduction of consciousness and seizures.
2. Cerebrospinal fluid examination shows normal cell counts and increased protein concentration.
3. Symmetrical and multiple brain lesions on head CT and/or MRI. Bilateral thalamic lesions are always observed. Lesions are often found also in periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellum. No lesions in the other areas.
4. Elevated serum transaminase levels with no elevation in serum ammonia levels.
5. Exclusion of other diseases:

A. Differential diagnosis from a clinical view: Severe bacterial and viral infections, fulminant hepatitis, toxic shock, hemolytic uremic syndrome, Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.

B. Differential diagnosis from a neuroimaging and neuropathological view: Mitochondrial disorders such as Leigh encephalopathy, glutaric acidemia, methylmalonic acidemia, infantile bilateral striatal necrosis, Wernicke encephalopathy, carbon monoxide poisoning, acute diffuse encephalomyelitis, acute hemorrhagic leukoencephalopathy, angiitis, arterial and venous infarction, hypoxia and traumatic head injury.

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Comments:

ANE was proposed by Mizuguchi et al. in 1995 [5]. Its diagnosis is made comprehensively by combining clinical symptoms, laboratory findings and neuroimaging findings (Table 8). The most frequent trigger of ANE is influenza followed by HHV-6 infection [8]. Familial or recurrent ANE related to *RANBP2* mutations has been reported in Europe and the United States [145].

Bilateral symmetric thalamic lesions are important in the diagnosis of ANE. During the acute period, thalamic lesions show low densities on CT, low intensities on T1-weighted images and high intensities on T2-weighted images on MRI (Fig. 2). During the subacute period, thalamic lesions may show concentric appearance [146,147]. It should be noted that acute encephalitis/encephalopathy other than ANE, such as acute disseminated encephalomyelitis (ADEM) and AESD, may also demonstrate thalamic lesions [148,149]. Other than the thalamus, brain lesions may be present in the cerebral and/or cerebellar white matter, midbrain, and pons. White matter lesions are generally localized around the thalamus and in the deep white matter, and do not exhibit a bright tree appearance [6].

Coma and seizures are very frequent symptoms of ANE, and vomiting and diarrhea are also common

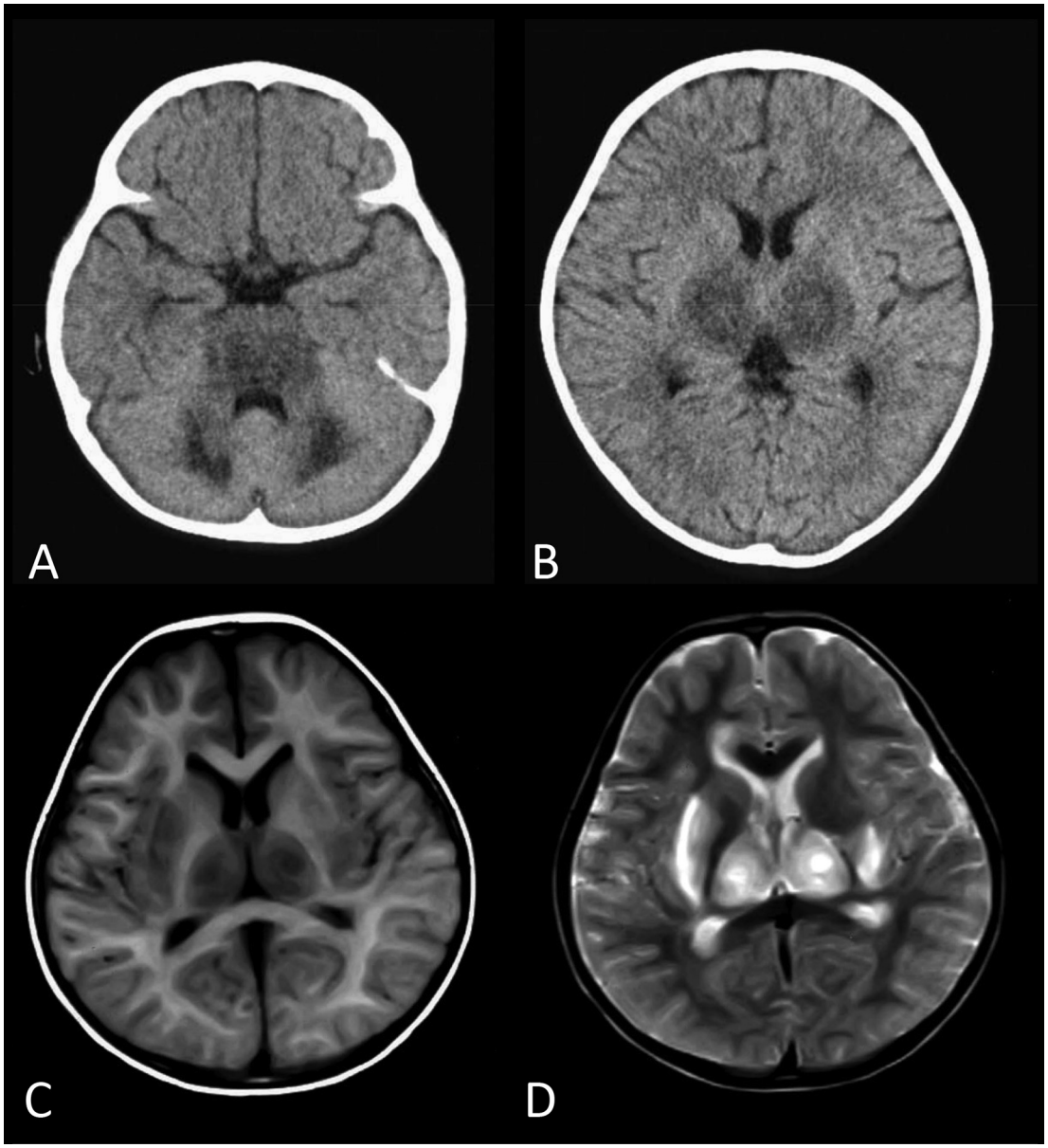

Fig. 2. CT and MRI findings of acute necrotizing encephalopathy (ANE). A and B: CT findings. Symmetrical low densities are observed in the bilateral thalamus, dorsal pons and cerebellar white matter. C and D: MRI findings. Lesions showing low intensities on T1-weighted images and high intensities on T2-weighted images are seen in the bilateral thalami, periventricular white matter and external capsule.

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[150]. Shock may occur early after the onset in severe cases. Delirious behavior sometimes precedes reduced consciousness [37]. Laboratory examinations often demonstrate an increase in AST, ALT, LDH and CK levels [150]. DIC is occasionally observed. Cerebrospinal fluid analysis shows normal cell counts and an increase in protein concentration in two-thirds of patients [150].

There have been few reports regarding treatment for ANE [139,151]. In a retrospective study in Japan, corticosteroids (steroid pulse therapy or intravenous dexamethasone) within 24 h after onset were associated with better outcome in patients without brainstem lesions [139]. Although sufficient evidence has not been established, steroid pulse therapy is recommended early after onset. The efficacy of intravenous immunoglobulin has not yet been proven. Some authors reported good outcome in cases treated with blood purification therapy. Effective ANE treatment remains to be established.

2.6. AE with convulsive status epilepticus (CSE)

2.6.1. (CQ6-1) diagnosis and treatment of AE with biphasic seizures and late reduced diffusion (AESD)

Recommendations:

(1) AESD is the most common syndrome of Japanese childhood AE, accounting for approximately 30%. (Grading not applicable)
(2) Diagnosis is based on the combination of biphasic clinical courses and characteristic imaging findings. (Grade B for cranial MRI)
(3) Treatment is based on supportive care. (Grade B)
(4) There is currently no evidence for the efficacy of specific or special treatment. (No grade)

Comments:

AESD has been recognized since the late 1990s and is the most common encephalopathy syndrome in Japan, accounting for 29% of all AE cases [8]. AESD is clinically characterized by biphasic seizures, i.e., a prolonged febrile seizure (early seizure) on days 1 to 2, followed by a cluster of complex partial seizures (late seizures) on days 3–7; it is radiologically characterized by delayed reduced diffusion in the subcortical white matter (so-called bright tree appearance) on days 3–9 (Fig. 3) [6,24,25]. The average age of onset is 1.7 years (median

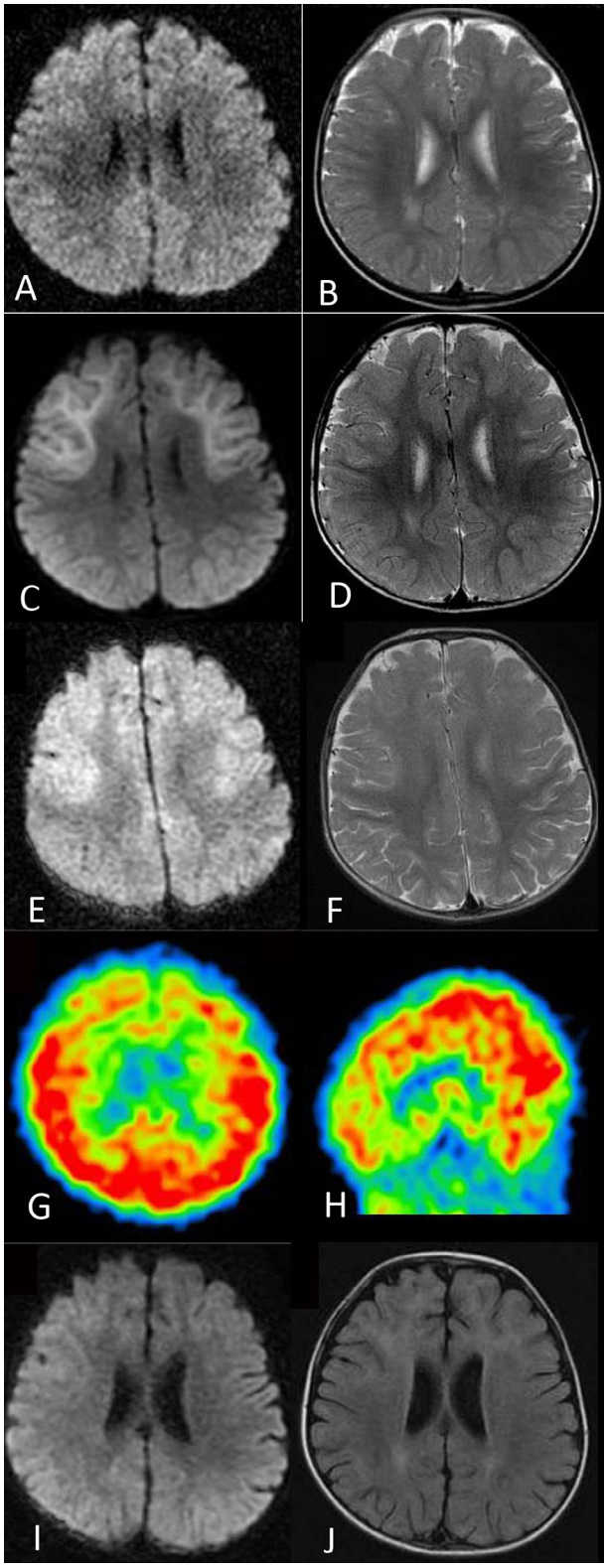

Fig. 3. MRI findings of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [10]. An 11-month-old girl presented convulsion lasting for 60 min. No abnormality was found on MRI on day 1 (A, B). Diffusion-weighted image (DWI) on day 3 (C) showed high signal lesions in the frontal subcortical white matter (bright tree appearance). No lesion was detected on T2-weighted image (D). On day 5, she exhibited skin rash after fever, leading to a diagnosis of exanthema subitum. She also presented a cluster of short convulsions. MRI on day 9 showed high signal mainly in the cortex on DWI (E), and in the subcortical white matter on T2 weighted-image (F). SPECT on day 14 (G, H) showed hypoperfusion in the frontal region. On day 16, the high signal on DWI disappeared (I), and FLAIR image showed mild atrophy and high signal lesions mainly in the subcortical white matter (J).

1 year), and 100–200 cases occur annually in Japan. The most common pathogens associated with AESD are HHV-6 (38%) and influenza viruses (10%). Between the early and late seizures, some patients (20–30%) have normal, clear consciousness with no neurological symptoms. MRI performed at days 1 and 2 usually show no abnormalities, including DWI. This may lead to an initial misdiagnosis of febrile status epilepticus. From the clinical and laboratory points of view, a scoring system has been proposed to differentiate between AESD and febrile status epilepticus [152,153]; however, clear discrimination remains difficult at present.

Delayed neuronal cell death due to excitotoxicity is assumed to be the pathomechanism, based on cytokine profile [16] and MR spectroscopy, showing increased glutamate followed by increased glutamine [6,24,25].

a. Diagnosis of AESD

Diagnostic criteria for AESD include the combination of clinical and radiological findings (Table 9).

b. Treatment for AESD

Supportive care should be provided for AESD patients, as described in Section 2.3.2 (CQ3-2). In particular, it is important to stop status epilepticus as early as possible. There is no specific or special treatment for AESD with sufficient evidence. The following is described on the assumption of this situation.

Specific treatments, such as methylprednisolone pulse therapy and high-dose gamma globulin therapy, are currently conducted in many Japanese hospitals. On the other hand, there may be an option of not taking these therapies with sufficient informed consent. Special treatments, including hypothermia [19,99], administration of cyclosporine, free radical scavengers and vitamin B_6, may be also considered. In any case, the establishment of effective treatment for AESD is urgently required.

2.6.2. (CQ6-2) diagnosis and treatment of acute encephalitis with refractory, repetitive partial seizures (FIRES/AERPPS)

Recommendations:

(1) The diagnosis of FIRES/AERRPS is based on the clinical features of status epilepticus following fever, consisting of extremely intractable and frequent, focal seizures, and on the exclusion of other known diseases. CSF, EEG and cranial MRI findings are non-specific but helpful for diagnosis. (Grade C1)
(2) FIRES/AERRPS is treated mainly with high-dose barbiturate and other antiepileptic drugs. The duration of barbiturate therapy should be shortened, since long-term barbiturate therapy may worsen the outcome. (Grade C1)
(3) Ketogenic diet may be efficacious in some cases. (Grade C1)

Comments:

Both FIRES [154] and AERRPS [30,155] denote a condition characterized by newly emerged, super-refractory status epilepticus following a febrile illness. FIRES/AERRPS is a subcategory of new onset refractory status epilepticus (NORSE) [156–158]. Exclusive criteria are structural, toxic and metabolic causes, as well as preexisting neurological disorders.

FIRES/AERRPS occurs in previously healthy children several days after preceding febrile illness. Seizure is a core and mandatory symptom of FIRES/AERRPS. Cryptogenic FIRES/AERRPS are characterized by unique seizure types (eye deviation or facial twitch) and acute repetitive seizures (with an interval of 5–15 min). Seizures are extremely resistant to conventional

Table 9
Diagnostic criteria of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD).

A diagnosis of AESD is made if there is any of 3) to 5) in addition to 1) and 2).

Clinical findings:

1) AESD occurs in children during the course of a febrile infection. Other conditions, such as head trauma, child abuse, hypoxic encephalopathy, other encephalopathy syndromes and encephalitis, are excluded.
2) The onset is on the day of fever or the next day, with a febrile seizure (early seizure) usually lasting longer than 30 min.
3) On day 3 to 7, secondary seizures (late seizures) most often in a cluster of complex partial seizures) or deterioration of consciousness level.

Image findings:

4) DWI shows high signal in the subcortical white matter (bright tree appearance) and/or in the cortex at day 3 to 14. Sparing of pre- and postcentral gyrus (central sparing) is usually observed.
5) After 2 weeks, residual lesions or atrophy on CT/MRI, or decreased blood flow on SPECT are observed in the frontal or fronto-parietal region, often with central sparing.

Reference findings:

(1) HHV-6 and influenza virus are the most frequent causative agents.
(2) After an early seizure, consciousness level improves.
(3) CT and MRI performed on days 1 and 2 are normal.
(4) Prognosis varies from mild intellectual disability to severe psychomotor impairment.

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AEDs and frequently require anesthetic agents, including high-dose barbiturates. Outcome is poor with most patients developing residual epilepsy and cognitive deficits. CSF analysis often reveals mild pleocytosis and increased pro-inflammatory cytokines. Other occasional findings include periodic discharges on EEG [159] and MRI lesions in the hippocampus, insular cortex, thalamus and basal ganglia.

Diagnostic criteria for cryptogenic AERRPS have been proposed (Table 10).

There has been no standardized treatment for FIRES/AERRPS. Although intravenous anesthetic agents, including barbiturates, have conventionally been used to control status epilepticus, the duration and dosage of barbiturate treatment should be minimized to avoid their adverse effects such as cardiorespiratory depression and paralytic ileus. A retrospective multicenter study on children with FIRES/AERRPS revealed that poor cognitive outcome was significantly associated with longer duration of burst-suppression coma [160]. Ketogenic diet is an alternative therapy for FIRES/AERRPS and is reported to improve not only seizure but also cognitive outcomes [161]. Additional therapeutic options include topiramate, potassium bromide and levetiracetam [162]. Although neuroinflammation has been implicated in the pathomechanism of FIRES/AERRPS, immunomodulatory treatments, including corticosteroid and intravenous immunoglobulin, have yielded disappointing results.

2.7. Miscellaneous AEs

2.7.1. (CQ7-1) diagnosis and treatment of AE associated with Dravet syndrome

Recommendations:

(1) Dravet syndrome is an epileptic encephalopathy of infantile onset characterized by repetitive status epilepticus induced by fever and hyperthermia. (Grading not applicable)
(2) AE is not uncommon in children with Dravet syndrome and may be fatal. (Grading not applicable)
(3) In children with Dravet syndrome, when recovery of consciousness is insufficient after the cessation of SEC, it is necessary to suspect AE and start intensive treatment. (Grade B)

Comments:

An outstanding feature of Dravet syndrome is seizures triggered by fever often resulting in SEC. Seizures are highly resistant to antiepileptic drugs, and it is difficult to prevent SEC. Development stagnates after the onset, which is associated with pyramidal signs. Various types of seizures, including myoclonic seizures, atypical absence seizures and focal onset seizures, appear between the ages of 1–4 years. Thereafter, the frequency of seizures decreases to some extent. Mutations in the *SCN1A* gene are present in 70–80% of children with Dravet syndrome [163]. Valproic acid and benzodi-

Table 10
Diagnostic criteria for cryptogenic acute encephalitis with refractory, repetitive partial seizures (AERRPS).

The presence of at least two of the following four criteria, one of which must be #1 or #4:

A. Symptoms
#1 Preceding febrile illness.
#2 Focal seizures predominating in face (eye deviation, hemifacial twitch).
#3 Clustering brief seizures (more than 4 times per hour).
#4 Super-refractory status epilepticus (requiring high-dose barbiturates or benzodiazepines).
#5 Chronic residual epilepsy.

B. Laboratory and neuroradiological findings
#1 Cerebrospinal fluid (CSF) pleocytosis.
#2 Increased pro-inflammatory biomarkers (neopterin, interleukin 6) in CSF.
#3 Interictal periodic discharges on electroencephalography (EEG).
#4 Recurrent seizure discharges on ictal EEG.
#5 MRI abnormalities on hippocampus, periinsular cortex, claustrum, thalamus or basal ganglia.
#6 Chronic cerebral atrophy.

C. Differential diagnosis
Viral encephalitis, virus-associated encephalopathy (acute encephalopathy with biphasic clinical course and late reduced diffusion), autoimmune encephalitis (acute limbic encephalitis, NMDA receptor encephalitis), metabolic disorders, angiitis and epilepsy syndrome (Dravet syndrome, PCDH19-associated epilepsy) need to be excluded.

Definite: All five of A, at least two of B, and C.
Probable: At least four of A, at least two of B, and C.
Possible: At least four of A and at least one of B.

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azepines are known to be effective. Stiripentol, bromides and topiramate are also considered to be effective. However, it is difficult to control seizures completely.

Sakauchi et al. reported that 63 of 623 patients with Dravet syndrome died from 13 months to 24 years of age [164,165]. Among them, 21 patients died due to AE with SEC. The age at death was 3 to 8 years. Furthermore, Okumura et al. reported the clinical manifestations of acute encephalopathy of 15 children with Drave syndrome [166]. The median age at the onset of acute encephalopathy was 3 years and 8 months (range, 8 months to 15 years). AE began with SEC in all cases, followed by deep coma despite seizures being suppressed with AEDs. Neuroimaging showed cortical dominant lesions in 5 cases and subcortical white matter dominant lesions in 2 cases (Fig. 4). The outcome was poor; 4 children died and 9 had severe neurological sequelae.

It is necessary to suspect AE and to start intensive treatment when recovery of consciousness is insufficient after the cessation of SEC in children with Dravet syndrome. At present, no specific treatment is known for AE in children with Dravet syndrome. Intensive antiepileptic treatment and continuous EEG monitoring will be necessary. The efficacy of corticosteroid pulse therapy and intravenous immunoglobulin remains unclear. There have been no reports on neuroprotection such as hypothermia.

2.7.2. (CQ7-2) diagnosis and treatment of AE associated with congenital adrenal hyperplasia

Recommendations:

(1) AE may occur in infants and children with congenital adrenal hyperplasia. Acute brain dysfunction is associated with features of adrenal crisis, such as diarrhea, vomiting and hypovolemic shock, which are commonly triggered by acute infectious illnesses. AE is usually irreversible, with neurological sequelae found in most cases. (Grading not applicable)
(2) Initial management to adrenal crisis includes bolus infusion of saline and glucose as well as high dose of hydrocortisone. High dose of methylprednisolone may be beneficial to AE. (Grade C1)

Comments:

Some patients with congenital adrenal hyperplasia develop AE in infancy and childhood characterized by acute CNS dysfunctions associated with features of acute adrenal insufficiency. Neurological sequelae of various degrees are encountered in spite of quick and appropriate managements [167,168]

Clinical features (diagnostic criteria) include the following:

1) Onset of AE during the course of congenital adrenal hyperplasia.
2) Convulsion and unconsciousness at the onset of AE, associated with features of adrenal crisis, including fever, vomiting, diarrhea and/or hypotension, as well as laboratory data such as hypoglycemia, hyponatremia, hyperkalemia and metabolic acidosis.
3) Localized or extensive brain edema detected as high signal intensity on DWI.
4) Diffuse high-voltage slow wave and/or paroxysmal discharges on EEG.
5) Poor recovery of AE despite management of adrenal crisis.

Laboratory tests are useful for diagnosis. Prior to the administration of corticosteroids, initial blood tests include glucose, electrolytes, cortisol, adrenal steroids (such as aldosterone and 17-hydroxyprogesterone), adrenocorticotropic hormone (ACTH) and renin activity. Urinary tests for electrolytes and fractional excretion of sodium (FENa) and potassium (FEK) are necessary.

Differential diagnosis includes hypoglycemic encephalopathy, hypoxic-ischemic encephalopathy and other acute neurological disorders causing encephalopathy. Endocrinological disorders causing acute adrenal insufficiency are also included for differential diagnosis.

Specific management for this AE has not been established. Appropriate treatments for adrenal crisis, as well as careful management for brain protection, are minimal requirements.

1) Intramuscular or intravenous injection of 50–75 mg/m^2 of hydrocortisone sodium succinate. The same dose of hydrocortisone should be given for over 24 h.
2) Bolus administration of 5% glucose with 0.9% saline, 20 mL/kg for 1 h. When hypoglycemia persists even after this treatment, administer a bolus injection of glucose 0.5–1 g/kg (10% glucose 5–10 mL/kg). The initial bolus administration of saline may be repeated up to 60 mL/kg until the disappearance of hypovolemia.

Fig. 4. MRI findings on diffusion-weighted images of acute encephalopathy in children with Dravet syndrome [166]. A and B. High intensities are observed in the entire cerebral cortex, thalamus and cerebellar hemispheres. C. High intensities are observed in the fronto-temporal areas, caudate nuclei and lentiform nuclei. D. High intensities are observed in the temporo-parieto-occipital areas. E. High intensities are observed in the entire cerebral cortex. F. High intensities are observed in the frontal and mesial occipital areas.

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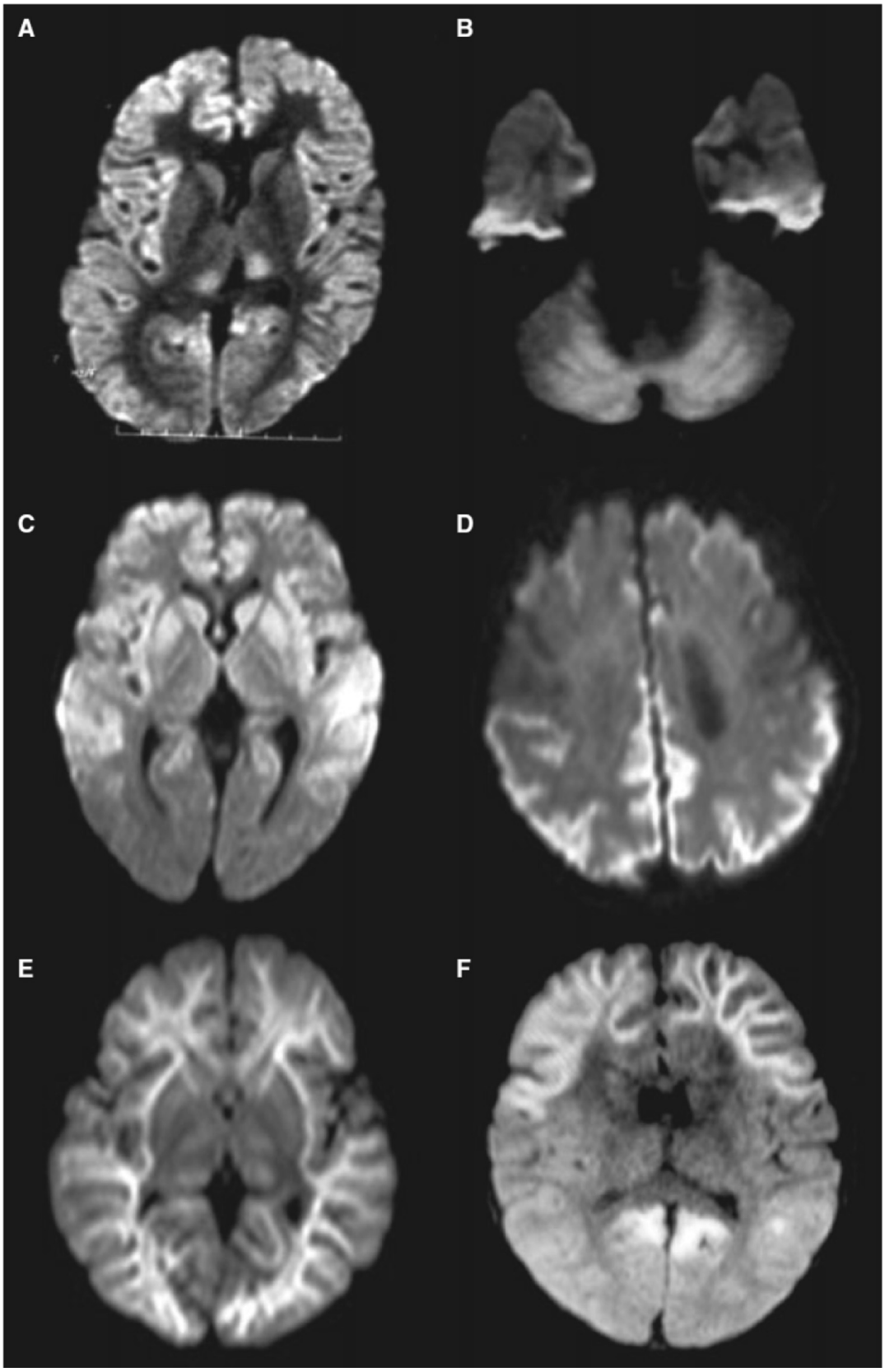

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Table 11
Diagnostic criteria of clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS).

Clinical findings:
1) Delirious behavior, consciousness disturbance or seizures within 1 week after fever.
2) Recovery without sequelae within 1 month after onset of neurological symptoms.
3) Exclusion of other neurological diseases such as ADEM, AESD and acute cerebellar inflammation.
4) Neurological symptoms persisting for more than 12 h.
Note: Delirious behavior may be intermittent.

Imaging findings:
5) DWI showing a reversible splenial lesion with homogenously reduced diffusion with mild T1 and T2 signal abnormalities.
6) Lesion involving at least the splenium. It may expand to the entire corpus callosum or symmetrical white matter.
7) Disappearance of lesion within 2 months, leaving no abnormal signal or atrophy.

3) Administration of methylprednisolone at a dose of 30 mg/kg for 2 h for three consecutive days may be beneficial to AE, although there is no sufficient evidence for its efficacy.

2.7.3. Diagnosis and treatment of MERS

Recommendations:

(1) MERS is the second most common pediatric AE in Japan, accounting for 16% of cases. (Grading not applicable)
(2) Diagnosis is based on mild neurological symptoms with a good prognosis, as well as characteristic imaging findings such as a reversible splenial lesion with homogenous reduced diffusion. (Grade B for MRI)
(3) Treatment is based on supportive care. (Grade B)
(4) There is currently no specific/special treatment with supporting evidence. (No grade)
(5) Methylprednisolone pulse therapy and high-dose gamma globulin therapy are not always necessary for typical cases of MERS. (Grade C2)

Comments:

A reversible splenial lesion in the corpus callosum with homogenous reduced diffusion may be detected in various conditions such as infection, withdrawal of antiepileptic drugs, altitude sickness, Kawasaki disease, electrolyte abnormalities (especially hyponatremia), hypoglycemia and X-linked Charcot-Marie-Tooth disease. In particular, encephalitis and encephalopathy with mild neurological symptoms and good prognosis have been reported as MERS [7,8,24,169–174].

MERS is the second most common childhood AE in Japan, accounting for 16% of all AE cases [9]. There is no clear sex difference, with boys accounting for 52%. The mean age of onset is 5.6 years; MERS is also common in schoolchildren and adolescents. The most common pathogen associated with MERS is influenza virus (34%), followed by rotavirus (12%) and mumps virus (4%) [8]. Diagnostic criteria for MERS (Table 11) are a combination of clinical and radiological findings. The most common neurological symptom is delirious behavior in 54%, followed by consciousness disturbance in 35% and seizures in 33% [7,24]. Patients who do not satisfy the clinical finding [169], i.e., those with delirious behavior or consciousness disturbance less than 12 h, are also considered to comprise the same spectrum (MERS spectrum). Patients with a callosal lesion only (at least involving the splenium) are classified into MERS type 1, and those with accompanying symmetric white matter lesions (from the deep white matter near the central sulci to the entire white matter) into MERS type 2 (Fig. 5) [169,170]. On laboratory examination, hyponatremia is common in MERS [171]. CSF cytokine profile in patients with MERS shows increased IL-6 and IL-10 in 50% of patients [172]. Steroids and gamma globulins may be theoretically effective for increased cytokines in CSF. However, the prognosis for many MERS patients is good regardless of treatment [7,8,24,169,171]. Methylprednisolone pulse therapy and high-dose gamma globulin therapy are not always necessary for typical patients.

2.7.4. Diagnosis and treatment of AE associated with enterohemorrhagic Escherichia coli (EHEC) infection

Recommendations:

(1) EHEC infection may cause AE in parallel with the onset of hemolytic-uremic syndrome (HUS). The most common symptoms are seizures and impaired consciousness. (Grading not applicable)
(2) Diagnosis is based on clinical symptoms and diagnostic imaging. Brain CT or MRI (Grade B) and EEG (Grade C1) are recommended at the stage of suspected encephalopathy.
(3) Treatment is based on supportive care. (Grade B)
(4) As specific treatment, methylprednisolone pulse therapy may be considered. (Grade C1)

Comments:

Patients with EHEC infection may develop CNS symptoms slightly later (within 24–48 h) than the onset of HUS. The frequency of CNS manifestations among HUS is around 10% [173,174]. Diagnostic criteria of

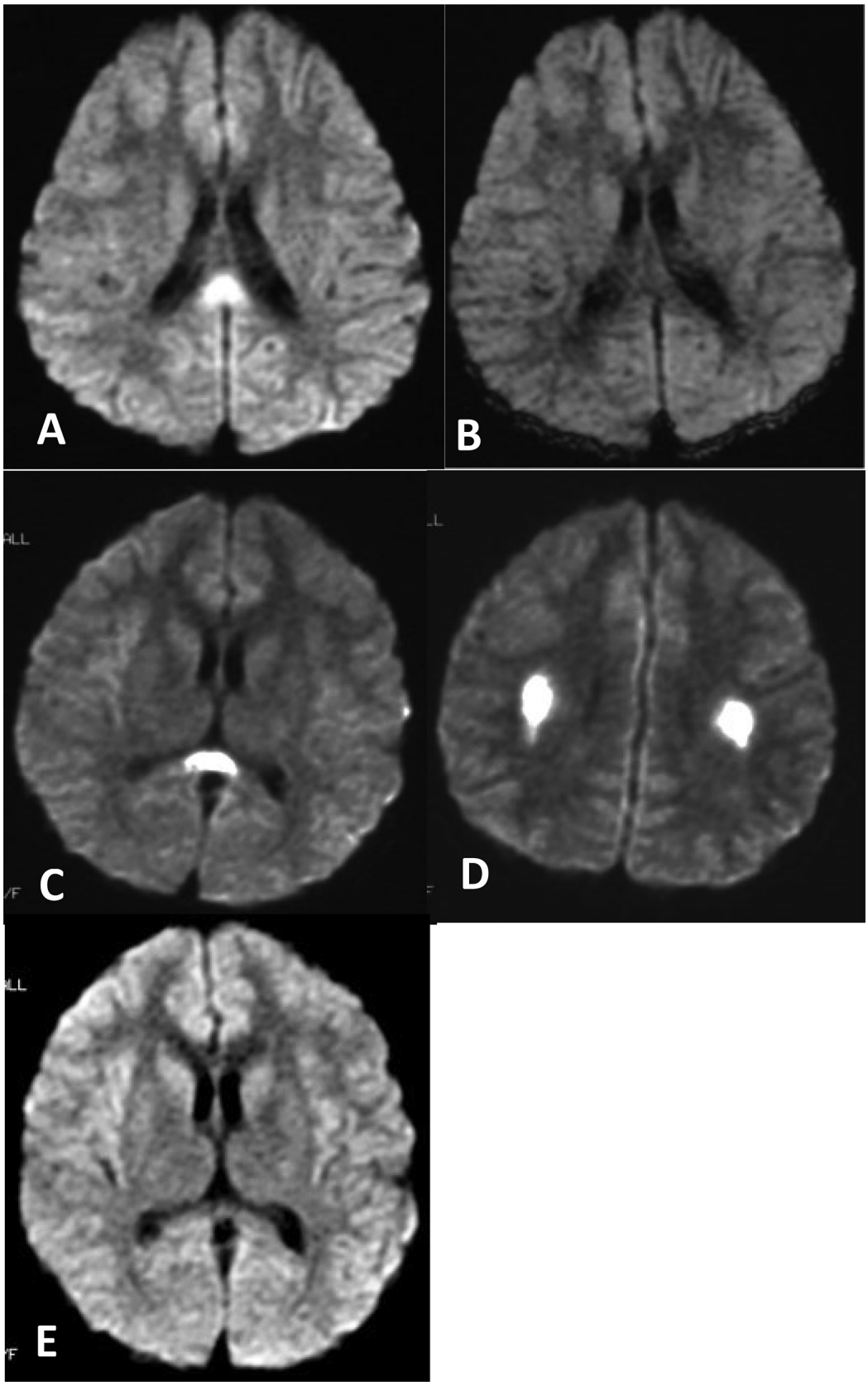

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Table 12
Diagnostic criteria of acute encephalopathy associated with enterohemorrhagic *E. coli* (EHEC) infection.

Definite:
Any of the following during the course of EHEC infection.
Convulsions or disturbance of consciousness and abnormal findings (bilateral deep gray matter lesions or diffuse brain edema) on brain CT or MRI.
Consciousness disturbance (Japan Coma Scale II ≥10, Glasgow Coma Scale ≤13) persisting for 24 h or longer.

Probable:
Convulsion or disturbance of consciousness occurring during the course of EHEC infection.

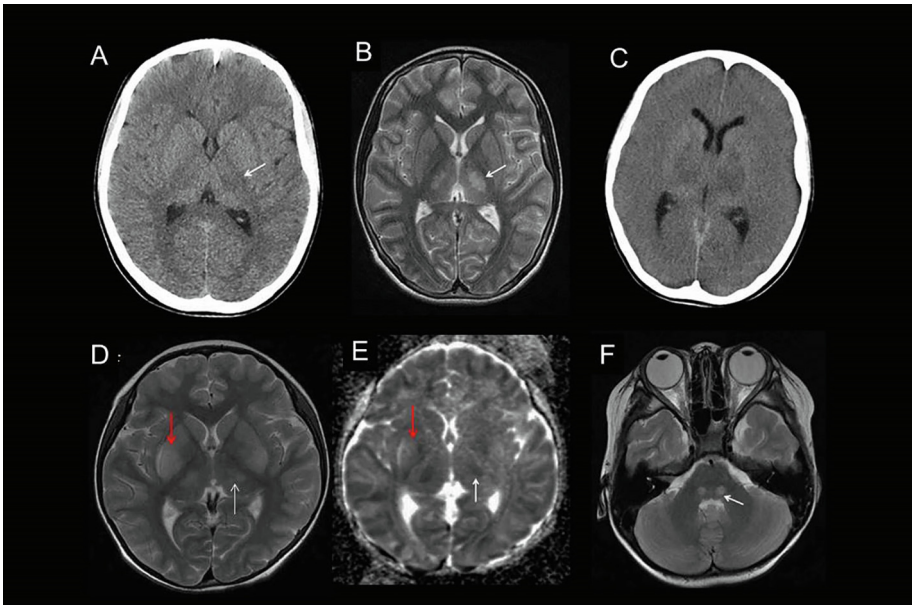

Fig. 6. Neuroimages in acute encephalopathy associated with EHEC O111 infection. A–C. Neuroimages in a teenage male on day 1 showed low density on CT (A, arrow) and high signal on T2-weighted image (B, arrow) in the bilateral antero-lateral thalamus. CT on day 2 revealed marked cerebral edema (C) with low density areas in the bilateral thalamus and globus pallidus. D–F. T2-weighted image (D) in a schoolgirl on day 2 showed symmetrical high signal lesions in the putamen (red arrow), external capsule and thalamus (white arrow). ADC map (E) showed increase ADC in the bilateral putamen (red arrow) and external capsule, and decreased ADC in the bilateral antero-lateral thalamus (white arrow). On the same day, symmetric high signal lesions were also recognized in the dorsal midpons (F, arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

AE associated with EHEC infection have been proposed by the 'Diagnosis and Treatment Guidelines for Hemolytic Uremic Syndrome' (Table 12) [175]. The diagnosis is based on the degree and duration of consciousness disturbance; however, in the presence of EHEC infection, treatment may be initiated with an early diagnosis of probable encephalopathy.

Brain imaging (CT or MRI) and EEG are useful for diagnosis. CT and MRI often show bilateral deep gray matter lesions (basal ganglia or thalamus) and diffuse brain edema (Fig. 6) [176–179]. EEG shows abnormalities of the basic activity (slow wave) even in mild cases, as well as paroxysmal discharges [180].

The pathophysiology is mainly cerebral vascular dysfunction, especially hyperpermeability (broken blood–brain barrier), caused by Shiga toxin and inflammatory cytokines [181,182]. Additional factors, such as the direct action of Shiga toxin that enters the brain, fluid abnormalities due to acute kidney injury, electrolyte abnormalities and abnormal circulation (e.g. hypertension), are also involved.

The basic treatment for AE associated with EHEC infection is supportive therapy. Systemic management

Fig. 5. Cranial MRI findings in clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). A, B. A 7-year-old girl with MERS type 1 associated with influenza. She presented with consciousness disturbance and hallucination on day 2, and recovered completely on day 4. DWI shows high signal lesions in the splenium of the corpus callosum on day 4 (A). The splenial lesion completely disappeared by day 10 (B). C–E. An 11-year-old boy with MERS type 2 associated with influenza. DWI on day 5 shows reduced diffusion in the splenium of the corpus callosum and symmetrical subcortical white matter (C, D), which completely disappeared by day 10 (E).

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and treatment for brain edema and seizures should preferably be performed in a PICU. There is no established treatment at present; however, efficacy of methylprednisolone pulse therapy has been shown for AE associated with EHEC O111 infection [176]. PE therapy may be considered after confirming safety, although evidence for its effectiveness has not been established.

3. Limitations and future direction

These guidelines are not intended to show a stereotype of medical management to which a strict compliance is required. The actual strategy of diagnosis and treatment should be decided according to each patient's condition, the clinician's experience and the environment of medical care.

In these guidelines, grades of recommendations are either very weak (grade C1) or absent (no grade) for most of the CQs, since little evidence of high quality was available. Thus, even if the diagnosis and treatment are in line with the guidelines, they are not necessarily good evidence-based. Studies in the near future should improve both the quality and quantity of evidence.

Because systematic review of the literature was conducted in 2014–2015, references that were published very recently were not included. Because the recommendations and comments were written by Japanese researchers in 2015, all the diagnostic tools and therapeutic measures, including medical drugs, are confined to those available in Japan at that time. In 2018, the JSCN reorganized the WG for revision of the guidelines. The WG, together with the Research Committee on Acute Encephalopathy supported by the Japanese Government, is currently striving to accumulate evidence of high quality for earlier diagnosis and more efficacious treatment of AE.

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Disclosure

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