Role of Antineuronal Antibodies in Children with Encephalopathy and Febrile Status Epilepticus

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Status epilepticus in childhood is more common, with a different range of causes and a lower risk of death, than convulsive status epilepticus in adults. Acute central nervous system infections appear to be markers for morbidity and mortality. Nevertheless, central nervous infection is usually presumed in these conditions. Many aspects of the pathogenesis of acute encephalitis and acute febrile encephalopathy with status epilepticus have been clarified in the past decade. The pathogenesis is divided into direct pathogens invasion or immune-mediated mechanisms. Over the past few decades, the number of antineuronal antibodies to ion channels, receptors, and other synaptic proteins described in association with central nervous system disorders has increased dramatically, especially their role in pediatric encephalitis and status epilepticus. These antineuronal antibodies are divided according to the location of their respective antigens: (1) intracellular antigens, including glutamic acid decarboxylase and classical onconeural antigens such as Hu (antineuronal nuclear antibody 1, ANNA1), Ma2, Yo (Purkinje cell autoantibody, PCA1), Ri (antineuronal nuclear antibody 2, ANNA2), CV2/CRMP5, and amphiphysin; and (2) cell membrane ion channels or surface antigens including voltage-gated potassium channel receptor, N-methyl-D-aspartate receptor, z-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-aminobutyric acid(B) receptor, leucine-rich glioma-inactivated protein 1, and contactin-associated protein-like 2. Identifying the mechanism of the disease may have important therapeutic implications.

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1. Introduction

The estimated incidence of status epilepticus in childhood ranges from 10 to 38/100,000/year. It is higher than 4-6/100,000/year, as reported in the epidemiological studies of status epilepticus in adults.\(^1\)\(^-\)\(^3\) There is evidence that etiology is an important determinant of the outcome of patients with status epilepticus, and therefore it is important to identify and classify the causes.\(^4\)\(^-\)\(^6\) Pediatric status epilepticus is more common, with a different range of causes, and a lower risk of death than that in adults. Acute central nervous system infections appeared to be markers for morbidity and mortality.\(^7\) Nevertheless, central nervous system infection is usually presumed in these conditions.\(^8\) The pathogenesis is divided into direct pathogens infection or immune-mediated inflammation mechanisms.\(^9\)\(^-\)\(^10\) When faced with children presenting with febrile status epilepticus, infectious pathogens are rarely found in the cerebrospinal fluid (CSF). However, a group of patients show evidence of infectious pathogens from the antibodies in serum and virus isolation from throat or rectum. Nevertheless, the etiology of all of these children with febrile status epilepticus was considered as presumed encephalitis.\(^8\)\(^-\)\(^11\)\(^-\)\(^12\) The immune-mediated mechanism and related brain inflammation process may play important roles.

2. Similar conditions of children with antineuronal antibodies related encephalopathy and febrile status epilepticus

Children with acute encephalopathy and febrile status epilepticus usually have a catastrophic course and are resistant to multiple antiepileptic drugs. The mechanism of these patients remains unknown, although the clinical features and experimental models point to a likely vicious cycle involving inflammation and seizure activity.\(^13\)\(^-\)\(^15\)

A similar pattern of clinical characteristics which suggests suspected but unproven encephalitis with febrile status epilepticus has been reported under various clinical medical names, including severe refractory status epilepticus in children,\(^12\) idiopathic catastrophic epileptic encephalopathy presenting with acute-onset intractable status epilepticus,\(^16\) and severe refractory status epilepticus due to presumed encephalitis.\(^11\)\(^-\)\(^12\) Moreover, several abbreviation medical terms in different areas and study groups described these similar conditions in the literature, which all represent unique characteristics as part of this condition (Figure 1).

Acute encephalitis with refractory, repetitive partial seizures (AERRPS) is defined by five criteria: (1) A prolonged acute phase of more than 2 weeks; (2) partial seizures with the same symptoms persisting from the acute phase until the convalescent phase; (3) seizures frequently evolving to status epilepticus, especially during the acute phase; (4) marked intractability of seizures; and (5) exclusion of related disorders such as known viral encephalitis or metabolic disorders.\(^13\)\(^-\)\(^15\)\(^-\)\(^17\) The clinical entity of AERRPS arose in 1986, when Awaya et al described five cases of peculiar onset postencephalitic epilepsy in Japan.\(^18\) He found a novel subtype of epilepsy characterized by refractory partial seizures persisting from the onset of encephalitis to the convalescent phase. In 2001, Sakuma et al proposed the term AERRPS to integrate the characteristics of these entities.\(^19\) From different clinical presentations with a focus on brain images, a further two cases were reported in Japan as acute infantile encephalopathy predominantly affecting the frontal lobes (AEIF) and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD).\(^20\)\(^-\)\(^21\)

Febrile infection-related epilepsy syndrome (FIRES) was first described by vanBaalen et al in 2010 with the following inclusion criteria: previously healthy children with recurrent seizures or status epilepticus (30 minutes or more) 2-28 days after onset of an acute, banal febrile illness and lacking evidence of infectious agents in CSF. Exclusion criteria were febrile seizures and seizures triggered by fever in children with epilepsy.\(^22\) Typically, banal febrile infection of different origins is followed by a similar clinical course, and it is characterized by an acute onset of refractory seizures. In fact, in 2009, another abbreviation FIRES was initially mentioned by van Baalen et al, which was defined as “fever-induced refractory epileptic encephalopathy in school-aged children”.\(^23\) This condition was first called “devastating epileptic encephalopathy in school age children” (DESC).\(^24\) A similar condition to FIRES has been reported in young adults and was referred to as new-onset refractory status epilepticus (NORSE).\(^25\) Seven women aged 20-52 years (mean 33 years) presented after a febrile illness of unknown etiology with severe long-lasting status epilepticus with neurological deterioration. All of these different medical terms emphasized preceding banal febrile infection followed by refractory seizures (status epilepticus) in different age groups and when pathogen detection in CSF failed.

Acute encephalopathy with inflammation-mediated status epilepticus (AEIMSE) was introduced by Nabbout et al in 2011.\(^13\) They focused on the pathogenesis of possible inflammation-induced status epilepticus. It seems that pediatric inflammation-mediated encephalopathies with status epilepticus are distinct from encephalitis. They probably result from the combination effects of inflammation and major seizure activity.\(^13\)\(^-\)\(^17\) The seizure activity itself results partly from inflammation and contributes to inflammation, generating a vicious cycle that leads to status epilepticus.\(^13\) Nabbout et al suggest that AEIMSE includes three different entities according to the age. The three conditions include: (1) Idiopathic hemiconvulsion—hemiplegia syndrome (IHHS) in infancy that mostly occurs in the age group of 1-4 years; (2) FIRES is reported in children between 4 years of age and adolescence; and (3) NORSE occurs in adulthood.\(^13\)\(^,\)\(^22\)\(^-\)\(^25\)\(^,\)\(^26\) AEIMSE is focussed on the inflammation process for the possible mechanism of these clinical conditions.\(^13\)

3. The role of antineuronal antibodies in encephalopathy and febrile status epilepticus

Over the past few decades, the number of antineuronal antibodies to ion channels, receptors, and other synaptic proteins described in association with central nervous system disorders has increased dramatically, especially
Antineuronal antibodies and febrile status epilepticus

Febrile status epilepticus

Encephalopathy

Yes

Evidence of infectious pathogen in CSF

Yes

Confirmed encephalitis with status epilepticus

No

Febrile seizure with status epilepticus

No

Febrile seizure with status epilepticus

Evidence of infectious pathogen in CSF

Yes

Confmed encephalitis with status epilepticus

Presumed encephalitis with status epilepticus

Evidence of infectious pathogens other than CSF (antibodies in serum; virus in throat/rectum)

No

Different clinical focus

Antecedent febrile infection + encephalopathy + refractory partial seizures

AERRPS

No

Antecedent febrile infection + encephalopathy + refractory seizures

FIRES

Antecedent febrile infection + encephalopathy + inflammation process + status epilepticus

AEIMSE

Spectrum of encephalitis/encephalopathy with febrile status epilepticus

Figure 1 Flow chart of clinical considerations from the presentation of febrile status epilepticus to the spectrum of related conditions of children with encephalitis/encephalopathy and febrile status epilepticus. The abbreviated medical terms used in different areas and study groups describes these similar conditions in literature, all of which represent the unique characteristics as a part of this condition. AIEMSE = acute encephalopathy with inflammation-mediated status epilepticus; AERRPS = acute encephalitis with refractory, repetitive partial seizures; CSF = cerebrospinal fluid; FIRES = febrile infection-related epilepsy syndrome.

considering their roles in pediatric encephalitis and status epilepticus. These antineuronal antibodies are divided according to the location of their respective antigens: (1) Intracellular antigens, including glutamic acid decarboxylase (GAD), and classical onconeural antigens such as Hu (antineuronal nuclear antibody 1, ANNA1), Ma2, Yo (Purkinje cell autoantibody, PCA1), Ri (antineuronal nuclear antibody 2, ANNA2), CV2/CRMP5 (collapsin response mediator protein 5 antibody), and amphiphysin; and (2) cell membrane ion channels or surface antigens including voltage-gated potassium channel receptor (VGKC), N-methyl-D-aspartate receptor (NMDA), \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA), \( \gamma \)-aminobutyric acid(B) receptor (GABA), leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) (Table 1).
forms of epilepsy or encephalitis in adults. Moreover, they are beginning to be identified in children. All of the above antibodies, except antibodies to GAD and classical onconeural antigens, are directed against the extracellular domains of membrane proteins and are highly likely to be pathogenic for seizure and status epilepticus. Nevertheless, intracellular antineuronal autoantibodies (antibodies to GAD and classical onconeural antigens) are also found to play a role in children with encephalopathy and febrile status epilepticus and related conditions.32–34

### 3.1. Anti-GAD antibody-related encephalopathy and febrile status epilepticus

High-titer GAD antibodies usually associate with nonparaneoplastic stiff-person syndrome and cerebellar dysfunction; however an increasing number of reports show that these antibodies also associate with subtypes of limbic encephalitis and refractory epilepsy.35 GAD is the rate-limiting enzyme for the synthesis of GABA, the major inhibitory neurotransmitter in the central nervous system. The mechanism underlying seizures in anti-GAD antibody-related epilepsy likely involves the downregulation of cortical GABAergic neurotransmission.36 The presence of anti-GAD antibodies suggests that the underlying neurologic syndrome may be immune mediated.37 Lin et al examined antibodies to GAD and cell membrane ion channels or surface antigens in acute-phase serum from 17 children with encephalitis and status epilepticus.32 Anti-GAD antibody titers were compared with those of control children manifesting therapy-resistant epilepsy. Anti-GAD antibody titers were significantly higher in children with encephalitis and status epilepticus than in those with therapy-resistant epilepsy. Six children exhibited positive anti-GAD antibodies. Three manifested postencephalitic epilepsy with neurologic deficits. Higher anti-GAD antibody titers were evident in children with encephalitis and status epilepticus. Although the study produced no direct evidence for the pathogenesis of anti-GAD antibodies, the potential role of anti-GAD antibodies in children with encephalitis and status epilepticus should be emphasized.

### 3.2. Anti-NMDA receptor antibody-related encephalopathy and febrile status epilepticus

The anti-NMDA receptor antibody-related encephalopathy was first reported in association with ovarian teratomas. It was mainly reported in teenage or young adult women, and very occasionally with other tumors.38,39 However, it is now clear that there are many patients, particularly younger children and both sexes older than 40 years of age, who have the nonparaneoplastic form.40,41 Dalmau et al reported on a series of 100 patients with anti-NMDA-receptor encephalitis, and observed a female (91%) predominance, with a median age of 23 years (range: 5-76 years). All patients presented with psychiatric signs or memory problems, and 86% exhibited a nonspecific viral-like illness with low-grade fever within 2 weeks before hospital admission.38 Seizures were evident in 76% of the patients with anti-NMDA-receptor encephalitis in the study by Dalmau et al, without the mention of the percentage of status epilepticus.38 However, nonconvulsive status epilepticus has also been reported.42–44 Antibody against glutamate receptor epsilon-2 subunit, also designated as NMDA receptor 2B subunit, is positive in serum or CSF in more than a half of the AERRPS patients. This antibody is usually detected within 2 weeks from onset.17 In the clinical course of anti-NMDA-receptor antibodies encephalitis, seizures and status epilepticus can resurface at any time during the illness.39

### 3.3. VGKC complex antibody-related encephalopathy and febrile status epilepticus

VGKC complex antibodies are reported in a range of central and peripheral neurologic disorders in adults. Recently, they have also been increasingly recognized in children, including limbic encephalitis, FIRES, early-onset epileptic encephalopathy, and unexplained encephalitis presenting with status epilepticus.28,34,45,46 Originally, the antibodies were thought to be directed against the VGKC themselves. However, these antibodies were subsequently found to bind to proteins that are part of a VGKC complex, including LGI1 and CASPR2. Thus, they are better termed as VGKC complex antibodies.47,48 In VGKC complex antibody-associated limbic encephalitis in adults, patients typically present with acute to subacute onset memory loss, confusion, medial temporal lobe seizures, agitation, and psychiatric features evolving over several days or weeks.5,10,30 Most patients are older than 40 years, with a male predominance (2:1 ratio).47 However, different clinical features of VGKC complex antibody-associated encephalitis have been reported recently in children.28,34,46 These were characterized by normal neurodevelopmental status before the onset of febrile illness, seizure at presentation, sometimes associated with status epilepticus, features of encephalopathy (e.g., behavior disturbance, confusion, disorientation, and hallucinations) and cognitive decline, without identifiable infectious etiology. Reviewing previous related literature, 11 patients (8 girls and 3 boys, aged 1-16 years) were reported with VGKC complex antibody-related encephalopathy. The major neurologic symptoms were seizure (n = 8, 72.3%) including status epilepticus (n = 5, 45.5%).28,34,46,49

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**Table 1** Antineuronal autoantibodies to intracellular antigens and cell-surface antigens.

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<thead>
<tr>
<th>Intracellular antigens</th>
<th>Cell-surface antigens</th>
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<tr>
<td>Onconeural antigens</td>
<td>GAD Glutamate receptors</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>MA2 Ri Yo Hu NMDA AMPA1 AMPA2</td>
</tr>
</tbody>
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| AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CASPR2 = contactin-associated protein-like 2; GABA = γ-amino-butyric acid; GAD = glutamic acid decarboxylase; LGI1 = leucine-rich, glioma–inactivated protein 1; NMDA = N-Methyl-D-aspartate; VGKC = voltage-gated potassium channel. |
4. Differential diagnosis of acute disseminated encephalomyelitis from spectrum of encephalopathy and febrile status epilepticus

From an immunological aspect, acute disseminated encephalomyelitis and a spectrum of encephalopathy and febrile status epilepticus are possible immune-mediated central nervous system diseases. Antineuronal antibodies are found to be the pathogenic mechanism of these diseases. Nevertheless, acute disseminated encephalomyelitis has a more favorable outcome, and fewer seizure occurrences. It is a monophasic inflammatory demyelinating condition of the central nervous system. It typically occurs following a viral prodrome or vaccination and usually presents with multifocal neurological disturbance accompanied by changes in mental status. Brain magnetic resonance imaging is regarded as the diagnostic imaging modality of choice and usually demonstrates white matter lesions, although the involvement of gray matter is not uncommon. Antimyelin oligodendrocyte glycoprotein antibodies are transient and continuously declined in the patients with acute disseminated encephalomyelitis.

5. Management of antineuronal antibodies-related encephalopathy and febrile status epilepticus in children

With regard to management, autoimmune encephalitis may be treatable with immunotherapy. Prompt diagnosis and treatment with immunosuppressants can improve or even reverse symptoms. Pediatric patients with encephalitis and febrile status epilepticus have common symptoms and signs of acute encephalitis and status epilepticus. However, it was still difficult to differentiate between viral and immune-mediated encephalitis by clinical manifestations. Thus, aside from empirical anti-infectious treatment and antiepileptic drugs, immune-modulating therapies were considered. Regardless of whether the infectious pathogens were found, other than in CSF, identifying an antineuronal autoantibody may be a reference for the option of immunotherapy treatment. In some antineuronal antibody-confirmed cases, if left untreated, retrospective case series have shown that these conditions can lead to irreversible cognitive deficits, ongoing seizures, and even death. Although the evidence is limited to retrospective series and case reports, the best available data suggest that early treatment with intravenous immunoglobulin or plasmapheresis (or both) followed by long-term immunosuppression (typically with corticosteroids) is associated with improved outcomes. Other treatments, including cyclophosphamide and rituximab, have been successful in individual patients. Seizures are often refractory to standard treatments, but may remit with immunotherapy. In the study of Lin et al, there was no evidence of the positive effects of immunotherapy in the anti-GAD-positive children compared with the anti-GAD-negative group. Future studies should include a greater number of cases and accumulate the experience of international studies.

Nakagawa et al reported 12 children with febrile refractory status epilepticus who underwent therapeutic hypothermia (34 °C) with general anesthesia, and they concluded that therapeutic hypothermia significantly improved the outcomes compared to conventional therapy. Lin’s group presented two pediatric cases of FIRES who were refractory to conventional medical therapy. Moderate therapeutic hypothermia of 33 °C resulted in fast and sustained control of refractory status epilepticus. After 3 months, both patients recovered with a Glasgow Outcome Scale of 4. Furthermore, a ketogenic diet was reported to be an alternative efficacious therapy for FIRES by Nabbout et al. Thus, both therapeutic hypothermia and a ketogenic diet are alternative therapies that can be applied in these similar clinical conditions of children with encephalitis and febrile status epilepticus.

6. Conclusion

From the clinical observation of children with status epilepticus, presumed central nervous system infection appears to be marker for morbidity and mortality. An Immunological mechanism might act as a trigger between presumed central nervous system infection and febrile status epilepticus. Antineuronal autoantibodies were found to play an important role in these patients in recent decades. Therefore, clinicians need to be able to recognize these clinical presentations because early diagnosis and optimal treatment may improve the outcome. Nevertheless, future studies with more experience accumulation are warranted.

Conflict of interest

The authors state that there is no conflict of interest regarding the publication of this article.

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