Rasmussen Syndrome and Other Inflammatory Epilepsies

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Abstract

Keywords

► Rasmussen syndrome
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► febrile infection-related epilepsy syndrome

An underlying immune basis is emerging in an increasing number of epileptic and encephalopathic syndromes. The immunopathological mechanisms may be categorized into antibody-mediated, T-cell cytotoxicity, and microglia-induced degeneration. The immune basis in Rasmussen syndrome is thought to be T-cell mediated. Antibodies to extracellular and intracellular epitopes are implicated in limbic and other encephalitides, characterized by seizures, movement disorder, sleep disorder, obtundation, psychosis, mutism, and other psychiatric symptoms. Extracellular antibodies are directed at cell-surface-expressed neuronal or glial proteins: glutamate receptors (N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid), voltage-gated potassium channel complex (contactin-associated-protein 2 [CASPR2], contactin-2 and leucin-rich, glioma-inactivated 1 [LGI1]), and γ-aminobutyric acid (GABA) receptors (GABA$_B$R and GABA$_A$R). Antibodies to intracellular antigens are less commonly seen (for example, glutamic acid decarboxylase). Diseases caused by antibodies to cell-surface-expressed antigens are better expected to respond to immune treatments than to those where the presumed mechanism is T-cell driven. Antibodies to the folate receptor FR1 are a cause of primary cerebral folate deficiency. Febrile infection-related epilepsy syndrome (FIRES) may also have an immune basis, although this is yet to be proven. For all these epilepsies, the best treatment and the long-term outcomes are not yet clear.

An immune basis is thought to be underlying an increasing number of epileptic and encephalopathic syndromes. This is of increasing importance, particularly in the optimization of management, considering a mechanistic basis to steroids and immunosuppressive therapy. Although traditionally the brain has been thought to be protected against the humoral immune system, the descriptions in the past 10 years of several different central nervous system (CNS) conditions associated with potentially pathogenic circulating antibodies to neuronal surface proteins demonstrate that this is not the case. Rasmussen syndrome (RS) is one such inflammatory epilepsy, long presumed to have an immune basis.[1] It was in this condition that an autoantibody was identified, against GluR3 (now termed GluA3), and not surprisingly antibody-mediated mechanisms subsequently dominated RS research.[2] Although it has become clear that antibodies are unlikely to drive RS, it is still thought to have an autoimmune basis (T-cell mediated). There are now other epilepsies in which the evidence strongly implicates autoantibodies as pathogenic and that respond to immunotherapies.[3,4] In general, these antibodies have extracellular targets, and seem to alter the function and localization of these target antigens. The diseases have various symptoms including seizures, movement disorder, sleep disorder, psychosis, mutism, limbic encephalitis, and

encephalopathy. The diagnosis is suspected on the clinical picture and confirmed with the detection of the antibodies in serum or in cerebrospinal fluid (CSF). The most important of these antibodies to date are those targeted against glutamate receptors and against the voltage-gated potassium channel (VGKC complex). The immunopathological mechanisms recognized to play a role in CNS disease can now be categorized into three types: antibody-mediated, T-cell cytotoxicity, and microglia-induced degeneration.

Mechanisms

Glutamate is the major excitatory amino acid in the CNS. Antibodies to the glutamate N-methyl-D-aspartate (NMDA) receptor are likely pathogenic in what is now termed NMDAR encephalitis.[5] Antibodies to the VGKC complex were described in the spectrum of limbic encephalitis.[6] It is now known that there several different antibodies involved in VGKC encephalitis, each targeting different extracellular domains of proteins complexed to the VGKC. Further target epitopes have been reported in the limbic encephalitides: α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptor,[7] γ-aminobutyric acid (GABA) receptors, first $GABA_BR$,[8] and most recently $GABA_AR$.[9,10] These antibodies all have in common target cell-surface-expressed neuronal or glial proteins.[3]

Autoantibodies to intracellular antigens, such as to glutamic acid decarboxylase (GAD) have also been described in antibody-mediated encephalitis and in temporal lobe epilepsy.[11] In contrast to the diseases characterized by antibodies to extracellular antigens, these diseases do not respond so well to immune treatments and it has been proposed that the pathogenic mechanism here is T-cell driven.

Before recent interest in surface versus intracellular antigens, the autoimmune encephalitides were often categorized according to whether there was a paraneoplastic basis, and whether the onconeural antigens continue to be interest. In adults, a paraneoplastic basis, often related to the presence of lung, thymoma, and gynecological tumors, is important in terms of diagnosis, as treatment of either the underlying malignancy or with immune therapies could lead to speedy resolution of the neurologic disease. Onconeural antigens have not been a significant factor in pediatric disease. Therefore, they are not discussed in detail here.

The electroclinical symptom complex now usually termed FIRES (febrile infection-related epilepsy syndrome) behaves as if it may have an immune basis. Classically, previously normal children present with increasing encephalopathy and seizures, often status epilepticus, after a history of a febrile illness. The illness can be quite devastating. However, although immunosuppressive therapy may be adopted, to which some response can be seen, only a small number have been determined to have positive antibodies.

For all these epilepsies, the best treatment and the long-term outcomes are not yet clear. Here we describe the main clinical syndromes associated with these epilepsies likely of immune origin (►Table 1). We do not discuss in detail the underlying immune bases or address in detail the arguments for or against cellular or humoral immune drivers. Epilepsies

or seizures arising secondary to known or presumed acute or infectious causes are not discussed here.

Clinical Syndromes

Rasmussen Syndrome

Clinical Syndrome

Rasmussen syndrome is a rare chronic progressive neurologic disease, characterized by unilateral inflammation and atrophy of the cerebral cortex, drug-resistant focal epilepsy, progressive hemiplegia, and cognitive deterioration. A European consensus panel proposed formal diagnostic criteria for Rasmussen encephalitis (RE) in 2005 that remain valid.[12] Rasmussen syndrome is mostly a disease of children, though adolescent and older adult cases probably comprise approximately 10%. No gender, geographic, or ethnic predominance has been noted. Recent studies have estimated an incidence of $2 \cdot 4$ cases/10^7 people per year aged ≤18 years in Germany and $1 \cdot 7/10^7$ people per year aged ≤16 years in the United Kingdom.[13,14]

The typical untreated clinical course is of a median onset at 6 years of age. Though a prodromal stage of mild hemiparesis or infrequent seizures may precede the onset of the acute stage by up to several years, typically the acute stage is characterized by very frequent unilateral seizures, which are drug resistant. In about half of patients, epilepsia partialis continua (EPC) is observed. As the disease progresses, different focal seizure semiologies emerge reflecting newly affected areas of inflammation in the hemisphere.[15] The disease progresses inexorably to hemiparesis, hemianopia, and cognitive decline, often within a year of epilepsy onset. If the language-dominant hemisphere is affected, speech will be affected. The child or young person is left with severe fixed neurologic deficits, motor and cognitive, and ongoing usually drug-resistant epilepsy. This final relatively stable "residual stage" is deceptively still often termed as "burnout."

As well as adolescent and adult presentations, other atypical presentations are described including unilateral movement disorders, hemiathetosis and hemidystonia, and less clearly RS without seizures.[15,16] Bilateral disease as confirmed by neuropathology is debated; if it exists, it is very rare.

Magnetic resonance imaging (MRI) of the brain has an essential role in diagnosis and in follow-up.[17] The greatest change is seen early in the disease process, usually the first 8 months, concordant with the acute clinical phase, and thereafter more gradual progressive unilateral signal change and atrophy (►Fig. 1). Immune-modulating therapies may be attenuating MRI changes. Likewise, the electroencephalogram (EEG) may reflect clinical progression. Initially, as in any of the epilepsies, the EEG may be normal followed within months of seizure onset by the emergence of persistent high-amplitude delta activity over the affected hemisphere. Epileptiform abnormalities become frequent and electrographic seizures are not uncommon. Independent interictal abnormalities over the nonaffected hemisphere emerge within 6 months in 25% and in 62% of patients within 3 to 5 years

Table 1 Key features of Rasmussen syndrome and other inflammatory epilepsies in presentation and investigation

Condition	Presentation	Age	Semiology	Neuroimaging (MRI)	Neuroimaging (PET)	EEG	CSF	Antibodies	Paraneoplastic association
Rasmussen	Acute or subacute	Children and less in adults	Children: Focal seizures, hemiparesis, cognitive decline Adolescent or adult life: clinical course slower, final deficits not as severe, seizure semiology may be more temporal	Progressive unihemispheric focal cortical atrophy Gray or white matter T2/FLAIR hyperintense signal Hyperintense signal or atrophy of the ipsilateral caudate head	Unilateral hypometabolism	Unihemispheric slowing with or without epileptiform activity and Unilateral seizure onset Independent interictal abnormalities over the nonaffected hemisphere	Oligoclonal bands	Not specific	No
NMDAR	Acute	Children and adults	Children: seizures, movement disorder Adults: neuropsychiatric	Nonspecific		Encephalopathic with or without epileptiform discharges Extreme delta brush pattern in adults	Lymphocytic pleocytosis; oligoclonal bands	NMDAR	Ovarian teratoma
Limbic encephalitis	Subacute	Children and adults	Adults - amnesia, confusion, seizures Hyponatremia Faciobrachial dystonic seizures may precede LGI1 LE	High signal in the hippocampus/limbic		Focal or generalized slow		VGKC-complex antibodies	Thymoma. Small cell lung cancer, testicular
FIRES	Acute or subacute	Children & adults	Refractory status epilepticus	Unremarkable		Multifocal	Normal	Not specific	No

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; FIRES, febrile infection-related epilepsy syndrome; FLAIR, fluid-attenuated inversion-recovery; LE, limbic encephalitis; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; PET, positron emission tomography; VGKC, voltage-gated potassium channel.
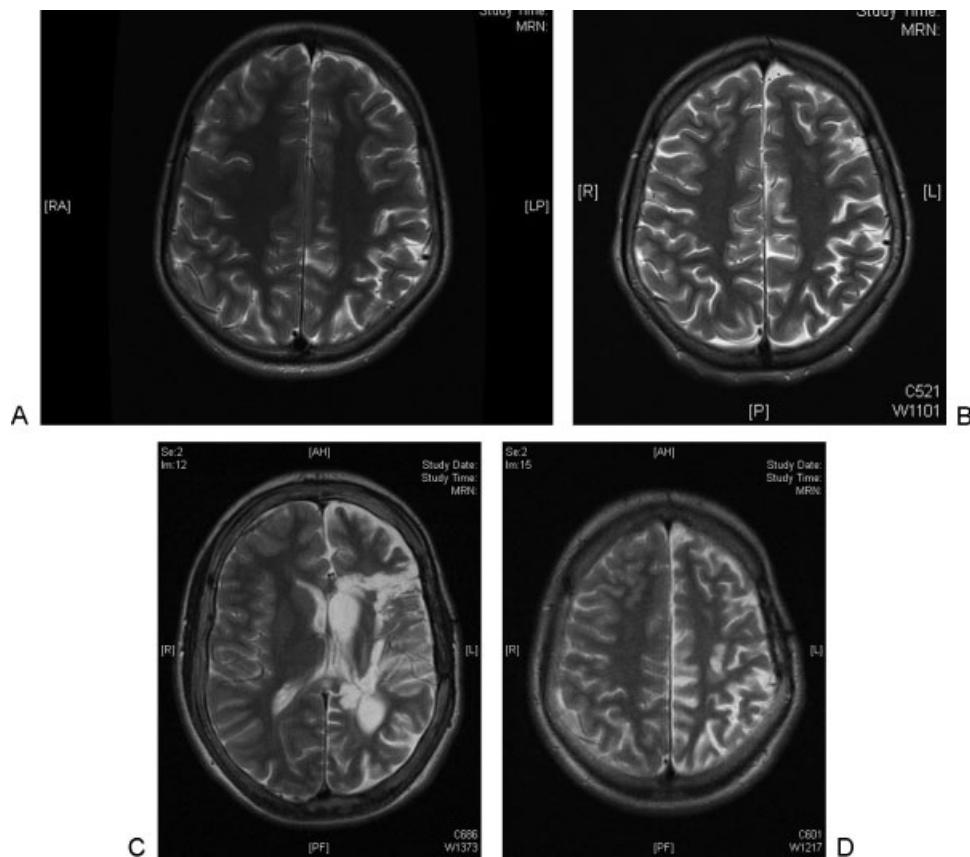
Fig. 1 (A–D) Series of brain axial T2-weighted magnetic resonance images of a boy with left dominant hemisphere Rasmussen syndrome, age of onset at 6 years. He had epilepsy characterized by drug-resistant focal seizures evolving to bilateral convulsive seizures, cognitive decline, and fluctuating right facial and hand weakness. He had a hemispherotomy at age 14 years (►**Fig.1 C**) and is now seizure-free 20 months later. Images (**A**) at age 11 years and (**B**) at age 13 years show progressive left cerebral hemisphere atrophy. (**D**) Image shows continuing atrophy (direct slice comparison to ►**Fig. 1A, B**).

from seizure onset and are a marker of cognitive decline rather than bilateral disease.[18] No specific EEG abnormalities distinguish RS from other causes of focal epilepsy. Epilepsia partialis continua is not always accompanied by ictal surface EEG change.

Immunohistopathology

The histopathological hallmarks of RE are unihemispheric cortical inflammation, neuronal loss, and gliosis. Microglial and lymphocytic "nodules," perivascular cuffing, neuronal death, and neuronophagia, are followed by cortical cavitation, marked astrogliosis and neuronal cell loss as end-stage features. Inflammation itself is multifocal within the hemisphere, may involve any area of the brain, and is progressive, consistent with an immunomediated process.[19]

Research for many years focused on antibodies. However, it became clear that relatively few RE patients have GluR3 antibodies.[20] Since then, other antibodies have been found against α-7 nicotinic acetylcholine receptor, and Munc-18–1, which is an intracellular neuronal protein essential for synaptic vesicle release.[21,22] Recently, VGKC complex antibodies have also been found[23]; nevertheless no one specific autoantibody has been consistently found in RS patients. The role of CNS autoantibodies in the pathogenesis of RE is still unclear.

As focus moved away from antibodies, the pathogenic role of cytotoxic T lymphocytes has become clearer, with a predominance of CD8$^+$ cells and around 10% of these cells positive for granzyme B (GrB$^+$), which release cytotoxic granules onto neurons.[24] These T cells may be specific to as yet undetermined brain antigens. The identity of such an antigen, auto- or foreign-, remains elusive. Microglial and astroglial activation mirror T-cell infiltration. Astrocytes have been thought to play a role in the pathology of a large variety of epileptic as well as inflammatory disorders of the brain[25,26] Genes related to activation of helper/inducer and memory/effector T cells are expressed at higher levels in RS than in patients with cortical dysplasia.[27]

NMDA Receptor Encephalitis

This severe, but potentially treatable encephalitis is characterized by the presence of antibodies to the N-methyl-D-aspartate receptor (NMDAR). The NMDAR is a ligand-gated receptor, permeable to both sodium and calcium, with a voltage-dependent Mg^{2+} block, activated by glutamate and coligand glycine. Autoantibodies were first reported in young women 15 to 45 years of age presenting with a severe encephalopathy in association with ovarian teratoma.[28] In adults, a paraneoplastic cause should be sought. The spectrum has since expanded to include both children and adults,

with emerging differences in presentation by age[29] 23% to 40% of cases are children. Neuropsychiatric features may be more florid in adults, whereas movement disorder and seizures may be more commonly seen in children,[30] with behavioral features still prominent.[31]

The classic presentation in adults is of sequential stages: (1) In a few, a prodromal phase, perhaps associated with infection; (2) an early stage with psychosis, confusion, amnesia, and dysphasia; and (3) within 1 to 2 weeks, movement disorders typically choreoathetoid, autonomic instability, hypoventilation, mutism, and catatonia and often reduced consciousness, requiring intensive care treatment. Epilepsy is not usually a predominant feature.[32]

In children, a prodrome is more frequently volunteered with fever and/or associated intercurrent infection. This is followed by seizures in the majority, generalized or focal. The majority also show behavioral changes and confusion. Neuropsychiatric symptoms (agitation, hallucinations) and movement disorder (choreoathetosis, myoclonus, startle, tremor) are observed. About half of these patients need intensive care admission for seizure control or obtundation.

In children and in adults, a brain MRI may not be helpful and in many may be unremarkable. Cortical (mainly limbic and mesial temporal), brainstem, basal ganglia, and cerebellum changes have been reported. Rarely, T2-weighted and fluid-attenuated inversion recovery (FLAIR) hyperintensities or contrast enhancement (in cortical meninges or basal ganglia) are detected. Reversible changes and atrophy have been observed in pediatric series (►Fig. 2). In adults, the EEG may be unremarkable initially, later it may show widespread changes with generalized high-amplitude slow activity. In children, the EEG at presentation, is more likely to be slow consistent with an encephalopathy and early epileptiform discharges may be seen.[33] One case is reported of anti-NMDAR encephalitis mimicking the acute phase of RS.[34]

In CSF, lymphocytic pleocytosis is frequent at onset, as are oligoclonal bands. There is debate as to whether diagnosis is better made from CSF or plasma.[35] Certainly, concentrations of NMDAR antibodies in serum are high, but there is also high intrathecal synthesis.

If a tumor is present, this should be resected. Early treatment has been associated with better outcome. First-line immunotherapy is usually steroids (intravenous and/or oral steroids, intravenous immunoglobulin, and/or plasma exchange (PLEX). Second-line immunotherapies, when needed, include cyclophosphamide or monoclonal antibodies (rituximab).[5]

Overall, the outcome is felt to be good, better in paraneoplastic associated disease, but recovery may be slow and relapse not infrequent in both children and adults (up to 25%).[36] Learning, memory, and behavioral sequelae may be elucidated with awareness of this disease. The frequency of relapse raises the issue of the need to consider the risks and benefits of longer-term immunosuppression in selected patients.

Limbic Encephalitis

First recognized as a paraneoplastic syndrome with amnesia, psychological disturbance, and seizures, knowledge of
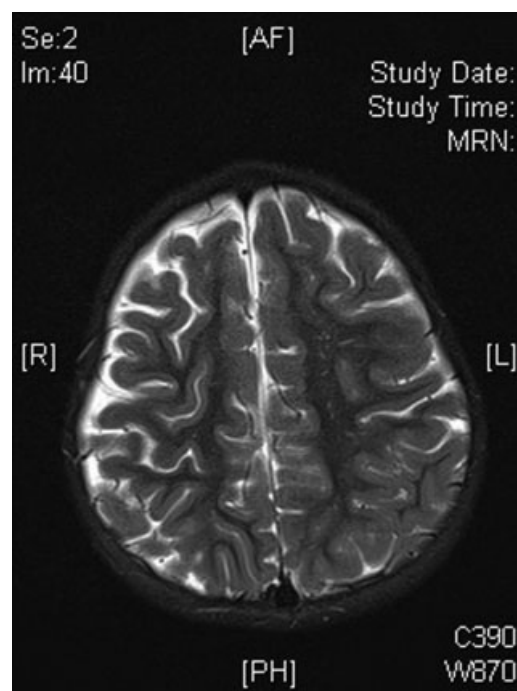

Fig. 2 Brain axial T2-weighted magnetic resonance image showing right cerebral hemisphere atrophy, predominantly frontal in a 2-year-old girl with N-methyl-D-aspartate receptor (NMDAR) encephalitis. The radiological features are similar to Rasmussen syndrome, but are nonprogressive and the clinical picture is different. The child presented at 19 months with poor feeding and vomiting, followed by seizures and a choreiform movement disorder. Recovery has been slow with developmental delay and oropharyngeal dyskinesia. Treatment has included intravenous immunoglobulin, methylprednisolone, and rituximab. NMDAR antibodies have persisted. This child was included in Hacohen et al study.[33]

etiology means that the cause now is more likely to be identified as nonparaneoplastic and antibody-mediated. The main players are antibodies to components of the VGKC-complex, specifically contactin-associated-protein 2 (CASPR2), contactin-2 and leucin-rich, glioma-inactivated 1 (LGI1).[37] Less frequently seen are antibodies to the NMDAR, AMPAR, GABAR, and GAD. The clinical semiology somewhat corresponds to the antibody detected.

Limbic encephalitis is a disease mainly of men (2:1 ratio), aged 40 years and above. The onset is usually acute or subacute with memory loss, confusion, agitation, and psychiatric symptoms emerging over weeks such that the initial diagnosis is often felt to be an organic psychiatric syndrome. Seizures have mesial temporal semiology and are drug resistant. Sleep disturbance, hypothermia, intestinal pseudo-obstruction, ataxia, and startle syndrome have been reported. The presence of hyponatremia may be a specific clinical clue. Antibody titers are high (> 400 pmol/L and often > 1000 pmol/L).[4]

The EEG shows interictal and ictal temporal, and sometimes frontal, epileptiform activity or slowing. Magnetic resonance imaging may not be helpful; it is normal in almost half of patients. Where it is abnormal, there is usually high signal on T2-weighted or FLAIR, unilaterally or bilaterally, in the mesial temporal lobes or amygdalae. Changes in the temporal lobes may be seen on fluorodeoxyglucose positron

emission tomography, with early hypermetabolism and late hypometabolism.

Similar to NMDAR antibody encephalitis, a good response to first-line immunotherapy is expected, symptomatically, biochemically, and serologically, with a fall in antibody titers. The disease is monophasic in most, but in a small number of patients, antibodies persist and the course may be chronic or relapsing/remitting. Again, similar to NMDAR antibody encephalitis, patients may be left with functional deficits. More recently, VGKC-complex antibodies are reported in children with limbic encephalitis, status epilepticus, prolonged seizures, and a less-specific encephalopathy syndrome with seizures and psychiatric features.[33,38] In children, the outcome is less favorable than in adults, with poor response to immunotherapy.[38]

LGI1 Antibody-Associated

LGI1 is a glycoprotein that associates with synaptic Kv1 VGKCs and is highly expressed in the hippocampus and neocortex. Mutations in *LGI1* are known to cause autosomal dominant lateral temporal lobe epilepsy.[39] As well as limbic encephalitis, antibodies to LGI1 have been found in patients with epilepsy, Morvan syndrome, and faciobrachial dystonic seizures (FBDS). Although FBDS may herald later progression to limbic encephalitis, it is not yet clear if immunotherapy of FBDS will prevent subsequent phenotypic spread.[3]

CASPR2 and Contactin-2 Antibody Associated

CASPR2 and contactin-2 are cell-adhesion molecules essential for the localization of VGKCs at neural juxtaparanodes. Mutations affecting CASPR2 are described in a family with cognitive impairment, seizures, and absent deep tendon reflexes.[40] Antibodies to CASPR2 have been found in limbic encephalitis, neuromyotonia, and in Morvan syndrome (where antibodies against CASPR2 are more frequent than against LGI1).[37]

Morvan syndrome is a rare also potentially treatable autoimmune disease. The onset is more insidious than in limbic encephalitis; the symptoms may be similar—sleep disturbance, psychiatric features, memory loss, and confusion. Clinical clues are caused by neuroendocrine and autonomic dysregulation: cramps, sweating, fasciculations, pain, cardiac arrhythmias, impotence, constipation, and urinary problems. Seizures do not seem to be a feature. Magnetic resonance imaging may be normal. Positive CSF oligoclonal bands may be present. As with the other antibody associated encephalitides, response to immune therapy is reported. An underlying tumor should be sought, especially thymoma.

GABA-Receptor Antibody Encephalitis

GABA is the main inhibitory neurotransmitter in the brain. There are two GABA receptors, $GABA_A$, the more predominant ligand-gated ion channel, and $GABA_B$, linked to G-proteins. $GABA_BR$ antibodies are reported associated with limbic encephalitis, and with an underlying malignancy in half of these patients.[8,41] $GABA_AR$ antibodies have been reported in the presence of high serum and CSF titers in patients with seizures and refractory status epilepticus, and with lower serum-only titers, in patients with neurologic syndromes including

stiff-person and adult-onset opsoclonus-myoclonus syndrome.[9] The spectrum has recently been expanded to include memory impairment with confusion or disorientation, and psychiatric features with hallucinations and anxiety.[10]

Anti-GAD Limbic Encephalitis

Glutamic acid decarboxylase irreversibly catalyses GABA synthesis from L-glutamic acid. Antibodies to GAD are usually associated with insulin-dependent diabetes and with the spectrum of subacute onset stiff-person disorders, but have also been reported, often at high levels, in up to 10% of adults with long-standing epilepsy and in limbic encephalitis.[12,42] Magnetic resonance imaging is more likely to show mesial temporal changes in keeping with inflammation and later scarring. Response to immunotherapy is poor. Like FBDS, there may be a phenotypic spread of the clinical syndrome as noted in the case described in ▸Fig. 3, which also illustrates the co-existence of antibodies directed against intracellular and neuronal or glial cell-surface expressed antigens.

Antibodies Implicated in the Epilepsies

Voltage-gated potassium channel, GAD, NMDAR, and glycine receptor antibodies have all been detected in adults with both
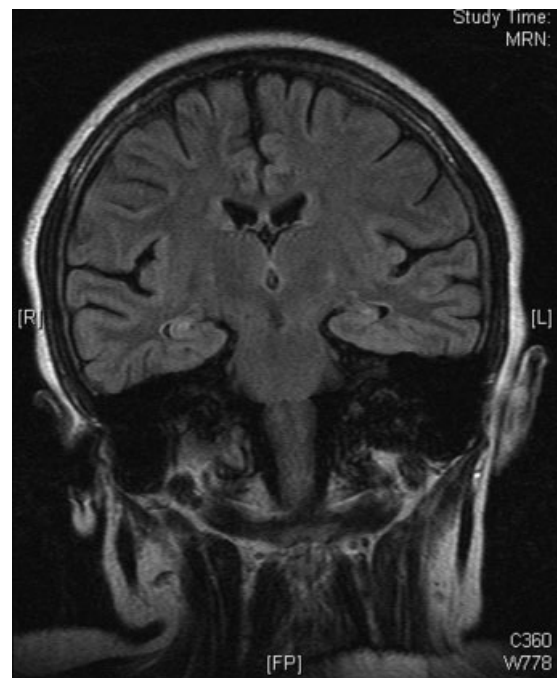

Fig. 3 Brain coronal fluid-attenuated inversion-recovery magnetic resonance image showing bilateral hippocampal sclerosis in a 14-year-old girl with voltage-gated potassium channel (VGKC) and glutamic acid decarboxylase (GAD) antibody-mediated disease. She presented at almost 13 years of age with focal dyscognitive seizures and visual and auditory hallucinations. Seizures continue and are drug resistant. Stiffness and pain, and insulin-dependent diabetes emerged in the year following presentation. She has significant memory and verbal cognitive ability impairment. Treatment has included intravenous immunoglobulin, steroids, plasma exchange, rituximab, mycophenolate, and alemtuzumab. Anti-GAD and anti-VGKC antibodies have been strongly and persistently positive, > 5000 U/mL and 1440 pM (picomolar).

established and newly diagnosed epilepsy, at higher prevalence than controls (11%).[43] The NMDAR and VGKC-complex antibodies can occasionally be present in patients with neurodegenerative disease, suggesting they are likely to be secondary to the pathology rather than causative. On a more cautious note, antineuronal antibodies are also prevalent in normal healthy controls as well as neuropsychiatric patients and so may not always be pathogenic,[44] though it is hypothesized that under conditions of BBB dysfunction, antibodies can have pathogenic effects.[45]

Autoantibodies in Cerebral Folate Deficiency

Cerebral folate deficiency (CFD) is defined as any neurologic syndrome associated with low CSF fluid 5-methyltetrahydrofolate (5MTHF) in the presence of normal peripheral folate metabolism.[46] Cerebral folate deficiency as a clue to the underlying diagnosis is underrecognized. There are many causes, in which seizures are a significant symptom. Primary CFD may be due to mutations in the gene encoding the folate receptor FR1 expressed in the CNS (*FOLR1*). Secondary causes include mitochondrial cytopathies and Aicardi-Goutieres syndrome. Autoantibodies against FR1 have been demonstrated in children with infantile-onset irritability, developmental delay, autism, movement disorder, acquired macrocephaly, and epilepsy characterized by myoclonic–astatic, absences, and generalized tonic–clonic seizures.[47] Treatment of CFD in general is with calcium folinate supplementation, but it is not clear yet in the various different causes whether this will be beneficial. In autoantibody CFD, a partial response to supplementation was reported, better in those treated at a younger age. It has been suggested that cross sensitivity with antigens in cow's milk leads to autoantibody formation. Intriguingly, autoantibody titers reduce on milk-free diets.[48]

Febrile Infection-Related Epilepsy Syndrome (FIRES)

The acute presentation of recurrent refractory seizures or status epilepticus following a febrile illness in a previously normal individual has been described in adults and children under a variety of names including encephalitis with refractory repetitive partial seizures (AERRPS), severe refractory status epilepticus due to presumed encephalitis, idiopathic catastrophic epileptic encephalopathy, new-onset refractory status epilepticus (NORSE), acute devastating epileptic encephalopathy in school-aged children (DESC), and febrile infection-related epilepsy syndrome (FIRES). The latter has become the adopted term among European authors. The proximity in almost all cases to a preceding febrile illness has raised the possibility that this remains an autoimmune disorder triggered by the infection. In contrast to febrile status epilepticus, the fever preceding the onset of encephalopathy is often low grade or absent. This argues against a fever-induced inflammatory process, but inflammation during the preceding infection may elicit a secondary immune response or may allow existing autoantibodies to access the

CNS. Although known antibodies have been detected in a few with this condition (e.g., anti-GAD 4/12,[49] neuropil,[50] and VGKC in isolated reports[51]), the numbers relative to cases reported have been small. Further, an underlying predisposition as the result of genetic mutations appears unlikely.[52–54]

Typically, children present following a nonspecific, febrile (in the majority) illness with escalating seizures, more often status epilepticus requiring barbiturate coma in the intensive care unit. Most patients experience focal seizures, reflected in the EEG. Extensive evaluation of CSF for infectious agents and evidence of inflammation has in general proved negative. Magnetic resonance imaging is reported as normal in a little over half; others predominantly show signal abnormalities in the hippocampi or peri-insular region.[49] Brain biopsies (or analysis of brain from postmortem) have been reported in isolated cases, but have not demonstrated features of inflammation. Response to treatment has been disappointingly poor; steroids and immunoglobulin are those most consistently used, but with variable effect. The only evidence of sustained effect has been reported by Specchio and colleagues who reported a positive response in 2 out of 10 children treated with immunoglobulin; neither of whom required barbiturate coma.[55] A ketogenic diet has also been reported to be effective in some series where antiepileptic drugs have failed.[48,56] Outcome is consistently poor with around 11% mortality.[49] After a period of weeks or months, seizures finally cease or stop, although ultimately 93% of survivors are reported as having refractory epilepsy, continuing after the acute phase with very few demonstrating preserved cognition. Magnetic resonance imaging in the chronic phase (after at least 6 months) might reveal bilateral mesial temporal atrophy and a T2 hyper signal, but remains negative in half of patients.

The lack autoantibodies and the disappointing response to immunomodulatory treatments raise the question as to the degree this may be an immune condition. Recent discussion has centered around the likelihood that inflammation plays an important role in the pathogenesis, but how treatment may limit the cascade or the inevitable process remains unclear.[57]

Treatment

Despite emerging evidence on inflammatory and autoimmune bases the mainstays of treatment remain little different from other encephalitides and epilepsy. On presentation with escalating seizures or overt established status epilepticus, acute supportive management is required, with treatment with appropriate antiepileptic drugs as per protocol. Often individuals will prove resistant to standard antiepileptics, with required continuation to barbiturate coma. There is no evidence that etiology at this stage requires a different approach, except a discussion as to the role of immunomodulatory agents in parallel to supportive treatment. This may differ in type and duration according to the presentation.

Acute presentation with repetitive seizures or overt status epilepticus often calls for more aggressive immediate treatment. Bolus methylprednisolone can be administered quickly

and effectively, with rapid determination of effect. In more subacute presentations oral steroids can be used. Immunoglobulin is usually reserved for treatment where definitive positive autoantibodies are found, although in an acute ITU situation a trial of treatment may be given where suspicion is high. The role of further immunosuppressive agents or plasma exchange in acute presentations will need individual consideration in the presence of positive autoantibodies, but where negative their role remains unclear, with little in the way of positive response reported.

Ketogenic diet has been reported to have a role in acute presentation with status epilepticus, but whether its role is an effect on inflammation over and above any antiepileptic effect remains unknown.

The treatment of Rasmussen syndrome has demanded a different approach, and with the progressive nature presumed to be autoimmune in nature, various groups have attempted immunosuppressive therapy. The natural history has been one of a progressive destruction of one cerebral hemisphere, with treatment with antiepileptic drugs to treat epilepsy, and inevitable surgery in the form of hemi-disconnection in time. The assessment has always been timing of surgery, with the concern about the inevitable functional consequence of hemiparesis, hemianopia, and in the case of a language-dominant hemisphere the possibility of dysphasia. Immunosuppressive treatments have been trialed (tacrolimus,[13] azathiaprine[14]). The progress of the disease appears to be slowed rather than halted, with delay in time to surgery compared with historical controls. Monoclonal antibodies have been reported in isolated cases to be of some success, but again the disease process only appears slowed.[58,59] Some lessons could be learned from other inflammatory disorders such as multiple sclerosis, but without further detail on underlying pathophysiology, the risk is outweighed by the benefit. There appears to be little role for surgery in the management of other immune epilepsies, recognizing that a single focus is unlikely to be responsible for the seizure onset.

Conclusion

An increasing number of epilepsies are thought to have an immune or possibly an additional inflammatory basis to the underlying pathophysiology. This is likely to have implications for management, looking beyond supportive treatment with conventional antiepileptic drugs. Although in some, definitive biomarkers in the form of recognized autoantibodies may be found, their temporal relationship to the course of the illness may remain unclear. The degree to which such antibodies is causative or secondary to a neurologic insult remains in some circumstances unclear. There appears to be little relationship between titers and the clinical course of the disease. However, there may be a role for such antibodies to play in other epilepsies beyond those with recognized presentations. As we collect more information from research into these disorders, new ways of thinking will develop with regard to management strategies, which in turn will bring improved outcomes.

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