epilepsy action

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CURRENT AWARENESS SERVICE

The prevention of epilepsy: a sequel

The prevention of epilepsy was the main article in the third issue of PECAS (September 2022; 16: number 3). In that article, I cited the results of the 'EPISTOP' trial which had been published in 2021 [Kotulska et al, 2021]. This study reported the outcome of 54 infants with tuberous sclerosis complex (TSC) treated at less than four months of age and followed up until two years of age. The results showed that of the 27 patients that had received preventative treatment with vigabatrin (VGB) at the onset of abnormal 'epileptiform activity' (EA) on the EEG, none had developed spasms by 24 months, all had a later onset of clinical seizures and all had a significantly lower frequency of anti-seizure medication (ASM)-resistant epilepsy, when compared with the 27 that had received VGB at the onset of clinical or electroencephalographic seizures (seizures captured on EEG). Importantly, the developmental outcomes and incidence of autism at 24 months were similar in the two groups. Adverse side-effects were few and similar in both groups. The authors, understandably, concluded that "Preventative treatment with VGB was safe and modified the natural history of seizures in TSC, reducing the risk and severity of epilepsy" [Kotulska et al, 2021]. Clearly, this was a very small study with full data available on only 54 children, and the diagnosis of autism at two years of age might seem somewhat premature and therefore inappropriate. Questions remained over the observed benefit being maintained after three, five or more years of follow-up and whether developmental progress and cognitive function would differ between the preventatively (prophylactically) and conventionally-treated groups.

Another 'preventative' study in infants with TSC had started in the US two years after the 'EPISTOP' study had ended; this was the 'PREVeNT' study which was subsequently published in 2023 [Bebin et al, 2023]. The study enrolled infants aged less than six months old, with the primary hypothesis that preventative treatment with VGB at the onset of abnormal interictal epileptiform activity on the EEG would improve developmental outcomes at 24 months and reduce the risk of ASM-resistant epilepsy. This was another very small study with identical numbers of patients to 'EPISTOP'. Twenty-seven infants were randomised to preventative treatment with VGB at the onset of EA and 27 randomised to treatment with placebo. Nineteen infants in the latter group then transitioned to receive VGB (because of the onset of clinical or electroencephalographic [EEG] seizures) with a median delay of 44 days after the initial randomisation. The proportion of patients in the two groups (treated and placebo) with focal seizures, ASM-resistant epilepsy or developmental delay (using the Bayley Scales of Infant and Toddler Development) was no different at 24 months post-randomisation. Infants treated with VGB at the onset of EA also showed a statistically significant reduction in

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the incidence, and time to onset, of infantile spasms. Delayed treatment of spasms (which was commenced on clinical presentation with seizures) in the placebo arm did not change the developmental outcome. The study also looked at the positive and negative predicative value of the interictal EEG activity (both were 0.73) on surveillance EEGs. The obvious conclusion is that some infants may show abnormal epileptiform activity on sequential EEGs but who do not develop seizures (of any type) by 24 months of age. A secondary outcome from this study was that a delay of up to 44 days (six weeks), which was the time from the identification of EA in 19 of the 27 patients in the placebo group, did not adversely affect developmental outcome at two years; however, it is important to understand that this was based on only a very small number of patients. This period of 44 days (six weeks) is similar to previously reported data which have suggested that either four (Widjaja et al, 2015), six (Bashiri et al, 2021) or eight (O'Callaghan et al, 2017) weeks from onset of spasms to treatment initiation is a watershed. Treatment that is initiated after this time is associated with a worse developmental outcome. Clearly, with infantile spasms and unlike with other seizure types, the difference between four and eight weeks is significant. It is likely that any watershed period may be influenced by other factors, but the pattern now seems to be clear that spasms should be treated within a maximum of eight weeks of their onset to maximise developmental outcome.

The 'take home' messages from both the 'EPISTOP' and 'PREVeNT' studies are the following:

- VGB remains the ASM of first choice in the treatment of infantile spasms. No surprise
- VGB may not be an effective ASM in the treatment of focal seizures. No surprise. This has been well-documented in the past, including in the international TuberOus SClerosis international registry to increase disease Awareness (TOSCA) which currently holds data on over 2,000 patients (Nabbout et al, 2021)
- The predictive value of the EEG is by no means absolute. Again, no surprise
- More work is required on fine-tuning the use of preventative medication in infants with TSC. Again, no surprise. This is inevitable in view of the heterogeneity of the cerebral lesions (focal cortical dysplasia, tubers and the recognisable MRI-negative neuronal network dysfunction) that characterises TSC

Since the late 1990s, there has been a major concern that VGB may cause irreversible visual impairment, particularly on peripheral vision. I was never convinced that this concern was entirely justified because of the heterogeneity of the epilepsies and specifically their different aetiologies, underlying comorbid conditions, poor visual assessment techniques in children and biased interpretation of visual findings. However, this issue led to the drug being 'Black-Boxed' by the Food and Drug Administration (FDA) in the US. The Medicines and Healthcare products Regulatory Agency (MHRA) also issued very strict guidance about its use. Fortunately, the National Institute for Health and Care Excellence (NICE) entirely appropriately now cites VGB as an ASM of first-choice in the treatment of infantile spasms (NICE 2022; pages 18-19). More recently, a comprehensive review of a registry of more than 9,000 patients treated with VGB in the US, reported no definite case of visual impairment that could be directly attributed to the drug (Foroozan 2018). This is quite amazing within the context of the previous global and almost manic concern over the safety of this ASM.

Studies are ongoing in an attempt to modify the symptoms and even the natural history of TSC. These include the 'STEPS' and 'ViRAP' studies. 'STEPS' (Sirolimus TSC Epilepsy Prevention Study) is a phase II* study (trial) which compares sirolimus against placebo with the primary outcomes of safety and time to seizure onset. 'ViRAP' (Efficacy and Safety of Rapamycin versus VGB in the prevention of tuberous sclerosis complex symptoms) is a phase II/III* study (trial) which compares sirolimus against VGB with the primary outcome of the incidence of clinical seizures and volume of TSC-tumours after a treatment period of two years. Both studies should have completed follow-up in 2026 and with publication in late 2027 or early 2028. Sirolimus has no recognised and as yet no identified anti-seizure or anti-epileptogenic actions, but it clearly modifies TSC. This has been demonstrated by its positive effect on its non-neurological (renal and cutaneous) and neurological (subependymal giant cell astrocytomas [SEGAs]) features with a reduction in the size of tumours and a prevention in their growth. Most recently, everolimus (which is the next generation of sirolimus) has been shown to reduce the frequency of seizures [Curatolo et al, 2018].

Disease-modification by medication is clearly well-recognised for many diseases but this may be the famous and frustratingly elusive 'Holy Grail' for most epilepsies. This is because epileptic seizures represent the manifestations (symptoms) of the disease rather than the disease itself. Nevertheless, the concept of, and research into, disease-prevention in the epilepsies should not be abandoned. In fact, this objective may prove to be more achievable than the prevention of epilepsy. Time will tell.

***Phase II**

These trials are performed on a relatively small patient group (50 – 300 participants). They are designed to assess the drug's efficacy (how well it works) as well as its safety. If shown to be effective, the drug may then be studied in a much larger group of participants often with different dose ranges (Phase III Trial).

***Phase III**

These trials are performed on larger patient groups (300 – 3,000 participants depending on the disease). They are designed to assess the effectiveness of the new treatment

or intervention and, therefore, its value in clinical practice. Consequently, these trials are seen as the definitive assessment of how effective the drug is, in comparison with any current 'gold standard' treatment.

Richard Appleton
Co-Editor

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Forthcoming courses and conferences

The following are details of forthcoming conferences and courses in epilepsy and general paediatric neurology.

2024

October
21-23
ILAE British Branch Annual Scientific Meeting
Liverpool, UK
ilaebritishconference.org.uk

November
9
2024 ILAE British Branch Clinical Epilepsy Course for Doctors in Training
Brimingham, UK
ilaebritish.org.uk/events/2024-ilae-british-branch-clinical-epilepsy-1-day-course-for-doctors-in-training

December
2-3
Encephalitis 2024
London, UK & Online
encephalitis.info/encephalitis-conference


Liverpool


Birmingham

2025

January
20-24
14th ILAE School on Pre-Surgical Evaluation for Epilepsy and Epilepsy Surgery
Brno, Czech Republic
ta-service.cz/epodes2025

March
20-22
19th World Congress on Controversies in Neurology
Prague, Czech Republic
cony.comtecmed.com

April
2-4
International Congress on Structural Epilepsy & Systomatic Seizures 2025
Gothenburg, Sweden
bit.ly/3X8FlOt

August-September
30-3
36th International Epilepsy Congress
Lisbon, Portugal
ilae.org/congresses/36th-international-epilepsy-congress

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Inflammatory and autoimmune epilepsies: a review

Dr Anand S. Iyer, consultant paediatric neurologist, Apollo Hospitals International Limited, Ahmedabad, India and Alder Hey Children's Hospital, Liverpool, UK

The autoimmune epilepsies are a group of disorders in which immune mechanisms generate and cause repetitive seizures. Most of these are due to an autoimmune encephalitis, of which several antibodies have been discovered and the phenotypes well characterised. Autoimmune encephalitis may present with a range of symptoms: memory loss, alteration in sensorium, psychiatric symptoms and movement disorders, as well as frequent seizures. Other cases present with new onset refractory status epilepticus (NORSE) which may be associated with fever (fever induced refractory epileptic seizures – FIRES) in children and can be challenging to diagnose and particularly to treat. Some epilepsies can also be triggered by other autoimmune processes going on within the brain, for example vasculitis. Or, they may be related to systemic autoimmune processes, for example systemic lupus erythematosus. This review will focus on a clinical approach to recognition and management of autoimmune epilepsies related to autoimmune encephalitis and FIRES mainly.

Presenting features in autoimmune epilepsy

Prodromal symptoms may be present in some children, and these can be similar to viral infections with upper respiratory tract symptoms, fever, headache, insomnia and irritability. Most of these are due to viral infections, however viral encephalitis should be suspected and excluded before considering the possibility of autoimmune encephalitis.

Autoimmune encephalitis

Seizures are the usual presenting feature in most of the autoimmune encephalitis. However, children also present with a wide range of other features like behavioural and sleep disturbances, mutism, movement disorders and encephalopathy [De Bruijn et al, 2020]. N-methyl-D-aspartate receptor (NMDAR) encephalitis has a well-defined phenotype in children and is characterised by encephalopathy, dyskinetic thrashing limb movements, orolingual dyskinesias, hypoventilation and autonomic dysfunction [Scheer and John, 2016]. Faciobrachial dystonic seizure (FBDS) and hyponatremia are unique features in leucine-rich glioma-inactivated protein 1 (LGI1)-antibody encephalitis, more commonly presenting in adults [Alotaibi et al, 2022; Rodriguez Cruz et al, 2016]. Refractory status epilepticus and epilepsia partialis continua frequently presents in γ-aminobutyric acid (GABA)-A encephalitis [Zhu et al, 2020a]. Patients with glutamic acid decarboxylase (GAD) encephalitis may develop limbic encephalitis (characterised by seizures and memory decline) or other neurologic syndromes, such as cerebellitis and stiff-person syndrome [Zhu et al, 2020b]. However, notably, the GAD antibody is also associated with type I diabetes mellitus. Thyroid peroxidase (TPO) antibody mediated hypothyroidism and encephalopathy (steroid responsive encephalopathy with autoimmune thyroiditis, Hashimoto encephalopathy) also presents with encephalopathy and seizures [Laurent et al, 2016]. These show the correlation between systemic autoimmune mediated disorders like hypothyroidism and diabetes, and similar immune-mediated neuroinflammatory disorders. Glycine receptor antibodies are reported with stiff-person syndrome in adults, but causes a unique presentation with progressive encephalomyelitis, rigidity and myoclonus (PERM) with refractory touch-induced myoclonus resembling tetanus in children [Carvajal-González et al, 2014]. Myelin oligodendrocyte glycoprotein (MOG) antibody can present with varying features, including acute disseminated encephalomyelitis and optic neuritis. It can co-exist with other autoantibodies like NMDAR antibody and cause autoimmune encephalitis [Ding et al, 2021; Kleerekooper et al, 2021]. A list of common autoimmune encephalitis and their presenting features is presented in *Table 1*.

Autoimmune epilepsies and encephalitis can be associated with a tumour as a paraneoplastic syndrome, and investigating to look for the common ones is prudent. Ovarian teratoma, thymoma, small cell lung cancer, and neuroendocrine tumours are especially prone to inducing paraneoplastic syndromes. Approximately 40% of patients with NMDAR encephalitis will be found to have an ovarian teratoma [Scheer and John, 2016]. Additionally, contactin-associated protein-like 2-antibody encephalitis is associated with thymoma in about 5% of patients. Small-cell lung cancer is detected in 70% of patients with GABA-B encephalitis, while lung cancer and thymoma are found in approximately 70% of patients with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) encephalitis [Jang et al, 2020]. On the other hand, no tumour has been found to be associated with GAD encephalitis. In most cases, screening with relevant investigations, such as chest x-rays, computed tomography (CT) and, occasionally, magnetic resonance imaging (MRI) scans should be undertaken to exclude any associated malignancies.

NORSE and FIRES

Sudden onset of refractory focal or generalised seizures is the usual presentation in school-aged children with FIRES. This is extremely rare and the estimated annual incidence and prevalence of FIRES amongst children and adolescents in Germany is respectively, 1: 1,000,000 and 1: 100,000 [Van Baalen et al, 2010]. Other systemic symptoms, including fever or autonomic disturbances, are not

Dr Anand S. Iyer, consultant paediatric neurologist, Apollo Hospitals International Limited, Ahmedabad, India and Alder Hey Children's Hospital, Liverpool, UK

Table 1. Common autoimmune encephalitis in children.

Type	Presentation	Tumour association	Treatment	Outcome
NMDAR	Seizures, orofacial and limb dyskinesias, behavioural change	Ovarian teratoma	PLEX, rituximab	Favourable
LGI-1 and CaspR2	Seizures, cognitive decline, movement disorders	None	Steroids, IVIG	Favourable
MOG	Seizures, focal neurological deficits, optic neuritis, encephalopathy	None	Steroids, monthly IVIG or rituximab for relapsing patients	Favourable
TPO (Hashimoto encephalopathy)	Seizures, hallucinations, encephalopathy	None	Steroids Rituximab	Favourable
GAD	Seizures, cognitive decline, psychosis, stiff person syndrome	None	Rituximab	Variable outcome, cognitive difficulties persist
GlyR	PERM, myoclonus, encephalopathy	None	PLEX Rituximab	Variable SPS persists
GABA-A and B	Status epilepticus, encephalopathy	Hodgkin lymphoma	Treatment of lymphoma Steroids	Recovery with appropriate treatment
GFAP	Encephalopathy, seizures, headache, meningeal symptoms	Paraganglioma	Rituximab	Favourable
Hu	Refractory seizures, psychiatric symptoms	Neuroblastoma Small cell carcinoma	Cyclophosphamide	Poor Cognitive decline and refractory seizures
Ma	Seizures, behavioural change, dystonia	Mediastinal tumours, testicular cancer	Cyclophosphamide	Poor Refractory seizures

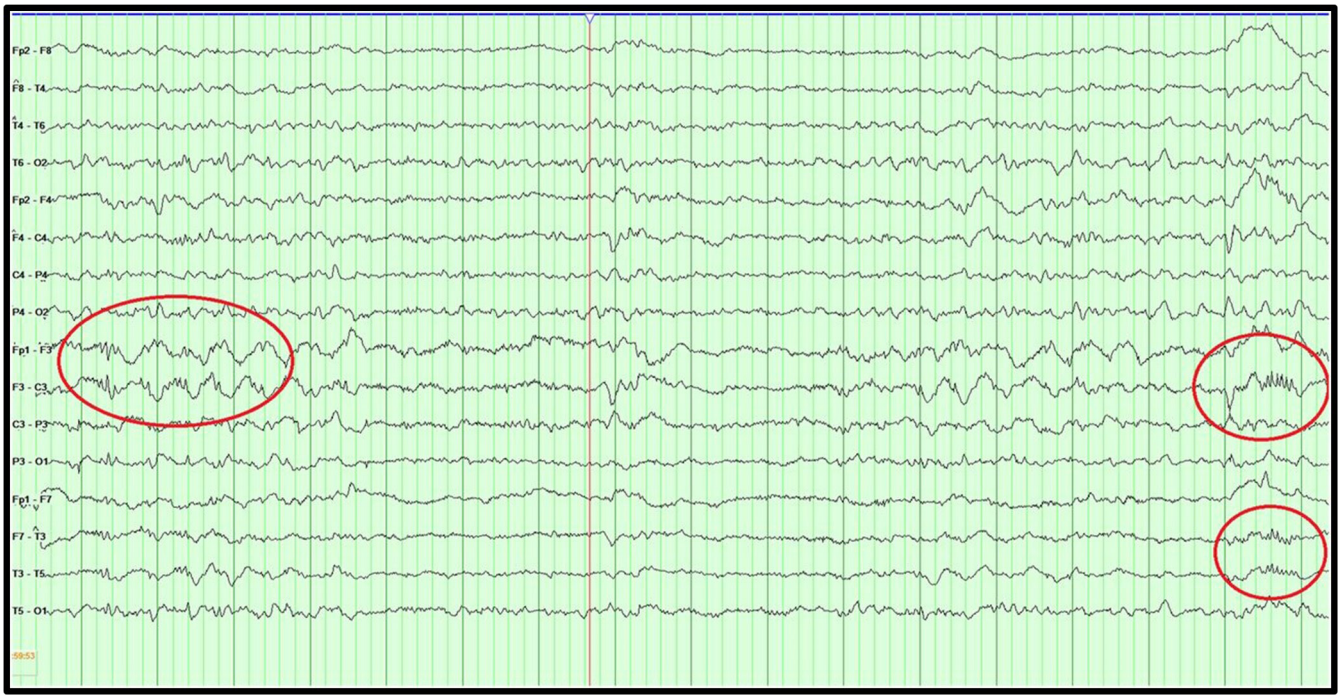
LGI leucine rich glioma inactivated protein, CASPR contactin associated protein, MOG Myelin oligodendrocyte glycoprotein, TPO Thyroid peroxidase, GAD Glutamic acid decarboxylase, GlyR Glycine receptor, GABA Gamma amino butyric acid, GFAP Glial Fibrillary Acidic Protein, PLEX plasma exchange

prominent at presentation, but may have been present in the days or weeks before presentation. The FIRES diagnosis requires a prior febrile illness starting between two weeks and 24 hours before the onset of refractory status epilepticus [Hirsch et al, 2018]. In most cases, there isn't an identifiable acute structural, toxic or metabolic cause. The seizures are very frequent, usually focal evolving to bilateral clonic seizures, and do not respond to conventional anti-seizure medications. Children usually require ventilatory support, midazolam and other anaesthetic infusions to try and stop the seizures. Continuous EEG monitoring typically show a significant seizure burden with accompanying severe encephalopathic or a suppressed background. The ILAE has recommended some practice parameters for the early identification and management of FIRES in children [Hirsch et al, 2018; Pavone et al, 2022; Wickstorm et al, 2022].

Rasmussen's encephalitis

This is a very rare and progressive disorder, characterised

Figure 1. Extreme delta brush pattern (delta waves with superimposed fast beta activity) seen in NMDAR encephalitis.



by medication-resistant focal epilepsy, progressive hemiparesis, hemianopia, cognitive decline and unilateral brain atrophy. The incidence is around 1.7 per 10 million people aged under 16 years [Varadkar et al, 2014]. It starts abruptly and acutely around six years and, usually, with a characteristic type of seizure called epilepsia partialis continua. This usually presents as focal motor status epilepticus involving one half of the face and limbs but with preserved awareness. This may then last for hours or days and can be refractory to most anti-seizure medications. It is presumed to be caused by an abnormal immune response, specifically by T lymphocytes. However, most investigations that have tried to identify an infectious or antibody-mediated cause have been negative or inconclusive. Formal diagnostic criteria have been developed by consensus [Cay-Martinez et al, 2020]. With early immunotherapy, some children remain stable for some time before progressing to unilateral neurological deficit and medication-resistant epilepsy.

Diagnostic investigations

Table 2 summarises the recommended investigations in cases of autoimmune epilepsies.

Cerebrospinal fluid analysis

Autoimmune encephalitis generally presents with an abnormal cerebrospinal fluid (CSF) profile, including moderately raised lymphocytes count and elevated protein levels. However, an infectious cause must always be excluded first. Atypical bacteria such as listeria, tuberculosis, or borrelia can mimic the symptoms of autoimmune epilepsy. The immunoglobulin G (IgG) index and oligoclonal band in the CSF are helpful to confirm the presence of intrathecal antibody synthesis which would support an auto-immune, rather than an infective, encephalitis. While the CSF protein in the acute stage is sensitive to active ongoing inflammation, high levels of CSF protein in the chronic stage can indicate residual inflammation. CSF Interleukin-6 levels are indicative of active inflammation in FIRES and regular monitoring of this marker can help determine response to therapies [Wickstrom et al, 2022]. Certain autoantibodies like NMDAR antibodies are commonly measured in the CSF and monitoring of these titres also help guide management.

Neuroimaging

Brain magnetic resonance imaging (MRI) with contrast and careful analysis of the arteries to look for any evidence of vasculitis would be recommended in most cases. The findings of brain MRI in patients with certain types of autoimmune encephalitis can vary from normal to T2-weighted hyperintensities in the mesial temporal lobes (NMDAR encephalitis) or multifocal brain lesions (MOG antibody mediated neuroinflammation) [Sanvito et al, 2024]. NORSE patients usually have normal MRI at presentation, although they may exhibit progressive medial temporal atrophy even after the NORSE stops, which might be due to the initial injury or an ongoing inflammatory process [Gaspard et al, 2018]. The hippocampal atrophy that occurs in NMDAR encephalitis is potentially reversible. On the other hand, the hippocampus of patients with LGI1-antibody encephalitis becomes atrophied (small and

Dr Anand S. Iyer, consultant paediatric neurologist, Apollo Hospitals International Limited, Ahmedabad, India and Alder Hey Children's Hospital, Liverpool, UK

Table 2: Investigative evaluation for children with a suspected autoimmune epilepsy

Initial	• Bloods – full blood count and blood film, electrolytes, liver function tests, ESR, CRP • Autoantibodies – anti-neuronal surface antibodies, MOG, GAD65, thyroid peroxidase, paraneoplastic, SLE panel, ANA, ANCA • Blood cultures • Save serology for further work up (viral serology, bacterial serology) • CSF – cell counts, cytology, protein, glucose, lactate, oligoclonal bands and IgG index • CSF cytokines (IL6), neopterin (FIRES) • CSF autoimmune/paraneoplastic antibody panel • CSF PCR for viral and bacterial causes of encephalitis • Chest X-ray, Abdominal ultrasound (looking for tumours)
Second-line in complicated cases	• Immunocompromised patients – HIV, Immunoglobulins, TB and other rare infectious disease review with ID consult • Whole body PET-CT, pelvic MRI (tumours) • Inborn errors of metabolism and mitochondrial screening • Genetic testing • Brain biopsy in selected cases

CRP C-reactive protein, CSF cerebrospinal fluid, ESR erythrocyte sedimentation rate

shrunken) if immunotherapy is delayed. Multifocal T2-weighted hyperintensities appear in the cortex and subcortex regions of the temporal and frontal lobes in GABA-A encephalitis. MRI in Rasmussen's encephalitis shows hyperintense T2/FLAIR signal in the cortical and subcortical region with perisylvian preference, along with progressive ipsilateral atrophy of head of caudate nucleus. Serial neuroimaging shows gradual atrophy of the hemisphere along with basal ganglia atrophy.

8F-fluorodeoxyglucose positron-emission tomography (18F-FDG PET) reveals remarkable occipital hypometabolism in NMDAR encephalitis as well as prominent hypermetabolism in the hippocampus and basal ganglia in LGI1-antibody encephalitis [Jang et al, 2020]. PET shows unihemispheric diffuse hypometabolism in Rasmussen's encephalitis which may manifest even when MRI atrophy is still minimal. However, this type of functional neuroimaging is rarely undertaken in routine clinical practice primarily because of its limited availability.

Electroencephalography

There is no specific electroencephalography (EEG) marker for distinguishing the different types of autoimmune epilepsy. The background is often slow and encephalopathic, correlating with the clinical state of the child in autoimmune encephalitis. The extreme delta brush pattern, which is superimposed fast activity over a delta wave, has been suggested to be a specific EEG sign of NMDAR encephalitis, and is found in 30% of patients [Moise et al, 2021] (*Figure 1*). It is noteworthy that faciobrachial dystonic seizures – FBDS (the pathognomonic feature of LGI1-antibody encephalitis) is diagnosed based on the phenomenology alone rather than using EEG. FBDS manifests as a brief (<3 seconds) dystonic movement of the arm that also includes the ipsilateral face or the leg. Focal or multifocal epileptiform discharges may be seen in autoimmune encephalitis with temporal emphasis. Unihemispheric slowing with epileptiform discharges are seen in Rasmussen's encephalitis, however epilepsia partialis continua is not always accompanied by visually recognisable changes on EEG.

Continuous or prolonged EEG monitoring is helpful in FIRES with the aim to capture the seizures on the EEG. The seizures can continue electrographically even though they may not be seen clinically. These children usually require management in PICU and multiple infusions of anaesthetic agents. This makes it difficult to monitor the patient's response to treatment. The seizures usually start in one hemisphere, with a frontal or temporal emphasis and then gradually spread to involve the entire hemisphere. Migration to involve the other hemisphere is quite common before stopping. When both hemispheres are involved, the EEG shows marked suppression (a very low amplitude pattern). Intravenous thiopentone or phenobarbital in doses high enough to cause burst-suppression on the EEG are sometimes used and it is important to use regular EEG monitoring in these children. This can be with continuous cerebral function monitoring (CFM), or at least daily, and rarely twice daily, 12-lead EEGs.

Autoantibody tests

Autoantibody detection provides a confirmatory diagnosis of autoimmune encephalitis, and thus is recommended in

all suspected patients. However, it is important to understand that no definite autoantibody will be found in 40–50% of cases [De Bruijn et al, 2020; Jang et al, 2020]. Autoantibody screening should be undertaken on both the blood (serum) and CSF. In NMDAR encephalitis, the disease severity is correlated with the antibody titre in the CSF but not in the serum. Although the presence of a systemic antibody (thyroid peroxidase antibody and antinuclear antibodies) may not be pathogenic, this can indicate the presence of an autoimmune response. Extended neuronal paraneoplastic antibodies would need to be considered and looked for in cases with significant clinical suspicion of associated malignancies and specifically where initial investigations have been normal. Several autoantibodies may co-exist in the same encephalitic like illness, including NMDAR and MOG antibodies. Consequently, this may present with a range of unusual clinical-radiological phenotypes [Ding et al, 2021]. The role of autoantibodies in the pathogenesis of Rasmussen's encephalitis is not clear.

Brain biopsy and other investigations

In certain cases, if there is an unusual lesion seen on neuroimaging which does not fit the typical clinical phenotype of autoimmune encephalitis, then a brain biopsy could be considered prior to starting an autoimmune-specific treatment regime. This specifically applies to a subset of children with NDMAR encephalitis who may have had latent or previous HSV encephalitis with residual lesions which may then require confirmation with brain biopsy prior to starting immunomodulatory treatment [Ellul et al, 2016; Nosadini et al, 2017]. MOG-autoimmune encephalitis may present with a clinical profile that may mimic herpes simplex encephalitis. Biopsy of the temporal lobe lesion shows only non-specific auto-immune features but the diagnosis is confirmed with the identification of MOG antibodies (personal communication with Richard Appleton) [Hamid et al, 2018].

Therapeutic approach

The treatment of autoimmune epilepsy can be categorised into two categories: 1) immunotherapy or immunomodulation, and 2) management of seizures or status epilepticus. For precise immunotherapy, careful history-taking, neurologic examinations, review of all investigation results and analysis of the likely pathophysiological mechanism of autoimmune epilepsy are mandatory. These children are usually managed on PICU and with regular input from other specialties, and particularly infectious diseases and rheumatology.

Immunotherapy

High-dose steroids and intravenous immunoglobulin (IVIg) have been the initial immunotherapies for autoimmune encephalitis, affecting a broad spectrum of autoimmune responses including humoral and cellular immune reactions. However, more than half of the patients do not respond to the initial therapy, in which cases rituximab has been effective as the next treatment of choice. Rituximab improved the prognosis in patients with autoimmune encephalitis which are antibody related. Most (60%) of the non-responders to initial immunotherapy showed a favourable outcome after rituximab treatment [Dhawan and Sankhyan, 2018; Suppiej et al, 2016]. This has led to rituximab being used earlier in the management of children and particularly those with NMDAR encephalitis [Dhawan and Sankhyan, 2018]. Plasma exchange in antibody positive cases has also shown to be promising, but is resource-intensive and can be difficult to do in children with significant autonomic disturbances or movement disorders [Suppiej et al, 2016].

Tocilizumab is the next treatment option, showing efficacy in 60% of the patients who did not respond to rituximab [Lee et al, 2016; Dinoto et al, 2022; Abboud et al, 2021]. However, approximately 10% of patients with autoimmune encephalitis do not respond well after receiving combined treatment with a high-dose corticosteroid, IVIg, rituximab, and tocilizumab. The optimal management of this group of patients remains unclear, but other drugs that might be effective include bortezomib, cyclophosphamide, tyrosine kinase inhibitors, and high-dose methotrexate [Dinoto et al, 2022].

Immunotherapy also remains one of the main treatments in FIRES. A few case reports suggested that plasma exchange (PLEX) therapy could stop refractory seizures in patients with NORSE [Jang et al, 2020; Wickstrom et al, 2022]. Combination therapy of high-dose steroid and IVIg was associated with good outcomes in patients with NORSE. The available data indicate that a certain proportion of patients with FIRES and NORSE respond well to treatment with high-dose steroids (11% and 15%, respectively), IVIg (both 5%), and PLEX (2% and 6%) [Jang et al, 2020].

In children with FIRES, overproduction of proinflammatory cytokines, such as interleukin (IL)-6 and IL-8, are implicated in its pathophysiology and can be measured in the CSF. IL1 receptor blockade with Anakinra has been found to be helpful in such children and often is the preferred second line therapy in FIRES [Stredny et al, 2020; Aledo-Serrano et al, 2022]. In some cases, tocilizumab mediated IL-6 receptor blockade can be helpful in Anakinra refractory cases [Stredny et al, 2020]. Similarly, intrathecal dexamethasone has been found to be helpful and well tolerated in some children with FIRES [Abboud et al, 2021].

Immunotherapy seems to reduce the rate of progression in Rasmussen's encephalitis with steroids and IVIG being used as the initial agent. Medications that target the T-cells and that are used in conditions like multiple sclerosis, such as natalizumab (a monoclonal antibody), or those that target both T and B cells, such as azathioprine, have shown some improvement in seizure control. However, these drugs do not halt the progressive hemiparesis or cognitive decline.

Dr Anand S. Iyer, consultant paediatric neurologist, Apollo Hospitals International Limited, Ahmedabad, India and Alder Hey Children's Hospital, Liverpool, UK

A brief summary of the available immunotherapies is presented in *Table 3*.

How rapidly should immunotherapy be started in autoimmune epilepsy?

Since NORSE is an emergency condition, immunotherapy should be administered as soon as possible, preferably within hours and certainly a few days. There is adequate evidence that early institution of immunotherapy can improve outcomes and reduce time in hospital [Wickstrom et al, 2022]. As empirical immunotherapy, IVIg can be the first treatment of choice because it is both effective in autoimmune epilepsy and safe in viral encephalitis. It is important that antivirals (such as

Table 3: Immunotherapy for the autoimmune epilepsies

Treatment	Mechanism of action	Side effects	Regime
Corticosteroids	Reduces lymphocyte activation Reduces cytokine synthesis and proinflammatory gene expression	Systemic infection Hyperglycemia Gastric ulcer Avascular necrosis and osteoporosis	Methylprednisolone 30mg/kg/day (maximum 1g) for 3-5 days, followed by oral prednisolone 1-2mg/kg/day
IVIG	Neutralises autoantibodies Inhibits complement and cytokine production Inhibits monocyte and macrophage activation	Infusion related fever, headache, chills Aseptic meningitis	2g/kg over 2-4 days Repeat dose can be given after 2-4 weeks
PLEX	Clears autoantibodies and inflammatory cytokines from plasma	Resource intensive Line sepsis Difficult in patients with hyperkinetic movement disorders	1-1.5 plasma-volume exchange, 5 sessions, 48 hour interval between sessions
Rituximab	Anti CD20 B lymphocytes	Systemic infection (viral) Lymphopenia Infusion related rash or serum sickness Elevated liver enzymes	375mg/m2 weekly for 4 weeks or 750mg/m2 every 2 weeks for 2 doses, then 3-6 monthly maintenance
Tocilizumab	Blocks IL-6 receptor	Systemic infection (bacterial and viral) Neutropenia, thrombocytopenia Hyperlipidemia Elevated liver enzymes	8-12mg/kg single dose, repeat after 2-4 weeks depending on clinical response
Anakinra	Blocks IL-1 receptor	Systemic infection Headache, nausea Local reaction at injection site	50-100mg sc injection daily for 2-4 weeks depending on clinical response
Cyclophosphamide	Alkylate DNA of actively proliferating lymphocytes	Bone marrow suppression Infertility Systemic infection Haemorrhagic cystitis	750mg/m2 monthly infusion, 3-6 months usually
Bortezomib	Inhibits proteasome, targeting plasma cell activation	Systemic infection Neutropenia Neuropathy	1.3mg/m2 bortezomib with 20mg IV dexamethasone, sc injection, twice weekly for 2 weeks
Mycophenolate	Inhibits purine synthesis suppressing actively proliferating lymphocytes	Bone marrow suppression Teratogenic	250-500mg twice daily
Azathioprine	Inhibits purine synthesis suppressing actively proliferating lymphocytes	Bone marrow suppression Teratogenic	1-1.5mg/kg/day, increase to 2-3mg/kg/day

aciclovir) should be used initially and with steroids until the autoimmune aetiology is confirmed if there is suspicion of infection and a rapid escalation in symptoms. If a patient does not fully respond to the initial immunotherapy, and certainly within two weeks, clinicians should then add an alternative immunotherapy such as rituximab, tocilizumab, anakinra, or cyclophosphamide, depending on whether the clinical suspicion is one of antibody-mediated autoimmune encephalitis like NMDAR encephalitis or one of FIRES.

It is important to evaluate the risks and benefits of the different immunotherapies and to discuss this with the families before starting treatment. In most cases, the effects can take some time to work and an objective evaluation of any improvement or deterioration is important to determine if the specific drug is working and should be continued or replaced.

Duration of immunotherapy

There are insufficient data to establish a consensus on how long to continue immunotherapy. This will primarily depend on how the patient responds to immunotherapy. In most cases, a response should be noticeable within four weeks, in which case the decision would be to continue maintenance therapy. In NMDAR encephalitis, initial administration of rituximab allows for adequate immunosuppression for nearly six months with regular monitoring of CD19 lymphocyte counts in the blood (serum). If these start to increase, then repeat administration of rituximab is required every six months for at least two years to maintain remission. In MOG antibody-mediated encephalitis or Hashimoto encephalopathy, these usually respond well to steroids alone. Other immunotherapies (such as rituximab) will be required only if there is inadequate response to steroids or recurrences. Oral immunomodulating agents may also be preferable in some cases where there may be cost restraints and these agents are well tolerated [Dinoto et al, 2022]. The risk of immunosuppression, fatal infections and long-term adverse effects on some organs must be included in any decision over the choice of the immunotherapeutic agent(s).

Management of seizures and status epilepticus

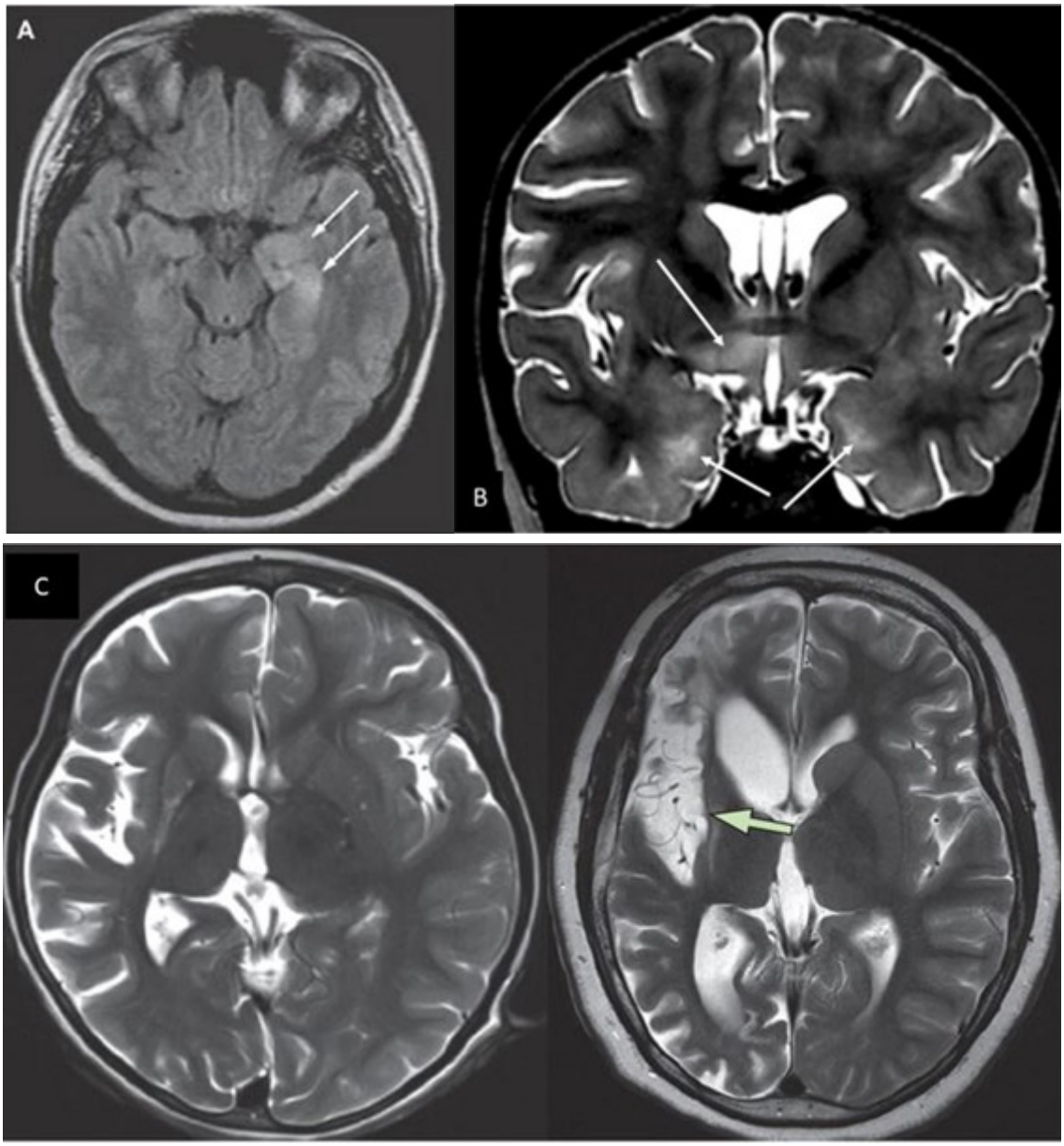
The choice of anti-seizure medication (ASM) depends on the treating clinician and the frequency of seizures at presentation. No significant difference has been found among ASMs in the management of seizures in autoimmune epilepsy. Fewer side effects, no drug-drug interactions, and rapid intravenous loading of the medication are major considerations when choosing the ASMs for autoimmune epilepsy. The candidate first-line treatments are next-generation ASMs which can be given intravenously. These are levetiracetam, lacosamide, phenytoin, phenobarbitone and valproate; levetiracetam is probably the most common first-line ASM. In most cases of autoimmune encephalitis, one or two ASMs are generally needed in controlling the seizures. Treatment must also focus on any additional symptoms of the encephalopathy including any movement disorder as well as trying to suppress the immune process causing the seizures and movement disorder. The specific pathogenesis in each type of autoimmune epilepsy will also help to determine which ASMs should be avoided. For example, in NMDAR encephalitis, NMDAR antagonists such as ketamine should be avoided. The safety of perampanel, which is an AMPA antagonist, has not yet been studied in AMPA-receptor encephalitis. On the other hand, GABA-promoting ASMs, such as benzodiazepines and barbiturates, might be considered as first or certainly second-line agents in treating patients with GABA-A encephalitis. The duration of ASM use also should be personalised in individual patients, and most ASMs can be tapered off when the autoimmune encephalitis has entered remission [Jang et al, 2020].

In FIRES, the acute phase of the illness is the most frustrating and difficult time for both doctors and the family. The universal approach is to try and suppress the clinical and subclinical (electroencephalographic) epileptic seizures with sequential use of ASMs, often guided by continuous or prolonged EEG monitoring. Experience will help determine the most appropriate and 'rational' combination of ASMs. Rarely, four or even five ASMs may need to be used simultaneously (even for a brief period) and this demands close monitoring for the development of any adverse side effects. Many of these children will require high dose midazolam infusions, followed by either thiopental or barbiturate infusions to induce burst suppression coma for a period of up to five or seven days [Gaspard et al, 2018]. Longer periods of burst suppression coma correlate with worse outcomes and more chances of systemic complications and particularly multi-organ dysfunction. Intravenous ketamine infusions have also been used and this medication also requires careful monitoring. In most cases, when there is clinical and electroencephalographic remission of seizures, premature attempts to wean the infusions can lead to a recurrence. In some cases lorazepam (administered through a nasogastric tube) may be helpful in successfully withdrawing intravenous midazolam [Jain et al, 2022]. High dose phenobarbital, perampenel and cannabidiol have all shown some promise in reducing seizures, although the numbers are small [Gofshteyn et al, 2017]. Ketogenic diet therapy may also be effective in the treatment of FIRES and can help to gradually withdraw intravenous ASMs that the child has been receiving [Nabbout et al, 2023]. Therapeutic hypothermia ('cooling') has been shown to be of benefit in some cases, as fever is the trigger to seizures and status epilepticus. Its mechanism of action is uncertain, but it may be through a reduction in the production of pro-inflammatory cytokines [Pavone et al, 2022; Wickstrom et al, 2022; Gaspard et al, 2018; Reppucci and Datta, 2022].

Epilepsy surgery remains the only cure for the medication-resistant epilepsy in Rasmussen's encephalitis. Hemispherotomy is recommended in cases where

Dr Anand S. Iyer, consultant paediatric neurologist, Apollo Hospitals International Limited, Ahmedabad, India and Alder Hey Children's Hospital, Liverpool, UK

Figure 2: Neuroimaging in autoimmune epilepsies



A: left medial temporal high signal changes in autoimmune encephalitis [Sansing et al, 2007], B: multiple hyperintensities in both medial temporal and right thalami in MOG encephalitis [Mishael et al, 2023], C: progressive atrophy of the right hemisphere in Rasmussen's encephalitis [Varadkar et al, 2014].

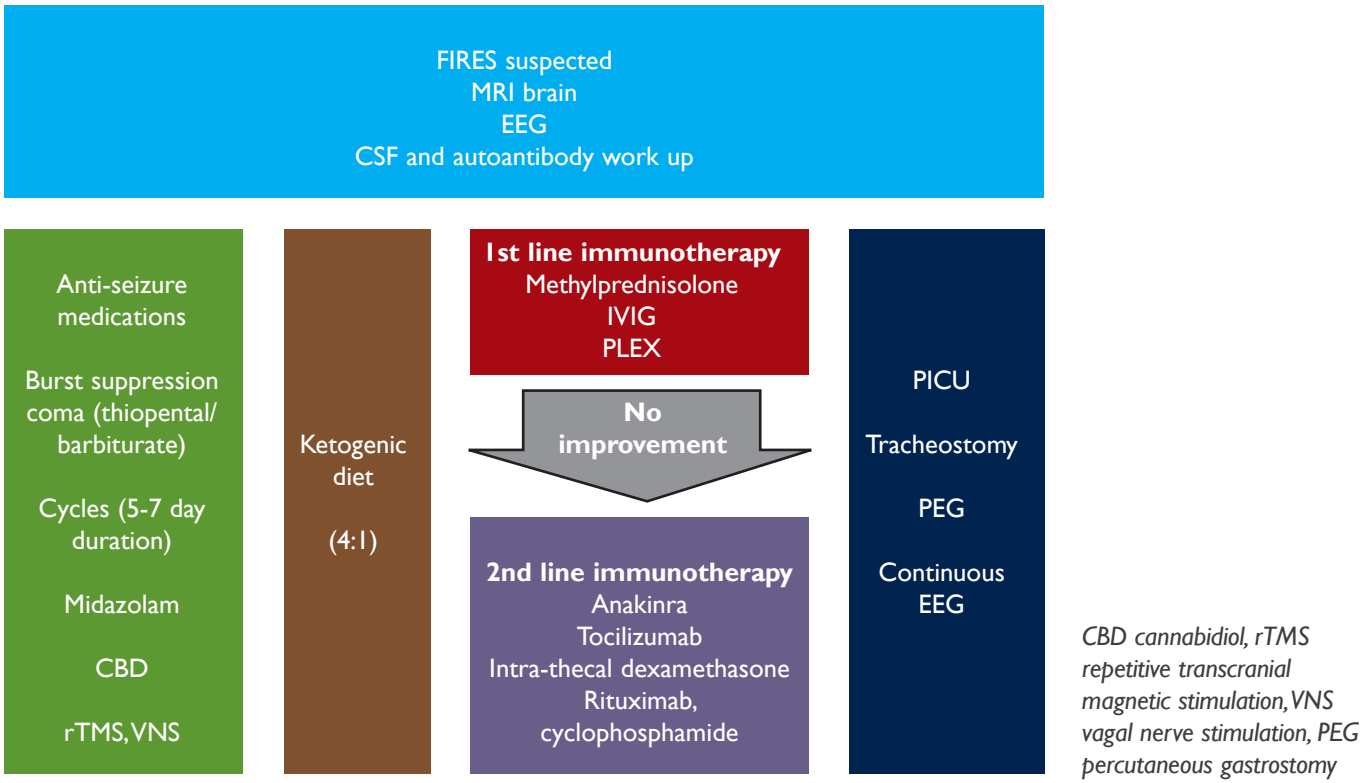
already there is hemiparesis and hemianopia and usually rehabilitation after surgery leads to independent walking. The chances of seizure freedom is approximately 70% in such cases [Varadkar et al, 2014]. The timing of the surgery and dominant hemisphere involvement are points of debate, however earlier surgery in non-dominant hemisphere disease has led to better cognitive outcomes in most case series [Varadkar et al, 2014; Thomé et al, 2024].

Figure 2 is a simplified algorithm for management of FIRES.

Management of movement disorders and other psychiatric manifestations

Movement disorders of some type were present in 40% of patients with autoimmune encephalitis. In children, approximately 50% of those with NMDAR encephalitis had a recognisable movement disorder characterised by marked dyskinesias affecting all four limbs and orolingual

Figure 3: Algorithm for management of FIRES in children



CBD cannabidiol, rTMS repetitive transcranial magnetic stimulation, VNS vagal nerve stimulation, PEG percutaneous gastrostomy

(mouth and face) areas [Dale and Mohammad, 2024; Mohammad et al, 2014; Siriratnam et al, 2023]. Faciobrachiodystonic seizures are common in anti-LGI1 antibody mediated condition and particularly in adults. Other movements, chorea, athetosis, myoclonus, catatonia and dystonia have also been reported in a number of autoimmune encephalitides. The risk of morbidity, including irreversible neurological sequelae, increases in those patients with co-existent movement disorders, and these can be difficult to fully control. Benzodiazepines are commonly used to try to control these movements. There is a risk of neuroleptic malignant syndrome with the use of other anti-psychotic medications such as risperidone and caution is advised in the use of other agents commonly used for movement disorders, including trihexyphenidyl and tetrabenazine [Caroff et al, 2017].

Prognosis in autoimmune epilepsies

Early identification and prompt and aggressive management can improve outcomes in autoimmune encephalitis. Approximately 90% of patients with NMDAR encephalitis responded within four weeks to first-line immunotherapy [Garg et al, 2020]. Most children with other antibody-mediated autoimmune encephalitis also show good outcomes. There is always a risk of a recurrence with the overall risk being 10%; it is higher in some autoimmune encephalitides. The most common complications include ongoing epilepsy and residual memory and learning difficulties, particularly in MOG-antibody associated disease. The overall prognosis in FIRES is poor, with survivors developing a life-long refractory epilepsy and significant cognitive difficulties. Some published papers have used the phrase, 'winning the battle, but losing the war' to emphasise the almost universal poor outcome in such cases [Van Baalen, 2023]. Mortality rates during the acute phase are high and related to infection-related complications associated with prolonged admissions on PICU.

Summary

Considerable progress has been made in recognising autoimmune epilepsies as a feature of the autoimmune encephalitides and FIRES in children. Children with these disorders require specialist paediatric neurology expertise combined with paediatric intensive care management in a tertiary centre. The mainstay of both of these conditions is immunotherapy which is tailored to the individual child depending on whether there is antibody-mediated illness with a recognised phenotype (e.g. NMDAR and MOG) or whether it is cytokine-mediated neuro-inflammation without any recognisable phenotype like FIRES. International work is in progress to better define these conditions and publish uniform protocols for the diagnosis and management of these auto-immune encephalitides. Further research is needed to see whether there may be newer treatment options including surgical neuromodulation with deep brain stimulation or repetitive transcranial magnetic stimulation.

Dr Anand S. Iyer, consultant paediatric neurologist, Apollo Hospitals International Limited, Ahmedabad, India and Alder Hey Children's Hospital, Liverpool, UK

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Recently published papers

This section highlights recently published papers. There are many (often more than 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded.

We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

BENNETT SD, Cross JH, Chowdhury K, Ford T, Heyman I, Coughtrey AE, Dalrymple E, Byford S, Chorpita B, Fonagy P, et al.
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Childs Nerv Syst. 2024 Sep 17.
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doi: 10.1111/epi.18124

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Seizure. 2024 Aug 31:121:243-252.
doi: 10.1016/j.seizure.2024.08.022.

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doi: 10.1111/dmcn.16091.

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Factors associated with poor sleep in children with drug-resistant epilepsy
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doi: 10.1177/08830738241279225.

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New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY, UK
tel: 0113 210 8800 | fax: 0113 391 0300 | Epilepsy Action Helpline freephone: 0808 800 5050 email: editor@epilepsy.org.uk epilepsy.org.uk
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