Autoimmune Epilepsy

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Key Points

1. A considerable proportion of patients (10–16%) with epilepsy of unknown etiology may have an autoimmune or paraneoplastic cause.
2. Among patients with epilepsy, coexisting clinical features such as subacute progressive cognitive decline, psychiatric symptoms, viral prodrome, autonomic dysfunction, inflammatory cerebrospinal fluid (CSF), medial temporal lobes hyperintensities on magnetic resonance imaging (MRI), or presence of underlying malignancy are suggestive of an autoimmune etiology.
3. A predictive scoring system (antibody prevalence in epilepsy and encephalopathy [APE2] score) can be utilized in identifying those patients with autoimmune seizures or epilepsy.
4. Early diagnosis and initiation of immunotherapy is critical for favorable clinical outcomes.
5. The field of autoimmune epilepsy is likely to expand further with discovery of several novel autoantibodies and improved mechanistic understanding.

Introduction

Epilepsy is a chronic debilitating disease affecting 0.5–1.0% of the world's population [1]. Although epilepsy can arise from different structural, metabolic, infectious, or genetic etiologies, the cause of a significant proportion of cases remains unknown [2]. The link between subset of epilepsies and neuroinflammation has been recognized for decades. This includes the suspected inflammatory pathogenesis of epilepsy syndromes such as Rasmussen's encephalitis [3] and favorable response to immunotherapy of others, for example, Landau-Kleffner syndrome [4]. Furthermore, in the 1960s, initial cases of paraneoplastic limbic encephalitis associated with epilepsy were described [5]. Over the past 2 decades, a plethora of neural autoantibodies targeting cell surface or intracellular antigens associated with encephalopathy and/or epilepsy have been discovered [6]. Many more biomarkers with specific clinical and/or oncological associations are likely to be discovered over the coming

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A. L. Piquet, E. Alvarez (eds.), *Neuroimmunology*, https://doi.org/10.1007/978-3-030-61883-4_13

years. The rate of discovery may be fueled by development and validation of phage immunoprecipitation sequencing and immunoprecipitation–mass spectrometry techniques [7, 8].

Diagnosis of autoimmune epilepsy, in a majority of the cases, is based on their clinical characteristics, magnetic resonance imaging (MRI) results, cerebrospinal fluid (CSF) analysis, and/or response to immunotherapy trials [9]. The International League Against Epilepsy (ILAE) has recognized autoimmune epilepsy as a distinct entity in the 2017 epilepsy classification [10]. However, diagnostic criteria for autoimmune epilepsy are lacking. A subset of these patients who have coexisting encephalopathy may be characterized using the autoimmune encephalitis diagnostic criteria proposed by Graus et al. in 2016 [11]. Diagnostic criteria for autoimmune encephalitis is further discussed in Chap. 12.

Epidemiology

The true incidence of autoimmune epilepsy remains unknown. Some information can be deduced from a population-based epidemiological study evaluating incidence and prevalence of autoimmune encephalitis. In Olmsted County, Minnesota, the incidence of autoimmune encephalitis was found to be 0.8/100,000 with a prevalence of 13.7/100,000 [12]. This study also showed significant increase in incidence of autoimmune encephalitis in the last decade, with increased recognition of neural-specific antibodies associated with autoimmune encephalitis [13]. However, in this study, proposed autoimmune encephalitis diagnostic criteria were utilized for selection of their cases. Among the selected cases, only a subset had epilepsy as a part of their syndrome. Additionally, autoimmune epilepsy cases without cognitive impairment were excluded.

A hospital-based prospective study reported that 20% of adult patients with epilepsy of unknown etiology were seropositive for neural-specific antibodies associated with autoimmune epilepsy or encephalopathy [14]. In another UK-based retrospective study, estimated frequency of neural-specific antibodies was 15% among patients without a genetic, structural, or metabolic etiology for epilepsy [14–16]. Epilepsies of unknown etiology are estimated to constitute one-third of all epilepsies among adults [17]. Therefore, the rate of autoimmune epilepsies based on these studies can be inferred to be around 5–7% of all epilepsies, at least in adults. The frequency of autoantibodies in pediatric epilepsy is more unclear. Wright et al. showed the presence of autoantibodies in about 10% of pediatric patients with new-onset epilepsy [18].

Clinical Presentation

Clinical presentations of autoimmune epilepsy are variable and evolving as new antibodies are being discovered. However, a majority of these cases have coexisting features of autoimmune encephalitis including subacute progressive cognitive decline, psychiatric symptoms, viral prodrome, autonomic dysfunction, inflammatory CSF, oncological association, or brain MRI changes consistent with autoimmune encephalitis [11]. In this regard, a predictive model based on clinical features and initial neurological assessment (antibody prevalence in epilepsy and encephalopathy [APE2] score) may aid in identification of these patients with autoimmune epilepsy [14, 15, 19]. Furthermore, a scoring system for response to immunotherapy (response to immunotherapy in epilepsy and encephalopathy [RITE2] score) may also be utilized for immunotherapy trials (Tables 13.1 and 13.2). The APE2 score of greater or equal to 4 was 99% sensitive and 93% specific for neural-specific-antibodies, while a RITE2 score of greater than or equal to 7 had 96% sensitivity and 86% specificity for favorable initial immunotherapy response [19].

Neural-Specific Antibodies Associated with Autoimmune Epilepsy

Cell Surface Epitopes

N-methyl-D-aspartate receptor (NMDA-R) encephalitis typically affects young women with a reported median age of 22 years (range:

Table 13.1 Components of the APE2 score. The assigned APE2 score is the sum of values for all components

1A: Antibody prevalence in epilepsy and encephalopathy (APE2score)	Value:
New onset, rapidly progressive mental status changes that developed over 1–6 weeks, or new onset seizure activity (within 1 year of evaluation)	(+1)
Neuropsychiatric changes; agitation, aggressiveness, emotional lability	(+1)
Autonomic dysfunction[a]	(+1)
Viral prodrome (rhinorrhea, sore throat, low-grade fever) to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset	(+2)
Faciobrachial dystonic seizures	(+3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)
Seizure refractory to at least to two anti-seizure medications	(+2)
CSF findings consistent with inflammation[b] (elevated CSF protein >50 mg/dL and/or lymphocytic pleocytosis >5 cells/mcL, if the total number of CSF RBC is <1000 cells/mcL)	(+2)
Brain MRI suggesting encephalitis[b] (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation)	(+2)
Neoplasm diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)
	Total (max: 18)

Abbreviations: CSF cerebrospinal fluid, *RBC* red blood cells, *MRI* magnetic resonance imaging, *FLAIR* fluid attenuated inversion recovery

Key: [a]Sustained atrial tachycardia or bradycardia, orthostatic hypotension (≥20 mm Hg fall in systolic pressure or ≥10 mm Hg fall in diastolic pressure within 3 minutes of quiet standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole, or gastrointestinal dysmotility. Scored only if no history of autonomic dysfunction prior to onset of suspected autoimmune syndrome and the autonomic dysfunction not attributable to medications, hypovolemia, plasmapheresis, or infection. [b]Patients scored zero if MRI brain or CSF analysis not performed

2 months to 85 years) [20]. Clinical presentation usually begins with a prodrome of a headache or fever, followed by psychiatric manifestations including delusions, hallucinations, mania-like episodes, alternating episodes of extreme agitation, and catatonia. Patients then progress to develop

Table 13.2 Components of the RITE2 score. RITE2 score included all the components of APE2 score and two additional variables: initiation of immunotherapy within 6 months of symptom onset and plasma membrane-specific autoantibody detected. The assigned RITE2 scores are the sum of values for all components

1B: Response to immunotherapy in epilepsy and encephalopathy score (RITE2 score)	Value:
New-onset, rapidly progressive mental status changes that developed over 1–6 weeks or new onset seizure activity (within 1 year of evaluation)	(+1)
Neuropsychiatric changes; agitation, aggressiveness, emotional labiality	(+1)
Autonomic dysfunction[a]	(+1)
Viral prodrome (rhinorrhea, sore throat, low-grade fever) only to be scored in the absence of underlying malignancy within 5 years of neurological symptom onset	(+2)
Faciobrachial dystonic movements	(+3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)
Seizure refractory to at least two anti-seizure medications	(+2)
CSF findings consistent with inflammation[b] (elevated CSF protein >50 mg/dL and/or lymphocytic pleocytosis >5 cells/mcL, if the total number of CSF RBC is <1000 cells/mcL)	(+2)
Brain MRI suggesting encephalitis[b] (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation)	(+2)
Neoplasm diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)
Immunotherapy initiated within 6 months of symptom onset	(+2)

(continued)

Table 13.2 (continued)

1B: Response to immunotherapy in epilepsy and encephalopathy score (RITE2 score)	Value:
Neural plasma membrane autoantibody detected (NMDAR, $GABA_AR$, $GABA_BR$, AMPAR, DPPX, mGluR1, mGluR2, mGluR5, LGI1, CASPR2 or MOG)	(+2)
	Total (max: 22)

Abbreviations: AMPAR amino-3-hydroxy-5-methyl-4-isoxazolepropionic, *ANNA-1* Antineuronal nuclear antibody-1, *ANNA-2* antineuronal nuclear antibody-2, *ANNA-3* antineuronal nuclear antibody-3, *CASPR-2* contactin-associated protein-2, *CRMP5* collapsin response-mediator protein-5, *CSF* cerebrospinal fluid, *DPPX* dipeptidyl-peptidase-like protein 6, *FLAIR* fluid attenuated inversion recovery, *GAD65* glutamic acid decarboxylase-65, *GABABR* γ(gamma)-aminobutyric acid-B receptor, *GFAP α(alpha)* glial fibrillary acidic protein, *LGI1* leucine-rich glioma-inactivated protein-1, *MOG* myelin oligodendrocyte glycoprotein, *MRI* magnetic resonance imaging, *NMDAR* N-methyl D-aspartate receptor, *PCA-1* Purkinje cell cytoplasmic antibody type 1, *PCA-2* Purkinje cell cytoplasmic antibody type 2, *RBC* red blood cells

Key: [a]Sustained atrial tachycardia or bradycardia, orthostatic hypotension (≥20 mmHg fall in systolic pressure or ≥10 mmHg fall in diastolic pressure within three minutes of quiet standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility. Scored only if no history of autonomic dysfunction prior to onset of suspected autoimmune syndrome and the autonomic dysfunction not attributable to medications, hypovolemia, plasmapheresis, or infection. [b]Patients scored zero if MRI brain or CSF analysis not performed

seizures, encephalopathy, oral dyskinesia, choreoathetosis, and autonomic dysfunction [21]. Seizures in NMDA-R encephalitis are usually focal non-motor seizures that might progress to refractory status epilepticus [22]. If untreated, patients will progress to a comatose state [21].

In about half of the patients, a trigger can be identified. The two main triggers are the presence of ovarian teratoma [23] and a history of herpes simplex virus (HSV) encephalitis [24]. Approximately two-thirds of adult women between the ages of 18 to 45 years with NMDA-R encephalitis have been reported to have ovarian teratoma [21]. However, the presence of this tumor is extremely rare in children younger than 12 years or older adults (≥45 years) [6, 21, 25]. Furthermore, prospective evaluation of HSV encephalitis patients showed that 17% of these cases developed NMDA-R encephalitis during follow-up. Three additional patients in this cohort were positive for NMDA-R immunoglobulin G (IgG) without any clinical features of autoimmune encephalitis on follow-up evaluation [24].

Leucine-rich, glioma-inactivated 1 (LGI1) immunoglobulin G is typically associated with seizures and memory deficits usually among older patients (>40 years). However, a few pediatric cases have also been described [26]. One characteristic phenotype described among the adult patients is faciobrachial dystonic seizures (FBDS). These are brief focal dystonic motor seizures and occur multiple times a day. They have a characteristic stereotypic contraction of the face, arm, and leg [27]. Another characteristic seizure semiology is unilateral piloerections episodes. More recently, paroxysmal dizzy spells have also been described in a subset of patients [28]. These "dizzy spells" or "out of body experiences" may precede encephalopathy by 2–12 months.

A minority (~2%) of patients with voltage-gated potassium channel-complex (VGKC) antibodies have coexisting contactin-associated protein-like 2 (CASPR-2) IgG. Peripheral nervous system involvement is more common (neuromyotonia, myokymia, or dysautonomia) among these patients. However, a considerable proportion of patients, especially older patients, may have coexisting epilepsy or encephalitis. Recent studies have highlighted that VGKC IgG in the absence of LGI1 and/or CASPR-2 IgG seropositivity is not a specific biomarker of autoimmunity [29].

α(alpha)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibody-associated encephalitis typically presents with classic limbic encephalitis symptoms (anterograde memory deficits, retrograde amnesia, mood changes, and temporal lobe seizures). Recent studies have supported direct antibody-mediated pathogenicity [30, 31]. Median age of onset is around 60 years old (range: 23–81 years), and it occurs more commonly in females (64%) [21]. Two-thirds of the patients have underlying

malignancy, mainly small cell lung cancer and thymoma [32]. A considerable proportion of patients have a refractory course and go on to develop diffuse cortical atrophy [30, 31, 33].

γ(gamma)-aminobutyric acid type B (GABA-B) receptor encephalitis usually presents as refractory non-convulsive status epilepticus [21]. Median age of onset is 61 years (range: 16–77 years) and tends to occur more commonly in males [6]. A subset of these cases have underlying malignancy, most commonly small cell lung carcinoma.

Fulminant encephalitis and refractory seizures or status epilepticus have been associated with GABA-A receptor encephalitis. These patients have characteristic multifocal cortical and subcortical T2/FLAIR hyperintensities [22]. Age of symptom onset tends to be younger (median age: 40 years) than cases with GABA-B encephalitis [6].

Patients with dipeptidyl-peptidase-like-protein 6 (DPPX) antibody-associated encephalitis can also have seizures as part of the syndrome. The usual clinical manifestations include gastrointestinal dysfunction, weight loss followed by cognitive dysfunction, hyperekplexia, myoclonus, parasomnias, and occasionally progressive encephalomyelitis with rigidity and myoclonus (PERM) [21, 34].

Metabotropic glutamate receptor 5 (mGluR5) IgG encephalitis patients usually present with subacute onset of encephalopathy, mood changes, movement disorder, and seizures [35]. Status epilepticus has been reported to be a common presenting feature especially among pediatric cases [36].

Intracellular Epitopes

Glutamic acid decarboxylase (65 kd, GAD65) antibodies (serum titers >20 nmol/L or detection in CSF) are associated with various autoimmune neurological diseases including autoimmune epilepsy, stiff person syndrome, cerebellar ataxia, limbic encephalitis, and PERM [37, 38]. Women are more frequently affected than men, and the median age of symptom onset is 30 years (range: 5–80 years) [22]. In a study of 112 patients with unexplained adult-onset focal epilepsy, 5.4% were found to have high titers of GAD65 antibodies (>1000 U/mL) [39]. Usually patients with GAD65 antibodies (serum titers >20 nmol/L or detection in CSF) are associated with a treatment-refractory course [38, 39]. Refractory nature of the disease is postulated to be secondary to cell-mediated cytotoxicity rather than a direct antibody-mediated pathogenesis.

Patients with antineuronal nuclear antibody type-1(ANNA-1, a.k.a. anti-Hu) IgG antibodies present with various central and peripheral nervous system manifestations. ANNA-1 IgG seropositivity has a strong association with small cell cancer (81%). Sensory neuronopathy and autonomic dysfunction, especially gastroparesis, are hallmarks of ANNA-1 autoimmunity [13]. However, a considerable proportion (10–17%) of cases present with limbic encephalitis or refractory seizures. Both temporal and extratemporal localization of the seizures have been reported [40].

Seizures and limbic encephalitis are less common among patients with ANNA-2 IgG (a.k.a anti-Ri). These patients usually present with a brainstem or cerebellar syndrome. Initial manifestations include opsoclonus-myoclonus, jaw opening dystonia, and laryngospasms [41].

Ma2 IgG patients usually have a limbic encephalitis or brainstem encephalitis phenotype. In a retrospective study, bilateral tonic-clonic or focal unaware seizures occurred in 12 out of 27 (44%) patients [42]. A majority of Ma2 IgG seropositive have testicular germ cell tumor [43].

Collapsin response-mediator protein-5 (CRMP5) IgG is a paraneoplastic biomarker of small cell lung cancer or thymoma [44]. Patients with CRMP-5 IgG usually manifest with various neurologic signs including chorea, cranial neuropathy, dementia, cerebellar ataxia, myelopathy, and peripheral neuropathy [22, 45, 46]. Focal aware and unaware seizures have also been rarely reported in patients with CRMP-5. Management of underlying malignancy and early initiation of immunotherapy may be associated with favorable outcomes [47].

Rasmussen's Encephalitis

Rasmussen's encephalitis is a rare chronic neurological disorder characterized by drug-resistant focal motor epilepsy (epilepsia partialis continua), cognitive decline, hemiplegia, and unilateral hemispheric brain atrophy [5]. Clinical onset is usually during childhood, although it has been reported during adulthood. The disease progresses over three stages, with the first being a "prodromal stage" with a relatively low seizure frequency and rarely a mild hemiparesis. Following that, the patient will enter the "acute stage," which is characterized by frequent intractable seizures along with progressive neurological decline (hemiparesis, hemianopia, cognitive deterioration, and aphasia if dominant hemisphere). During the final "residual" stage, the patient develops permanent and stable neurological deficits and intractable focal motor seizures [48]. CSF examination may be normal or may show inflammatory changes (lymphocytic pleocytosis and elevated CSF protein). Electroencephalogram (EEG) shows unilateral inter-ictal epileptiform discharges, slowing, and ictal rhythms with occasional spread to the contralateral side due to bilateral synchrony. No specific electrographic signatures have been associated with Rasmussen's encephalitis. MRI brain scan shows FLAIR/T2 hyperintensity and atrophy involving unilateral cortical and/or subcortical regions with a predilection for perisylvian area. Fluorodeoxyglucose positron emission tomography (FDG-PET) scan may show increased uptake in the affected hemisphere [5, 48]. Multiple case reports have demonstrated favorable response to immunotherapy. In 2013, a randomized trial of tacrolimus and intravenous immunoglobulin showed slowing down of tissue and function loss with either therapies, but without improvement in seizures [49]. At present, hemispherectomy remains the best option of seizure control and arresting the neurological decline [50].

New-Onset Refractory Status Epilepticus

In new-onset refractory status epilepticus (NORSE), a previously healthy individual develops refractory de novo seizures and status epilepticus with no readily identifiable etiology. A retrospective study exploring NORSE in the adult population has shown a significant percentage of these patients to have immune-mediated etiologies—primarily antibody-mediated encephalitis with anti-NMDA receptor being the most common etiology [51]. Various treatments have been tried, including anti-seizure medications, achieving burst suppression with anesthetics, and dietary therapy with modest and variable effects [52]. Use of immunotherapy has been associated with favorable outcomes in a few cases (5–33%) [52].

Steroid Responsive Encephalopathy with Autoimmune Thyroiditis (SREAT) or Hashimoto's Encephalopathy

Clinical characteristics of Hashimoto's encephalopathy include encephalopathy, seizures, stroke-like episodes, and myoclonus [13]. These patients typically have thyroid peroxidase (TPO) antibodies but may or may not have a history of thyroiditis. Seizure presentations are variable including new-onset refractory status epilepticus or progressive myoclonic epilepsy [5, 53]. A triad of encephalopathy, evidence of thyroid autoimmunity (clinically or serologically), and a favorable response to steroids have been traditionally utilized for identification of these cases [11].

Electroencephalogram

EEG plays a vital role in diagnosis and management of autoimmune epilepsy and encephalitis. It is essential to look for epileptiform or seizure activity. Long-term monitoring is utilized among

patients with subclinical or clinical status epilepticus [54]. Additionally, EEG can also be utilized to evaluate response to immunotherapy and antiepileptic drugs in some instances.

EEG findings in autoimmune encephalitis are variable and may be nonspecific. Extreme delta brush (EDB) was first described in NMDA encephalitis patients by Schmitt et al. [55]. This EEG pattern consists of rhythmic delta activity at 1–3 Hz with superimposed burst of rhythmic beta activity at 20–30 Hz riding on each delta wave [55]. EDB has been reported in about 30% of acutely ill or hospitalized NMDA encephalitis patients and is associated with a more prolonged illness. Although it was thought to be fairly specific initially, recent studies have described the presence of EDB with other metabolic and structural causes of encephalopathy [56].

FBDS, a pathognomonic feature of LGI1 autoimmune epilepsy, usually has no ictal EEG correlate. Occasionally preceding electrodecrement or sharply contoured rhythmic delta activity has been reported over the contralateral frontotemporal region [57]. In a small series of LGI1 patients, frequent subclinical temporal lobe seizures associated with hyperventilation were reported. This ictal activity had similar morphology to subclinical rhythmic electrographic discharges of adults (SREDA) [58]. A more recent study of EEGs with 16 LGI1 encephalitis patients reported multiple frequent seizure semiologies or subclinical seizures associated with temporal and frontal discharges [57]. Additionally, multifocal interictal epileptiform discharges and interictal slow-wave activity were observed in 25% and 69%, respectively.

Imaging

Brain MRI is usually included in initial evaluation of autoimmune epilepsy and encephalitis. Features considered suggestive of autoimmune encephalitis include T2/FLAIR hyperintensity restricted to one or both medial temporal lobes (Fig. 13.1) or multifocal T2/FLAIR hyperintensities in the gray matter, white matter, or both compatible with demyelination or inflammation [11]. However, MRI may be normal, especially early in the course of the disease [59, 60]. Brain MRI also provides valuable information regarding differential diagnosis of new-onset epilepsy and/or subacute onset cognitive dysfunction such as tumors, brain abscess, neuro-sarcoidosis, and other inflammatory and infectious diseases. Beside brain MRI, abnormalities in functional MRI [61], diffusion tensor imaging (DTI) [61], FDG-PET/CT [62], and single photon emission tomography (SPECT) [63] have been described in patients with autoimmune epilepsy and can provide valuable diagnostic and at times prognostic values.

In the initial phase of NMDA-R encephalitis, the brain MRI abnormalities are typically discrete and nonspecific [20, 64]. However, resting state functional MRI shows disrupted hippocampal functional connectivity. Moreover, DTI has detected a more widespread white matter damage that correlated with disease severity [61]. Decreased occipital lobe metabolism on FDG-PET/CT has been described as a unique finding in these patients [65]. Resolution of lateral and medial occipital hypometabolism may correlate with better outcomes.

Brain MRI findings in patients with LGI1 encephalitis varies depending on the stage of the disease and the progression [65]. In the early phase of the disease, brain MRI is typically normal, although basal ganglia abnormalities including increased FLAIR signal, restricted diffusion, and contrast enhancement have been reported [66]. Patients with FBDS may develop T1 hyperintensity in region of basal ganglia [67]. As the disease progresses, unilateral or bilateral T2/FLAIR hyperintensities of the medial temporal lobes and basal ganglia are observed. On follow-up imaging, hippocampal atrophy is frequently seen [65]. FDG-PET/CT reveals basal ganglia hypermetabolism, a specific finding, and frequently the earliest finding on imaging studies [68].

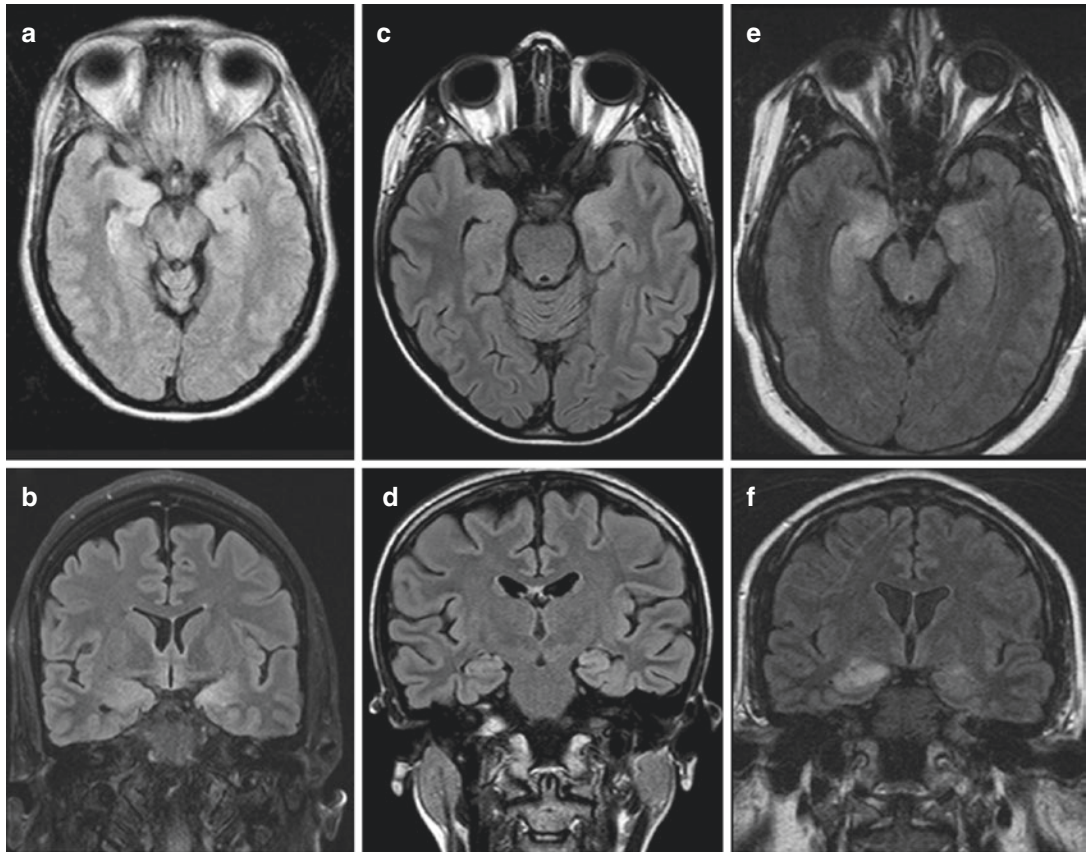

Fig. 13.1 Patient 1 with LGI1 IgG limbic encephalitis. MRI brain (FLAIR sequence) showing bilateral medial temporal hyperintensities on axial (**a**) and sagittal sections (**b**). Patient 2 with ANNA1 IgG limbic encephalitis. MRI brain (FLAIR sequence) showing bilateral medial temporal hyperintensities on axial (**c**) and sagittal sections (**d**). Patient 3 with Ma2 IgG limbic encephalitis. MRI brain (FLAIR sequence) showing bilateral medial temporal (right greater than left) hyperintensities on axial (**e**) and sagittal sections (**f**). *Abbreviations:* ANNA-1 antineuronal nuclear antibody-1, MRI magnetic resonance imaging, FLAIR fluid attenuated inversion recovery, LGI1 leucine-rich, glioma inactivated 1

Among patients with GAD65 antibody-associated autoimmune epilepsy, brain MRI demonstrates disproportionate parenchymal atrophy for age and abnormal cortical/subcortical T2 hyperintensities. Hippocampal abnormalities are seen only in a minority (26%) of patients [69].

Patients with mGluR5 antibodies have abnormal brain MRI in 45% of the cases, with involvement of both limbic and extralimbic (thalamus, pons, cerebral, and cerebellar cortices) regions. Additionally, FDG-PET in some of these cases demonstrates hypometabolism of the temporoparietal cortex or cerebellum [36]. Whereas GABA-A receptor encephalitis has a unique pattern of widespread and extensive cortical and subcortical FLAIR hyperintensity [70].

Medial temporal lobe involvement has been reported in multiple antibody specificities including AMPA-R [71], GABA-B receptor IgG [72], ANNA-1 IgG [40], Ma2-IgG [42], adenylate kinase 5 [73], etc. A majority of these cases do not have associated gadolinium enhancement

except for Ma2 IgG-associated limbic encephalitis [42].

Cancer Screening

CT of the chest, abdomen, and pelvis with contrast is recommended as initial evaluation for cancer association. Scrotal ultrasounds should be performed in all males, especially those presenting with brainstem, diencephalic or limbic encephalitis. In women, mammograms should be performed for evaluation of breast cancer. Pelvic sonography and pelvic MRI are recommended for ovarian teratoma or adenocarcinoma screening. If initial radiological evaluations did not reveal any malignancies and clinical suspicion for paraneoplastic neurological syndrome is high or the patient has neural specific antibody with strong oncological association (Table 13.3), PET-CT should be pursued [74, 75]. If the patient's evaluation reveals a neoplasm other than that predicted by the antibody present, further cancer evaluation should be performed as more than one cancer can coexist [74]. Paraneoplastic syndromes and associated malignancies are further discussed in Chap. 16.

Treatment

Management of autoimmune epilepsy is focused on immunotherapies. Multiple studies have demonstrated favorable effects of early immunotherapy on seizure frequency and cognition [9, 15, 76, 77]. However, randomized control trials evaluating efficacy immunotherapy in autoimmune epilepsy are limited. Therefore, immunotherapy recommendations are largely based on case series and clinical experience [20, 78]. Recently, a placebo-controlled trial of IVIg for LGI1 and CASPR2 IgG-associated autoimmune epilepsy was published [79]. In this study of 17 patients, 75% of the patients receiving IVIg achieved more than 50% seizure reduction by 5 weeks compared to only 22% of patients in the placebo arm [79]. In some instances, a positive response to a treatment trial of immunotherapy can aid in the diagnosis of seronegative autoimmune epilepsy [9]. In this regard, the RITE2 score may be a useful scoring system for managing clinician prior to immunotherapy initiation [15].

Immunotherapeutic agents are classically divided into first-line and second-line therapies (Table 13.4). First-line therapies include high-dose intravenous methylprednisolone (IVMP), intravenous immunoglobulin, or plasmapheresis. Second-line agents such as rituximab, cyclophosphamide, mycophenolate, azathioprine, or bortezomib are used in refractory cases or as a maintenance therapy to prevent relapses.

Treatment of autoimmune epilepsy should be based on the severity of the clinical course (Fig. 13.2). In patients with rapid progression and refractory course, more aggressive immunotherapy is needed including both first- and second-line therapies. Conversely, some patients with autoimmune epilepsy have a more benign course, and their epilepsy can be controlled with antiepileptic drugs and a short course of immunotherapy. In all cases, cancer surveillance, as discussed previously should be pursued as treatment of the underlying cancer, is pivotal for the successful treatment of autoimmune epilepsy.

Proposed immunotherapy trials include 6 or 12 weeks of high-dose IV methylprednisolone (IVMP). Intravenous methylprednisolone 1000 mg per day for 3 days followed by once weekly for 5 weeks (6 IVMP week trial), followed by once every 2 weeks for 6 weeks (12 IVMP week trial). If the patient has contraindications for IVMP (active infections, poorly controlled diabetes, chronic hepatitis, or tuberculosis), a 6- or 12-week course of intravenous immunoglobulin[1] may be considered. These include 0.4 g/kg IVIg daily for 3 days followed by 0.4 g/kg every week for 6 weeks (6 IVIg week trial) and then every 2 weeks for 6 weeks (12 IVIg week trial). A treatment response can be ascertained using a seizure diary to assess seizure frequency and/or change in semiology and neurological examination including screening mental status examination after completion of immunotherapy trial. The quality of life in epilepsy (QOLIE-31) can be utilized as well. EEG,

Table 13.3 Clinical features of specific neural autoantibody-associated syndromes

Antibody	Neurological presentations	Epilepsy association (3+, 2+, 1+)	Epilepsy presentations	Brain MRI	Cancer association (3+, 2+, 1+)	Specific cancer type
LGI1	FBDS, piloerection seizures, peripheral nervous system disease symptoms, limbic encephalitis	3+	FBDS, unilateral piloerection, paroxysmal dizzy spells	medial temporal FLAIR hyperintensity, T1 basal ganglia hyperintensity (FBDS cases)	1+, 2+[a]	Thymoma
GABA-B	SE, limbic encephalitis	3+	Crescendo seizures, SE is frequent.	medial temporal FLAIR hyperintensity	2+	Small cell lung cancer
GABA-A	SE, autoimmune encephalitis	3+	Crescendo seizures and status epilepticus	Multifocal cortical and subcortical hyperintensity	1+	Thymoma
NMDA-R	Oral dyskinesia, catatonia, neuropsychiatric dysfunction, autonomic dysfunction, refractory epilepsy	2+	Crescendo seizures, status epilepticus and encephalopathy (EEG: extreme delta-brush)	normal or nonspecific cortical and/or subcortical changes	2+	Ovarian teratoma
GAD-65	SPS, hyperekplexia, brainstem encephalitis (especially African Americans)	2+	Multifocal epilepsy, drug-resistant epilepsy, rarely SE	multifocal cortical and subcortical hyperintensity or brainstem hyperintensity	1+	Thymoma
AMPA-R	Limbic encephalitis	2+	SE has been reported	Cortical atrophy, deep gray nuclei FLAIR hyperintensity	2+	Thymoma, small cell lung cancer, breast adenocarcinoma
mGluR5	Encephalopathy, mood changes, movement disorder and seizures	2+	Seizures are common, SE in children.	Normal in 50%, limbic/cortical FLAIR changes	2–3+	Hodgkin lymphoma
ANNA-1/Hu	Limbic encephalitis, Sensory neuronopathy, autonomic dysfunction	2+	Temporal and/or extra-temporal seizures. Rarely SE	normal or medial temporal FLAIR hyperintensity	3+	Small cell lung cancer, neuroendocrine tumors
ANNA-2/Ri	Stridor, laryngospasm, jaw dystonia, opsoclonus myoclonus	1+	Seizures are rare	brainstem FLAIR hyperintensity and/or atrophy	3+	Small cell lung cancer, breast cancer
Ma-1/Ma-2	Limbic encephalitis, Brainstem encephalitis	2+	Focal unaware seizure or bilateral tonic-clonic	brainstem FLAIR hyperintensity or medial temporal FLAIR hyperintensity	3+	Testicular germ cell tumor[b], small cell lung cancer[c]
Amphiphysin	SPS, PERM, transverse myelitis	2+	Limbic encephalitis and seizures can occur in up to 30% of patients.	normal or nonspecific cortical and/or subcortical changes	2+	Small cell lung cancer, breast cancer
CASPR2	Neuromyotonia, Morvan's syndrome, limbic encephalitis, refractory epilepsy, sleep disorder	1+	Focal unware seizures or focal motor/sensory seizures.	normal or medial temporal FLAIR hyperintensity	1, 2+[a]	Thymoma

Glycine	SPS, PERM	1+	Rarely associated with seizures.	normal or nonspecific cortical and/or subcortical changes	Rare (<5%)	Thymoma
DPPX	Diarrhea, hyperekplexia, Ambiguous sleep, parasomnias, PERM,	1+	Rarely associated with seizures.	normal or nonspecific cortical and/or subcortical changes	Rare (<10%)	Lymphoma
GFAPα(alpha)	Meningo-encephalomyelitis, tremor, ataxia, autonomic dysfunction	1+	Rarely associated with seizures	Peri-radial/patchy enhancement or diffuse subcortical hyperintensity	1+	Ovarian teratoma
CRMP5	Choreo-athetosis, optic neuritis, retinitis, limbic encephalits, ataxia, transverse myelitis, polyradiculoneuropathy	1+	Rarely associated with seizures (Focal aware and focal unaware)	normal or medial temporal FLAIR hyperintensity	3+	Small cell lung cancer, thymoma
IgLON5	Parasomnias, REM and NREM dysfunction, brainstem dysfunction, hyper-excitability disorder	Rare	Rarely associated with nocturnal frontal lobe epilepsy	normal or nonspecific cortical and/or subcortical changes	Unknown	–
Neurexin-3a:	prodrome of fever, headache and gastrointestinal symptoms followed by development of encephalopathy and seizures	1+	Limited data available.	Normal	None	None
MOG	ADEM, ON, TM	1+	Rarely associated with refractory seizures and status epilepticus	Multifocal demyelination, involvement of corpus callosum, deep gray nuclei	–	–
Adenylate kinase 5	Limbic encephalitis	Rare	Limited data available. One patient reported to have seizure 6 months after disease onset.	Bilateral medial temporal FLAIR hyperintensity	None	None

Abbreviations: ADEM acute disseminated encephalomyelitis, *AMPA-R* amino-3-hydroxy-5-methyl-4-isoxazolepropionic, *ANNA-1* antineuronal nuclear antibody-1, *ANNA-2* antineuronal nuclear antibody-2, *CBA* cell based assay, *CASPR2* contactin-associated protein-like 2, *CRMP-5* collapsin response-mediator protein 5, *DPPX* dipeptidyl-peptidase-like protein-6, *EEG* electroencephalogram, *EMG* electromyography, *FBDS* faciobrachial dystonic seizures, *FLAIR* fluid attenuated inversion recovery, *GABA-A* gamma-aminobutyric acid type A, *GABA-B* gamma-aminobutyric acid type B, *GAD-65* glutamic acid decarboxylase 65, *GFAP* glial fibrillary acidic protein, *LGI1* leucine-rich: glioma inactivated-1, *MOG* myelin oligodendrocyte glycoprotein, *MRI* magnetic resonance imaging, *NMDA-R* N-methyl-D-aspartate receptor, *ON* optic neuritis, *PERM* progressive encephalomyelitis with rigidity and myoclonus, *REM* rapid eye movement, *SE* status epilepticus, *SPS* stiff person syndrome, *TM* transverse myelitis, *WB* western blot
Key: 1+, 10–30%; 2+, 30–60%; 3+, >60%
[a]coexisting LGI1 and CASPR-2 antibodies
[b]Ma2 antibodies
[c]Ma1 antibodies with or without Ma2 antibodies

Table 13.4 Review of dosing, mechanism of action, adverse effects, and monitoring of various immunomodulatory agents

Immunomodulatory Agent	Route of Administration	Dosing/Regimen	Mechanism of action	Adverse effects	Monitoring and Prophylaxis
Corticosteroids	IV or PO	Initial dose: IV methylprednisolone (1 g per day for 3–5 days) 6 week trial: 1 g per day for 3 days followed by once weekly for 5 weeks 12 week trial: 1 g per day for 3 days followed by once weekly for 5 weeks, followed by once every 2 weeks for 6 weeks. Oral Maintenance: 60–80 mg prednisone daily, duration of taper variable (usually over 4–8 weeks)	Acts on nuclear glucocorticoids receptors to reduce cytokine and chemokine production Reduces migration of leukocytes to the target tissue	Insomnia, psychiatric dysfunction, hyperglycemia, electrolyte imbalances, fluid retention, hypertension, peptic ulcer, Cushing syndrome, cataracts, infections, osteoporosis and avascular necrosis. Addisonian crisis on rapid withdrawal of corticosteroids	Blood pressure, serum electrolytes and glucose monitoring PJP ppx: TMP/SMX osteoporosis ppx: Vitamin D + calcium GI ppx: PPI or H2 blocker
Plasmapheresis	IV	1 exchange every other day for 10–14 days	Extracorporeal blood filtration designed to remove large molecular weight molecules, including immunoglobulins, immune complex, and complements	Hypotension, electrolyte imbalance, perioral paresthesia (hypocalcemia), coagulopathy, central line infection, hemorrhage, thrombosis, and pneumothorax	PT, INR, PTT, Fibrinogen
IVIg	IV	Initial dose: 0.4 g/kg daily for 5 days 6 week trial: 0.4 g/kg daily for 3 days followed by 0.4 g/kg every week for 5 weeks. 12 week trial: 0.4 g/kg daily for 3 days followed by 0.4 g/kg every week for 6 weeks and then every 2 weeks for 6 weeks.	Remains unclear Interaction with antigen-binding fragment on the antibodies and/or crystalizable fragment on the antibodies or the antigen presenting cells	Headache, aseptic meningitis, acute renal failure, thrombotic/thromboembolic events anaphylaxis due to IgA deficiency	Electrolytes, renal function

Rituximab	IV	1000 mg followed by 2nd dose in 2 weeks, 375 mg/m^2 weekly for 4 weeks	B-cell depletion by antibody dependent cellular cytotoxicity, complement dependent cytotoxicity and apoptosis	Allergic reaction, opportunistic infection, reactivation of tuberculosis infection or hepatitis B infection, PML	Hepatitis B antibodies, Quatiferon test (for latent tuberculosis), pregnancy test, Liver function test
Cyclophosphamide	IV or PO	IV: 600–1000 mg/m^2. PO dosage based on renal function: GFR >100: 2 mg/Kg GFR 50–99: 1.5 mg/Kg GFR 25–49: 1.2 mg/Kg GFR 15–24: 1.0 mg/Kg GFR less than 15 or on dialysis 0.8 mg/Kg	Alkylating agent with interferes with DNA synthesis	Gastrointestinal (nausea, vomiting), hair loss, mucositis, hemorrhagic cystitis, infertility and myelosuppression	CBC, liver function test, creatinine CBC at 8–14 days post infusion. CBC and urinalysis (for red blood cells) should be checked weekly for a month, every 2 weeks for 2 months and then once a month. Increased hydration recommended
Mycophenolate	PO	Initially 500 mg twice daily, target 1000–1500 mg twice daily.	Inhibition of inosine monophosphate dehydrogenase-mediated guanosine nucleotide synthesis	Gastrointestinal (nausea, vomiting, diarrhea), hypertension, peripheral edema, infections, myelosuppression, lymphoma	CBC, creatinine, urine pregnancy test CBC once per week for 1 month, then once every 2 weeks for 2 months then once every 1–3 months for the duration of therapy
Azathioprine	PO	Initially 1.5 mg/kg/day, target 2–3 mg/kg/ day (guided by 5-point MCV increase from baseline)	Converted to cytotoxic 6-thioguanine nucleotides, which leads to incorporation as a false base into DNA inducing lymphocyte apoptosis	Gastrointestinal symptoms (nausea, vomiting, diarrhea), hypersensitivity reactions, hair loss, cytopenia, hepatotoxicity, lymphoma and infections	CBC, liver function test, creatinine, TPMT and urine pregnancy. CBC should be checked once per week for 1 month, then once every 2 weeks for 2 months, then once every 1–3 months for the duration of therapy
Bortezomib	SC	1–6 cycles, each cycle consists of 4 injections (1.3 mg/m^2)	Proteasome inhibitor, decreasing levels of plasma cells.	Bone marrow suppression, GI side effects, peripheral neuropathy, opportunistic infections.	CBC, liver function and electrolytes

Abbreviations: GFR glomerular filtration rate, *GI* gastrointestinal, *IV* intravenous, *PO* per oral, *PLEX* plasmapheresis, *IVIg* intravenous immunoglobulin, *PT* prothrombin time, *INR* international normalized ratio, *PTT* partial thromboplastin time, *CBC* complete blood count, *TPMT* thiopurine S-methyltransferase, *TMP* Trimethoprim, *SMX* Sulfamethoxazole, *PPI* proton pump inhibitor, *PJP Pneomocystis jiroveci* pneumonia, *ppx* prophylaxis, *SC* subcutaneous

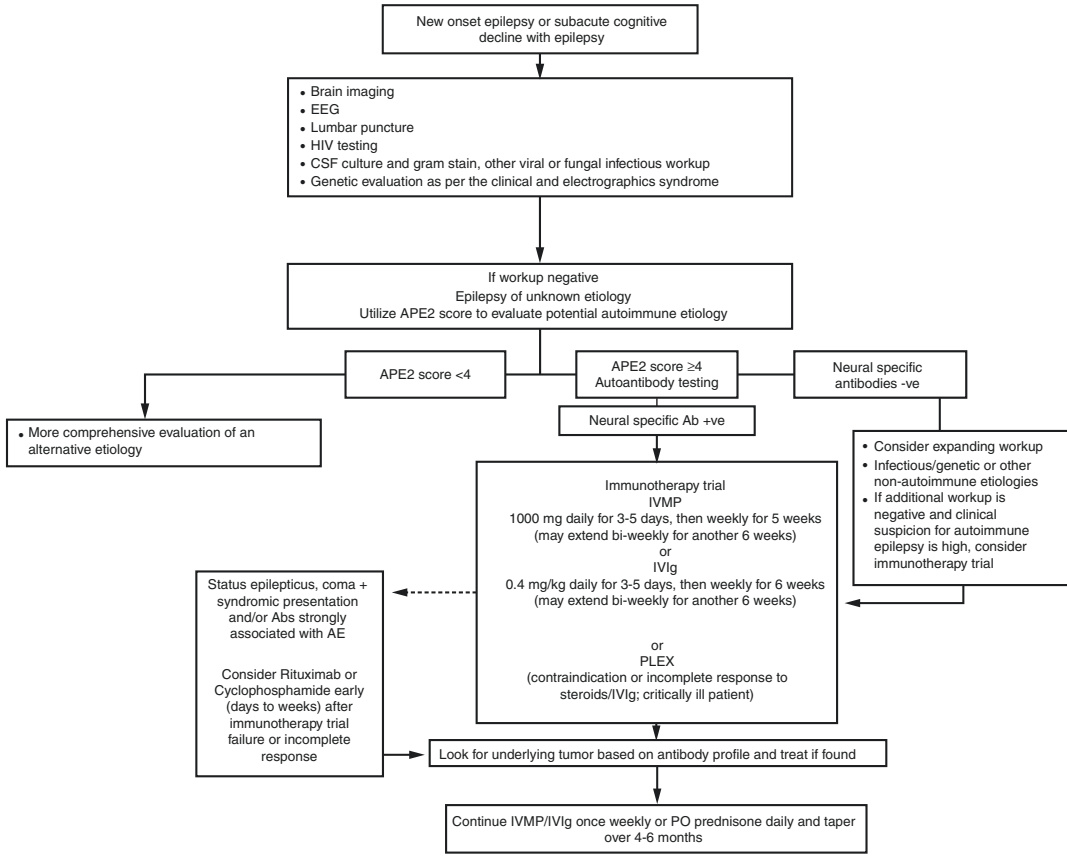

Fig. 13.2 Management algorithm for autoimmune epilepsy. *Abbreviations:* Ab antibody, CSF cerebrospinal fluid, EEG electroencephalogram, HIV human immunodeficiency virus, IVIg intravenous immunoglobulin, IVMP intravenous methylprednisone, PLEX plasmapheresis, PO per oral

brain MRI with gadolinium, PET brain, and formal cognitive tests are additional parameters that can be monitored. Seizures in autoimmune epilepsy may show early improvement within 4–6 weeks of initiating immunotherapy. Conversely, cognitive impairment and amnesia, if present, recover more slowly. For patients who have incomplete or lack of response to IVMP or IV, or those who have contraindication to IVMP and/or IVIg, a course of plasmapheresis (5–7 cycles) should be considered followed by a second-line immunotherapy (rituximab or cyclophosphamide). A gradual taper of prednisone if feasible is advised following the initial treatment, as abrupt discontinuation might lead to relapses. Chronic maintenance immunotherapy should be initiated to decrease the likelihood of a relapse. Azathioprine, mycophenolate mofetil, rituximab, and cyclophosphamide are agents typically utilized. The exact duration required for maintenance immunotherapy is not known, although a trial of immunotherapy withdrawal may be considered after 2 years of treatment if the patient has not had any relapses.

Antiepileptic Drugs (AEDS)

Even though seizures in autoimmune epilepsy are characteristically resistant to antiepileptic drugs (AEDs) alone, they continue to play an important role in symptomatic management. In all autoimmune epilepsy patients, AEDs should be used along with immunotherapy treatment. There are no randomized trial data to support one AED over another. Levetiracetam is com-

monly employed for management of seizures given the favorable side effect profile and minimal drug-to-drug interaction. In some instances, it can be difficult to ascertain if the psychiatric manifestations are due to levetiracetam adverse effects [80] or due to disease pathology. Anti-inflammatory effect for levetiracetam has been hypothesized to play a beneficial role [81]. However, a recent retrospective study evaluating AED in autoimmune epilepsy found none of the patients on levetiracetam achieved seizure freedom [82]. Whereas seizure freedom rates were considerably higher with the use of sodium channel blocking AEDs (carbamazepine, phenytoin, oxcarbazepine, and lacosamide). [82]. The reason for better efficacy of sodium channel-blocking AEDs remains unclear. Interestingly, both carbamazepine and oxcarbazepine have been shown to reduce levels of interleukin-1 (IL)-1 and IL-2 in healthy subjects [81]. Medications such as carbamazepine and phenytoin have enzyme induction properties, which can alter the pharmacokinetics of immunosuppressive therapies. Therefore, newer sodium channel blocking AEDs with more favorable pharmacokinetic profiles (such as oxcarbazepine and lacosamide) could be preferred in management of autoimmune epilepsy.

Follow-Up

Patients with autoimmune epilepsy should be followed up regularly, preferably by an epileptologist in conjunction with a neuroimmunologist. On long-term follow-up, some patients continue to have drug-resistant epilepsy, despite initial treatment with immunotherapy and continued treatment with AEDs. Whether the disease is now at a "burn out" stage or an acute inflammatory process continues is hard to discern. Ancillary data including repeating brain MRI with gadolinium contrast, CSF analysis, and PET brain can be helpful in guiding treatment decisions. Serum and/or CSF antibody titers have poor relationship to clinical course. Epilepsy surgery has been tried in select cases of autoimmune epilepsy [83]. However, outcomes seem to be worse than that expected in other etiologies of drug-resistant epilepsy.

Conclusion

Future Directions

Many challenges continue to face us as we move forward in the field of autoimmune epilepsy. Several novel biomarkers are likely to be discovered over the next few years. The use of phage immunocepitation sequencing and protein microarrays might help us to identify novel antibodies that were not discovered using traditional immunoprecipitation mass spectrometry techniques [84–86].

Further insights into the mechanisms of antibody-mediated epilepsy syndromes will allow us to better utilize the various AEDs and immunotherapies. Additionally, investigations into the role of cytokines and chemokines in diagnosis and prognostication of autoimmune epilepsy will also aid in seizure management and relapse prevention [87, 88]. Finally, randomized controlled trials are needed to determine optimal therapeutic agents, doses, and treatment duration for autoimmune epilepsy management.

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