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Autoimmune Encephalitis

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Abstract

The term autoimmune encephalitis is used to describe a group of disorders characterised by symptoms of limbic and extra-limbic dysfunction occurring in association with antibodies against synaptic antigens and proteins localised on the neuronal cell surface. In recent years there has been a rapidly expanding knowledge of these syndromes resulting in a shift in clinical paradigms and new insights into pathogenic mechanisms. Since many patients respond well to immunosuppressive treatment, the recognition of these disorders is of utmost importance. In general, there are no brain-imaging modalities or biomarkers specific of these disorders other than the demonstration of the neuronal antibodies. A disease classification based on these antibodies provides information on prognosis and paraneoplastic aetiology. This article focuses on recent clinical advances, newly characterised antibodies and treatment approaches to these disorders.

Keywords

Encephalitis; limbic encephalitis; stiff-person-syndrome; basal ganglia encephalitis; anti-NMDA-receptor encephalitis; synaptic autoimmunity; neuronal surface antigen antibody; GABA(b)

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receptor antibody; AMPA receptor antibody; glycine receptor antibody; dopamine D2 receptor encephalitis; VGKC complex antibody; SREAT; Hashimoto encephalopathy

The first type of autoimmune limbic encephalitis, reported in 1968, was a paraneoplastic disorder occurring in association with small-cell lung cancer (SCLC).[1] Until 2001, it was believed that 'limbic encephalitis' almost always associated with cancer and had a poor outcome. In 2001, a form of immunotherapy-responsive limbic encephalitis with IgG antibodies initially considered against voltage gated potassium channels (VGKC) was described.[2,3] Four years later, antibodies against other cell surface neuronal antigens with intense immunostaining of the hippocampal neuropil, were detected in several patients with different forms of immunotherapy-responsive encephalitis.[4] Indeed, one of these patients was a young woman with ovarian teratoma who developed prominent psychiatric symptoms and coma. Further studies with serum and cerebrospinal fluid (CSF) of this patient and several additional patients with a remarkably similar immunotherapy-responsive syndrome resulted in the characterisation of the antigen as the NR1 subunit of the N-methyl-D-aspartic acid receptor (NMDA-receptor).[5] In quick succession, further neuronal cell surface antigens were characterised in patient cohorts with autoimmune encephalitis. They included the α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor (AMPA-receptor),[6] γ-amino-butyric acid (GABA)(b)-receptor,[7] α1-glycine receptor (GlyR),[8] metabotropic glutamate receptor 5 (mGluR5),[9] leucine-rich, glioma-inactivated 1 (LGI1),[10,11] contactin-associated protein-like 2 (CASPR2),[11,12] dopamine receptor 2 (D2-receptor)[13] and dipeptidyl-peptidase-like protein-6 (DPPX, a regulatory subunit of the KV4.2 potassium channel).[14] The main clinical features, diagnostic clues and treatment of these disorders are the subjects of this review.

Epidemiology

With an annual incidence of 2–3/100,000 in northern Europe,[15] encephalitis of any aetiology is half as common as newly diagnosed multiple sclerosis (4–8/100,000/year).[16] While 40 % of cases are infectious and 40 % are due to unknown causes, at least 20 % are immune mediated, with the largest groups being anti-NMDA-receptor encephalitis (4 %) and VGKC-complex antibody positive encephalitis (3 %).[15] One per cent of all young patients admitted to a large German neurointensive care unit[17] were retrospectively identified as NMDA-receptor antibody positive. Less is known about the incidence of the other neuronal surface antibody-associated syndromes. However, GABA(b)-receptor antibodies are responsible for the majority of paraneoplastic limbic encephalitides in patients with SCLC who were previously considered seronegative.[18]

Immune Mechanisms

Antibody-associated encephalitides can be subdivided into those in which the antibodies are directed against neuronal surface or intracellular antigens. The latter group of antibodies define diseases that are usually of paraneoplastic origin and have a poor prognosis despite oncological and immunosuppressive therapy. These disorders are often described as encephalitis with onconeural (intracellular) antibodies or 'classical paraneoplastic neurological syndromes'.[19] The corresponding antibodies (Hu, Yo, Ri, CV2/CRMP5, Ma2,

Amphiphysin, Tr) occur in association with cytotoxic T-cell mediated mechanisms which appear to be the main pathogenic effectors.[20,21]

In contrast, the neuronal surface antibodies so far studied exert a direct effect on their target antigens. In anti-NMDA-receptor and AMPA-receptor encephalitis, the antibodies result in a specific decrease of the corresponding synaptic receptors. The best studied disorder is anti-NMDA-receptor encephalitis, in which the antibodies produce a titre-dependent decrease of receptors by a mechanism of capping, cross-linking and internalisation of the receptors. These effects are reversible upon removing the antibodies from cultures of neurons. Continuous infusion of antibodies to animals results in similar effects.[22–24] Patients' autopsy data shows a decrease of NMDA-receptors and supports the concept that cytotoxic T-cell and complement-mediated mechanisms are not hallmarks of this entity.[21,22,25] The pathogenic mechanisms in other neuronal surface antibody mediated syndromes are less clear, some data indicates a role of complement in VGKC-complex antibody-mediated encephalitis.[21]

To exert their direct pathogenic effect, the antibodies have to reach the target antigens in the central nervous system (CNS). In anti-NMDA-receptor encephalitis there is evidence of local production of antibodies in brain and meninges, supported by the demonstration of intrathecally produced antibodies and the presence of infiltrating B-cells and plasma cells in autopsy studies.[5,26] A similar high intrathecal synthesis of antibodies appears to occur in anti-AMPA- and GABA(b)-receptor encephalitis, but the relative contribution of intrathecal versus systemic production is less clear for the other disorders.

All these syndromes occur with and without the presence of systemic tumours, whose frequencies and types vary according to the encephalitis subtype (see Table 1). As occurs with classical paraneoplastic syndromes, the associated tumour usually expresses the neuronal antigen. For example, in patients with anti-NMDA-receptor encephalitis the underlying ovarian teratoma contains nervous tissue that expresses the NMDA-receptor.[7,18,25,28] The ectopic expression of this receptor in the tumour appears to contribute in breaking immune tolerance. Possible host factors and the mechanisms involved in homing and enhancing the immune response in the CNS are topics of investigation.

The immunological trigger in the non-paraneoplastic form of these disorders is unknown. The frequent occurrence of prodromal symptoms resembling a viral infection has suggested an infectious process but it might as well be the first manifestation of systemic immune activation.[29] The recently identified link between herpes simplex virus 1 (HSV-1) encephalitis (HSE) and anti-NMDA-receptor encephalitis is interesting and suggests that in some patients a syndrome called 'post-HSE choreoathetosis' is in fact anti-NMDA-receptor encephalitis.[30,31] Whether the link represents a mechanism of immune activation by molecular mimicry between the virus and the NMDA-receptor, or an immune response against NMDA-receptors released by infected neurons is currently unclear.

Clinical Spectrum of Autoimmune Encephalitis

Most forms of encephalitis associated with antibodies against neuronal surface antigens share a core syndrome of limbic encephalitis (epileptic seizures, short-term memory deficits, behavioural and psychiatric disturbances) with additional features that vary according to the immune response (see Table 1). Antibodies that occur without symptoms of limbic encephalitis include, mGluR1 (cerebellar symptoms),[32] GlyR (spectrum of stiff-person syndrome, encephalomyelitis with rigidity)[33] and dopamine-receptor D2 (basal ganglia encephalitis).[13]

In contrast, the clinical picture of anti-NMDA-receptor encephalitis described below defines a new syndrome and is almost pathognomonic. It should not be referred to as limbic encephalitis because the syndrome reflects diffuse encephalitis. About 13 % of patients develop partial forms of the syndrome characterised by predominant psychiatric disturbances, refractory seizures, status epilepticus, or movement disorders. In most of these cases a thorough neurological and neuropsychological examination reveals other features of the syndrome. Truly monosymptomatic manifestations are rare (1 %).[34]

Anti-NMDA-receptor Encephalitis

Since the description of this disorder in 2007,[4,35] it has become one of the most frequently recognised autoimmune encephalitis.[15] In a centre focused on the aetiology and epidemiology of encephalitides, anti-NMDA-receptor encephalitis was more prevalent than any single viral form of encephalitis.[36] The disease predominates in women (81 %) and young patients (37 % <18 years, 95 % <45 years); however, in the age groups younger than 12 years and older than 45 years, almost 50 % of patients are male.[34]

About 50 % of patients have prodromal symptoms: fever, headache, nausea, vomiting and upper gastrointestinal symptoms.[29,34] In adults, this is followed a few days or weeks later by psychiatric symptoms and behavioural abnormalities (>95 %) often overshadowing other symptoms such as memory deficits (60–80 %). Affective, psychotic and obsessive-compulsive syndromes can occur. Seizures and status epilepticus are common (70 %); they are often the initial symptoms in children (>30 %) and pose a problem in differentiating them from non-epileptic abnormal movements (70–90 %).[34] The latter typically include, repetitive oro-facio-lingual dyskinesias, pseudorhythmic arm and leg movements, choreoathetosis, oculogyric crisis, opisthotonus, dystonia and generalised rigidity.[29,37] These symptoms are usually accompanied by progressive loss of consciousness (60–70 %) and autonomic instability (50 %). While adults are more prone than children to develop central hypoventilation the latter may exhibit atypical symptoms (ataxia, hemiparesis).[34]

The magnetic resonance image (MRI) of the brain is often normal or shows non-specific abnormalities. A recent study showed that 67 % of the patients with anti-NMDA-receptor encephalitis had normal brain MRI at symptom onset.[34] Non-specific periventricular and juxta-cortical T2 hyperintensities, mild and transient gadolinum uptake, and rarely myelin abnormalities can be observed in 20 % of these patients.[5,29,38]

In contrast, the CSF is abnormal in most patients, including mild to moderate lymphocytic pleocytosis (96 %), oligoclonal bands (65%), or both.[5,34] At symptom onset, the abnormalities are only noted in 80 % of the patients.[29] As occurs in many autoimmune encephalitides, including all classical paraneoplastic encephalitides, the presence of pleocytosis is more common during the first weeks of the disease and during the course of the disease the prevalence of oligoclonal bands increases.[29,39]

The electroencephalograph (EEG) of these patients usually shows generalised diffuse (90 %) or focal slowing (30 %); seizure activity has been reported in 24–60 % of the patients.[34,40] A highly characteristic pattern described as “extreme delta brush”, occurs in 30 % of adults (and some children) with this disorder. It consists of diffuse generalised slowing 1–3 Hz with superimposed beta-activity (20–30 Hz) “on top”of the slow delta waves.[31,40]

In anti-NMDA-receptor encephalitis, fluorodeoxyglucose brain positron-emission-tomography (PET) shows an increase of frontal and temporal metabolism relative to occipital areas. This gradient correlates with clinical severity and normalises with recovery.[41]

Encephalitis with LGI1 Antibodies

The most frequent neuronal surface antibodies found in patients with limbic encephalitis are LGI1 antibodies.[15] This syndrome affects mostly elder men (m:f 3:1; median 60 years). Myoclonic-like movements have been described in 40 % of the patients and autonomic symptoms occur in around 10 %.[10–12] Recent studies have shown that the myoclonic-like movements probably correspond to tonic seizures,[42] which have also been reported as faciobrachial-dystonic seizures.[43] These types of seizures may precede or occur simultaneously with encephalitis and their prompt recognition and treatment may prevent progression to more severe symptoms. The presence of hyponatremia in 60 % of the patients is also suggestive of this type of autoimmune encephalitis. In addition to classical limbic encephalitis, patients may develop neuromyotonia in rare instances. Many patients with encephalitis associated with LGI1 antibodies have normal or near normal routine CSF studies. Despite this, the large majority of these patients have antibodies detectable in the CSF (see Table 1).[12,44] In anti-LGI1 encephalitis, approximately 80 % of EEGs are abnormal, including epileptic seizures and focal or diffuse slowing.[10]

In anti-LGI1 encephalitis the MRI usually shows T2-fluid attenuated inversion recovery (FLAIR) medial temporal lobe abnormalities suggestive of limbic encephalitis. This is similar in GABA(b)-receptor and AMPA-receptor encephalitis. However, these findings should be viewed with caution given that seizures can result in similar initial findings. Only anti-CASPR2 encephalitis and especially Morvan’s syndrome exhibits less frequent MRI abnormalities.[11,12,45]

Encephalitis with CASPR2 Antibodies

CASPR2 antibodies usually occur with diffuse encephalitis with or without dysautonomia and peripheral nerve hyperexcitability (Morvan’s syndrome).[12] Neuropathic pain can be a prominent feature (60 %.[45] The significance of antibodies against VGKC-complex proteins,

different from LGI1 and CASPR2 is unclear; the identity of the antigens and whether they are neuronal or extraneuronal, intracellular or extracellular is unknown.

Encephalitis with AMPA-receptor Antibodies

The anti-AMPA-receptor encephalitis has been described mostly in middle-aged women (90 % women, range 38–87 years, median 60 years) with symptoms of classical limbic dysfunction[6,46,47] or pure psychiatric manifestations.[6,46,47] Patients often respond to immunotherapy, but they tend to relapse (60 %).[6] The memory dysfunction decreases the patients' compliance with treatment, which after several relapses may develop irreversible memory and cognitive deficits.

Encephalitis with GABA(b)-receptor Antibodies

The clinical syndrome associated with GABA(b)-receptor antibodies is a limbic encephalitis (memory dysfunction, behavioural abnormalities and seizures) in which seizures and status epilepticus are especially prominent.[7] The patients' median age is 60 years and men and women are affected equally. Most patients with SCLC and limbic encephalitis who are Hu antibody negative, have GABA(B)-receptor antibodies in serum and CSF.[18] Many patients have additional antibodies, including thyroid-peroxidase (TPO), glutamic acid-decarboxylase (GAD), Sry-related HMG box 1 (SOX1) or N-type voltage dependent calcium channels (VGCC).

Encephalitis with Other Neuronal Surface Antibodies

The association of limbic encephalitis with Hodgkin's lymphoma has been termed Ophelia syndrome and currently, three cases with mGluR5 antibodies have been described.[9,32] Another antibody found in four patients with limbic encephalitis and prominent diarrhoea is directed against dipeptidyl-peptidase-like protein-6, a regulatory subunit of the Kv4.2 potassium channels.[14] Dopamine-D2-receptor antibodies have been reported in children with basal ganglia encephalitis, Sydenham chorea and a subgroup of patients with Tourette's syndrome; further work is needed to determine the frequency and relevance of these antibodies.[13] Glycine-receptor antibodies occur in a few patients with stiff-person syndrome spectrum disorders: progressive encephalomyelitis with rigidity and myoclonus (PERM), myoclonus, and hyperekplexia.[33,48,49] Stiff-person-syndrome (SPS) is a disorder characterised by progressive axial and appendicular stiffness and paroxysmal painful spasms triggered by movement, auditory, tactile or emotional stimuli. This syndrome occurs in a paraneoplastic and idiopathic context, women are affected more often (7:3) and there are several variants, e.g. stiff-limb-syndrome and PERM. Antibodies against GAD and glycine-receptor can be found in idiopathic SPS (50–90 %).[33,48,50] The paraneoplastic form of stiff-person syndrome associates with amphiphysin antibodies, although some patients may have GAD or glycine-receptor antibodies.[51]

Encephalitis associated with GAD Antibodies

GAD catalyses the synthesis of GABA, the major inhibitory neurotransmitter of the CNS. Antibodies against GAD were originally described in patients with juvenile onset diabetes

but subsequently were found, usually at higher titres, in serum and CSF of patients with stiff-person-syndrome (SPS) with or without diabetes.[52] They have also been reported in patients with late onset cerebellar degeneration, temporal lobe epilepsy and limbic encephalitis. The latter can be preceded by a purely epileptic syndrome.[53] Patients with neurological symptoms are usually young women (median age 23 years, range 17–66)[51] with high titres of antibodies,[52,54] elevated intrathecal antibody synthesis,[55,56] frequent oligoclonal bands (60 %) and sometimes CSF pleocytosis (30 %).[53,57] Some patients with cerebellar dysfunction have muscle stiffness and spasms which can be overlooked unless a milder form of stiff-person syndrome is suspected.[53,57] GAD antibodies may occur in patients with other anti-neuronal antibodies, e.g. GABA(b)-receptor antibodies.[4,7,18] Due to the frequent occurrence of serum GAD antibodies in patients with diabetes and in the normal population, the significance of these antibodies is unclear in patients with neurological symptoms of unclear aetiology, particularly if the antibodies are only detected in serum or at low levels in the CSF. Although GAD is an intracellular protein, there is some evidence that antibodies may have a direct pathogenic role.[58]

Steroid Responsive Encephalopathy with Autoimmunity to Thyroid (SREAT)

This syndrome, previously known as Hashimoto encephalopathy, encompasses a heterogeneous group of clinical syndromes and courses, whose common denominator is the response to immunotherapy and the presence of thyroid antibodies (thyroid peroxidase and thyroglobulin). However, the prevalence of these antibodies is high in the general population (up to 20 %)[59] and the neurological syndrome is poorly defined. The vast majority of published cases have not been tested for all other relevant antibodies.[60] This syndrome should only be considered after exclusion of other autoimmune encephalitis. Most patients diagnosed with Hashimoto’s encephalitis have in fact other disorders.[60]

Differential Diagnosis of Limbic Encephalitis

In any patient suspected to have autoimmune encephalitis, metabolic/toxic, nutritional, vascular, structural, malignant, rapid progressive neurodegenerative diseases and especially infectious aetiologies of encephalitis have to be excluded. Only few differential diagnoses pose difficulties if history and clinical syndrome is precisely known.

HSV-1 encephalitis can be initially indistinguishable from autoimmune limbic encephalitis. Aciclovir treatment has to be promptly initiated until HSV-1 is ruled out. HSV-1 PCR has a sensitivity of 98 % and a specificity approaching 100 % but can be negative within the first 24 h after symptom onset. In immunocompromised patients, HHV6 can be the cause of limbic encephalitis; its clinical and radiological presentation can be identical to the encephalitides described above. Previously unknown HIV-infection can cause diffuse or limbic encephalitis with only slight pleocytosis and non-specific white-matter changes on MRI. Chronic infections with atypical bacteria, e.g. Treponema pallidum, can also mimic limbic encephalitis. Special consideration has to be given to sporadic Creutzfeldt-Jakob’s disease (CJD) since it can mimic many of the features described in this review. Phenotypic overlap is especially pronounced with Lgi1 antibody encephalitis; patients with this disorder may develop symptoms suggesting a rapidly progressive dementia with myoclonic-like

movements (which usually represent tonic seizures) and the protein 14-3-3 can be positive as occurs with other paraneoplastic and autoimmune encephalitis.[61]

Other autoimmune entities have to be taken into consideration. Primary CNS vasculitis and systemic autoimmunity, e.g. systemic lupus erythematosus, can result in neuropsychiatric symptoms, which may be difficult to distinguish from the above described disorders. In Sjögren's syndrome seizures and cognitive dysfunction with CSF pleocytosis can occur. An overview of the most common differential diagnosis is given in Table 2.

Antibodies

The syndromes covered in this review (see Table 1) are defined by the presence of neuronal antibodies. However in testing and interpreting antibody findings some pitfalls have to be avoided. In anti-NMDA-receptor encephalitis, isolated serum testing misses 15 % of cases.[34] In contrast, finding the neuronal antibodies only in serum has to be interpreted with caution. None of over 500 patients with anti-NMDA-receptor encephalitis had isolated serum antibodies.[34] Furthermore, all the above mentioned syndromes are defined by the presence of IgG isotype antibodies against the respective antigen. Non-IgG isotypes are not markers of these diseases and their significance and specificity for any neurological syndrome is currently unclear.

Requesting the correct antibody test is essential and failure to do so can result in false-positive results. Antibodies against the NR2 subunit of the NMDA-receptor have been reported in many disorders but are unrelated to the entity of anti-NMDA-receptor encephalitis discussed in this review. There are patients with serum antibodies in VGKC radioimmunoassays (RIA), which are negative for LGI1 and CASPR2 antibodies. The significance of these VGKC-RIA antibodies is currently unknown. It is also unknown whether the antibodies detect neuronal surface or intracellular antigens.

Treatment decisions largely based on CSF and/or serum titre changes should be avoided. Although a correlation with clinical improvement has been shown in single cases and case series, the detection of antibodies persists in many patients in spite of clinical recovery.

In summary, paired serum and CSF samples should be initially tested for the presence of neuronal antibodies to prevent false-negative and false-positive test results. In the following situations it is advisable to send samples to a reference laboratory for re-examination: clinical syndromes unknown to be associated with the identified antibody, detection of antibodies only in serum, positive results without further molecular characterisation (e.g. voltage-gated potassium channel-radioimmunoassay (VKGC-RIA) and non-IgG isotypes. Treatment decisions should be based on clinical parameters rather than on titre changes.

Paraneoplastic Association

The frequency of an underlying tumour varies according to the immunological subtypes of encephalitis (see Table 1). Generally, the frequency of tumours is lower in the encephalitides associated with neuronal cell-surface antibodies compared with antibodies against onconeural antigens.

In anti-NMDA-receptor encephalitis the presence of a tumour is dependent on age, gender and ethnicity. Women between 12 and 45 years of age have the highest chance of an underlying tumour (53 %), usually ovarian teratomas (94 %); other tumours are rare and may include extra-ovarian teratomas, and cancer of the lung, breast, testis, thymus, pancreas and ovaries. These unusual tumours are more common in patients older than 45 years. Ethnicity also plays a role; tumours were more prevalent in Asians and Afro-Americans (45–48 %) compared to Caucasians and Hispanics (27–30 %). Men and young children (<12 years) have a low prevalence of tumours (6 %).[34] The clinical presentation between paraneoplastic and idiopathic variants of the NMDA-receptor encephalitis does not differ, although the course and number of relapses might be different (see below).[5,29] Over 50 % of patients with GABA(b)-receptor antibodies have a small-cell lung cancer (SCLC). AMPA-receptor encephalitis has a paraneoplastic origin in 80 % of cases (lung, breast cancer, thymomas).[6,7,46]

Underlying tumours are less prevalent in LGI1 antibody associated syndromes (<10 %), nevertheless thymomas and lung cancer should be ruled out. Also, a few cases of thyroid, breast, ovarian and renal cell cancer have been described.[10,44] The frequency of thymoma and other tumours in CASPR2 antibody associated encephalitis varies according to centres performing the studies and their patterns of referrals, ranging from 10 to 40 %.[12,45] The neurological syndromes associated with GAD antibodies are rarely paraneoplastic,[56] however, GAD antibodies can co-occur in association with other antibodies, such as onconeuronal and cell surface antibodies, in which case the patients may have underlying tumours.[18]

Tumour Search

In the absence of reliable biomarkers that could assist in the identification of paraneoplastic variants, all patients with the syndromes reported here should be screened for the presence of a tumour. The chance of identifying a tumour varies according to the type of immune response and patient's age. According to current guidelines,[62] the initial tumour screening should be directed towards the organ(s) suggested by the associated antibody (see Table 1). In addition, the techniques used for tumour screening not only depend on the type of tumour but also on the patient's age. For example, adult women suspected to have an ovarian teratoma, usually undergo pelvic or transvaginal ultrasound and/or CT or MRI of the pelvis; in contrast, young girls are examined with pelvic ultrasound and MRI of the pelvis (CT are usually avoided to prevent radiation). Whole body FDG-PET is usually negative in patients with ovarian teratoma, while this test combined with CT of the chest are the best techniques to demonstrate lung cancer. The extent of tumour screening also depends on the type of antibody. For example, antibodies to AMPA-receptor associate to several tumour types (breast, lung, thymus), while antibodies to NMDA-receptors preferentially associate with teratomas, antibodies to LGI1 rarely occur with tumours.

For syndromes or antibodies frequently associated with tumours (NMDA-receptor antibodies in young adult women, AMPA-receptor, GABA(B)-receptor and perhaps CASPR2 antibodies) if the initial screening does not reveal a tumour, repeated periodic screening (e.g., every 6 months) for 2–4 years or upon clinical relapse is reasonable. Only in

children younger than 12 years of age and male patients with anti-NMDA-receptor encephalitis, the benefit of repeated screening might be limited due to their low overall tumour risk. The experience with other antibody-associated encephalitis (mGluR1, mGluR5, DPPX, glycine-receptor) is too limited to suggest any guidelines. On the other hand, due to the low frequency of tumour association in patients with LGI1 and GAD antibodies, the tumour screening in these patients should be considered at onset of the disease, without need of repeated, periodic screenings. Whether relapses indicate the necessity of repeated screenings in these syndromes is currently unknown.

Therapy and Outcome

Although there are no controlled clinical trials in autoimmune encephalitis, large case series of the more common entities demonstrate good neurological outcomes after immunotherapy and if applicable tumour removal.[34] The best studied disorders due to their relative high frequency are anti-NMDA-receptor encephalitis and anti-LGI1 encephalitis. The therapeutic approach in other autoimmune encephalitides is usually done following strategies used for anti-NMDA-receptor encephalitis.

A recent study considered treatment outcomes in 501 patients with anti-NMDA-receptor encephalitis with at least 4 months follow-up, of which ~50 % of those treated with first-line immunotherapy and tumour removal (when appropriate) improved within the first four weeks and had a favourable outcome (97 % complete or near full recovery at 24 months).[34] Of the remaining 50 % of patients who did not respond to first-line therapy, 60 % received second-line therapy (rituximab, cyclophosphamide or both) and 40 % did not. Seventy-eight per cent of those who received second-line immunotherapy had a favourable outcome at 24 months compared with 55 % of those who did not receive second-line therapies.[34] Factors related to a good outcome included lower severity of symptoms not necessitating intensive care treatment, prompt initiation of immunosuppression/tumour removal and second-line immunotherapy in patients failing first-line therapy.[34] Similar findings occurred in the subgroup of 177 children.[34,63]

Within the first 24 months of the disease, relapses occurred in approximately 12 % of the patients; one-third of them had multiple relapses. The overall mortality was calculated to be approximately 7 %, mostly resulting from autonomic dysfunction and complications arising during intensive care treatment.[34]

Anti-LGI1 encephalitis often responds well to first-line immunotherapy with steroid, plasma exchange or IVIg. Although the published series of patients are considerable smaller than those related to anti-NMDA-receptor encephalitis, approximately 80 % of patients have a favourable outcome; mortality appears to be around 6 % and the relapse rate is close to 15 %.[10,11] The long-term outcome of patients with anti-LGI1 encephalitis has not been well defined; studies suggest that these patients respond faster to immunotherapy than patients with anti-NMDA-receptor encephalitis, but the long-term outcome (measured by return to normal activities) does not appear to be as good as that of patients with anti-NMDA-receptor encephalitis (personal observation of the authors).

Conclusion

The autoimmune encephalitides comprise a growing group of antibody-mediated disorders with favourable response to immunotherapy. Neuroimaging and CSF studies are necessary but their specificity and sensitivity are limited. Detection of neuronal antibodies is important for the diagnosis, treatment planning and prognostic evaluation. Immunotherapy and if applicable, tumour removal are crucial to expedite neurological improvement and to attain substantial clinical recovery. Future studies will identify new antibodies and the pathogenic mechanisms involved and will clarify the spectrum of symptoms of these disorders. Controlled trials are necessary to establish the best initial therapies and their use to prevent relapses.

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Table 1

Encephalitic Syndromes associated with Antibodies Against Neuronal Surface Antigens

Antigen	NMDA Receptor NR1	LGI1	CASPR2	AMPA Receptor	GABA(b) Receptor	Glycine Receptor α1	mGluR5	DPPX
Age (median)	0.6–85 (21)	30–80 (60)	46–77 (60)	38–87 (60)	24–75 (62)	5–69 (43)	46, 15	45–76
Gender f:m	4:1	1:2	1:4	9:1	1:1	6:5	1:1	1:1
Clinical syndrome	**1** Prodomal syndrome **2** Psychiatric syndrome, seizures, amnesia **3** Movement disorders catatonia, autonomic instability	Limbic encephalitis, tonic or facio-brachial dystonic seizures, myoclonus	Morvan syndrome, encephalitis, neuromyotonia	Limbic encephalitis, psychiatric syndromes	Limbic encephalitis	Encephalomyelitis with rigidity and myoclonus, hyperekplexia, stiff-person syndrome, (retinopathy)	Limbic encephalitis, myoclonus	Limbic encephalitis, myoclonus, diarrhoea 3/4
MRI hyperintensities	Only 33 % abnormal! 25 % mesiotemporal FLAIR, few enhancing lesions	>80 % mesiotemporal FLAIR	40 % encephalitis: mesiotemporal FLAIR	90 % mesiotemporal FLAIR	70 % mesiotemporal FLAIR	90 % normal	1 patient mesiotemporal, 1 cortical FLAIR	2/3 unspecific T2 hyperintensities
CSF: pleocytosis or ocb	95 % (at onset 80 %)	40 %	25 %	90 %	90 %	Some ocb	2/2	4/4
Tumour	Age-dependent 10–50 % ovarian teratomas	<10 %* (lung, thymoma)	<20 %* (lung, thymoma)	70 % (lung, breast, thymoma)	60 % (lung)	rare ≈ 10 %	2/2 Hodgkin lymphoma	0/4
Relapses	12–25 %, mostly idiopathic cases without initial immunosuppression	15 %	Common in encephalitis	50 %	Rare	Unknown	0/2	Unknown
Miscellaneous	EEG in 90 % abnormal, 30 %, “extreme delta brush“[55]	Hyponatremia (60 %)	Limbic encephalitis	Common relapses	Prominent seizures and status epilepticus	Few cases known	Only 2 cases known	Only 4 cases, prominent diarrhoea
Relative frequency[a]	55 %	30 %	4 %	4 %	5 %	2 %	<1 %	<1 %

* True tumour incidence unknown.

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid; CASPR2 = contactin-associated protein-like 2; CSF = cerebrospinal fluid; DPPX = dipeptidyl-peptidase-like protein-6; EEG = electroencephalograph; FLAIR = fluid attenuated inversion recovery; GABA = γ-amino-butyric acid; LGI1 = leucine-rich, glioma-inactivated 1; mGluR5 = metabotropic glutamate receptor 5; MRI = magnetic resonance image; NMDA = N-methyl-D-aspartic acid receptor; ocb = oligoclonal bands. Relative frequencies estimated based on.[27]

Table 2

Differential Diagnosis of Limbic Encephalitis

	HSV-1 Encephalitis	HHV6	VZV	SLE	Sjögren Syndrome	PACNS
Clinical syndrome	Seizures, headache, personality changes, confusion and fever	Confusion, agitation, short-term memory loss, seizures, tremor, ataxia, focal signs, headache, fever	Headache, confusion, fever, meningeal signs (20–30 %). Seizures are rare. Dermatomal rash in 50%	Anxiety, mood disorders, psychosis, seizures, headache	Seizures, meningeal signs, cognitive dysfunction, long tract signs	Headache, cognitive dysfunction, focal signs
MRI: uni- or bilateral temporomesial T2/ FLAIR hyperintensities	Very frequent 90 %	Frequent	Less frequent 40–70 %	Very rare	Very rare	Very rare
CSF	Pleocytosis, moderate protein increase. Red blood cells frequent	Lymphocytic pleocytosis, moderate protein increase	Pleocytosis, moderate protein increase. Red blood cells uncommon	Sometimes increased protein, pleocytosis rare	Pleocytosis, increased protein	Increased protein, sometimes pleocytosis
EEG	80 % abnormal, paroxysmal sharp waves and spikes. Temporal bi- and triphasic waves and PLEDs	Diffuse slowing, occasionally spikes and sharp waves	Paroxysmal sharp waves and spikes.	Diffuse slowing, spikes and sharp waves	Diffuse slowing, spikes and sharp waves	Focal and diffuse slowing
Diagnostic tests and distinctive features	HSV-PCR in CSF Seizures very common	HHV6-PCR in CSF Immunocompromised patients	VZV-PCR in CSF Herpes zoster rash 50 % Immunocompromised patients	dsDNA-antibodies Systemic SLE features	SS-A, SS-B antibodies salivary gland imaging and biopsy	Biopsy Angiography
Therapy	Aciclovir, neurological sequelae common, high morbidity and mortality	Foscarnet, cidofovir, ganciclovir	Aciclovir, neurologic sequelae common.	Steroids, azathioprinecyclophosphamide, rituximab	Steroids, immunosuppressants	Steroids, cyclophosphamide

CSF = cerebrospinal fluid; EEG = electroencephalograph; FLAIR = fluid attenuated inversion recovery; HHV-6 = human herpes virus 6; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus 1; ocb = oligoclonal bands; MRI = magnetic resonance image; PACNS = primary angiitis of the central nervous system; PLEDS = periodic lateralised epileptiform discharges; SLE = systemic lupus erythematosus; VZV = varicella zoster virus.