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Limbic Encephalitis and Autoimmune Encephalitides: Pathophysiology, Classification, Clinical Presentation, and Treatment

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Abstract

Limbic encephalitis represents a cluster of autoimmune disorders, with inflammation in the medial temporal lobe characterised by the subacute onset of neuropsychiatric symptoms such as anxiety, affective symptoms, psychosis, short-term memory impairment, as well as faciobrachial and grand mal seizures. The limbic system is a complex anatomical structure which this paper seeks to explain in terms of its anatomy and physiology, before exploring what happens when it is impaired as is the case of autoimmune and limbic encephalitis. We will discuss the pathophysiology, clinical symptomatology and diagnosis of autoimmune encephalitis, a cluster of symptoms which can be easily overlooked or misdiagnosed within psychiatric settings. Characteristic indicators of autoimmune encephalitis include neurologic symptoms such as facial twitching, seizures, confusion, and cognitive decline; however, our experience realises that autoimmune encephalitis is not easy to identify as most patients initially present with psychiatric symptomatology rather than these neurological symptoms. Furthermore, immunological and laboratory testing take a long time to diagnose the condition. Importantly, few psychiatrists consider the autoimmune nature of the neuropsychiatric presentation. It is hence vital to consider autoimmune encephalitis in all patients with atypical presentations.

Keywords

Limbic System, Limbic and Autoimmune Encephalitides, Symptomatology, Treatment

1. Introduction

Autoimmune illnesses develop when the body's innate immune response incor-

rectly targets normal body cells and tissues. The immune system usually recognises and ignores the antigens naturally found in the body—self-antigens. The recognition system can malfunction, however, and when it does, the activated B (bone marrow) cells produce antibodies against other body cells and tissues. These misguided antibodies are termed autoantibodies. The trigger may be a reduction in suppressor T (thymic) cell activity, excessive stimulation of helper T cells, tissue damage that releases copious quantities of antigenic fragments, haptens bound to compounds normally ignored, viral or bacterial toxins, or a combination of these factors. The symptoms produced rely heavily on the specific antigen targeted by these autoantibodies [1].

The term "autoimmune encephalitis" refers to a group of intricately connected conditions that share overlapping clinical symptoms, but which nevertheless are differentiated by the specific antibody subtypes driving the underlying immune-mediated attack on different brain structures [2]. The exact aetiology of autoimmune encephalitis is not known; however, Dropcho (1989) [3] was one of the first researchers to advocate the autoimmune aetiology of these conditions. Earlier cases of autoimmune encephalitis were associated with malignancy, and it was understood that the antibodies were generated as a response to tumour antigens and later developed molecular imitation against autoantigens, thereby producing neurological syndromes [4].

2. Classification of Autoimmune Encephalitis

Autoimmune encephalitis comprises several diverse disease types that possess different pathophysiology and clinical manifestation. Based on antibody type, autoimmune encephalitis is divided into the following groups:

1) Disorders coupled with antibodies to intracellular antigens such as:

a) Anti-Hu or anti-neuronal nuclear antibody 1 (ANNA-1) limbic encephalitis

b) Anti-Ri or anti-neuronal nuclear antibody 2 (ANNA-2) encephalitis

c) Anti-Yo or Purkinje cell autoantibodies 1 (PCA-1) encephalitis

d) Anti-collapsin response mediator protein 5 (CRMP-5) encephalitis

e) Anti-Ma limbic encephalitis [5]

These conditions cause irreversible neuronal damage, are strongly associated with cancers, have limited response to treatment and have a poor prognosis [6]-[11].

2) Disorders associated with autoantibodies to extracellular epitopes of ion channels, receptors, and other associated proteins, such as:

a) Anti-N-methyl-D-aspartate (NMDA) receptor-encephalitis

b) Anti-a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-limbic encephalitis

c) Anti-g-Aminobutyric acid B ($GABA_B$) receptor-limbic encephalitis

d) Anti-g-Aminobutyric acid A ($GABA_A$) receptor-encephalitis

e) Anti-metabotropic glutamate receptor 5 (mGluR5)-encephalitis

f) Anti-dopamine 2 receptor-basal ganglia encephalitis

These conditions are linked with underlying cancers yet have a better progno-

sis [5].

3) Syndromes related with antibodies to intracellular synaptic proteins such as:

a) Anti-leucine-rich glioma inactivated protein 1 (LGI1)-limbic encephalitis

b) Anti-contactin-associated protein-like 2 receptor (CASPR2)-limbic encephalitis (Morvan's syndrome) (both anti-LGI1 and anti-CASPR2 were formerly called anti-voltage-gated potassium channel (VGKC) complex antibodies-associated encephalitis)

c) Anti-dipeptidyl-peptidase-like protein 6 (DPPX)-encephalitis

d) Anti-myelin oligodendrocyte glycoprotein (MOG)-acute disseminated encephalomyelitis

e) Anti-aquaporin 4-encephalitis

f) Anti-GQ1b-Bickerstaff's brainstem encephalitis [5]

3. Limbic System

The limbic system (**Figure 1**) includes nuclei and tracts along the border between cerebrum and diencephalon. This system is a functional grouping rather than an anatomical one and includes portions of the cerebrum, diencephalon, and mesencephalon [1]. The limbic system is comprised of a set of closely interrelated brain parts that involve the cingulate gyrus, the anterior thalamus, the hypothalamus, mammillary bodies (from Latin *corpus mamillare* "breast-shaped" bodies), the hippocampus (seahorse, from Greek *hippos*, meaning "horse", and *kampos*, meaning "sea monster"), and the amygdala (from Greek *amygdale* meaning "almond") [12]. The limbic system was first described in 1872 by the French anatomist Paul Broca (1824-1880), who coined the term "limbic" (from Latin *limbus* for "border"). American neuroanatomists James Papez (1983-1958) in 1937 and Paul Donald MacLean (1913-2007) in 1952 have extended the basic layout of Broca to what is currently known as the limbic system [13] [14].

Recent research has afforded more in-depth evidence of the structure and physiology of the limbic system and one can simply conclude that the limbic system is not one uniform or single system [15]. The functions of the limbic system are complex and include the establishment of baseline emotional state, addiction and motivation, appetite and eating behaviours, sleep and dreams, memory, sexual behaviours, and social cognition. The cingulate gyrus is involved in autonomic functions regulating heart rate and blood pressure as well as cognitive attentional and emotional processing [13] [14] [16]. The hippocampus has vital functions in spatial navigation and the consolidation of information from short-term to long-term memory [14] [17] [18].

The amygdala as the central subcortical emotional brain structure continuously assesses and integrates a mixture of sensory information from the environment and allocates them suitable values of emotional dimensions, such as power, intensity, and approachability. Additionally, the amygdala participates in the regulation of autonomic and endocrine functions, decision-making and adaptations of instinctive and motivational behaviours to changes in the environment through

implicit associative learning, changes in short- and long-term synaptic plasticity, and activation of the fight-or-flight response [1] [19]. Furthermore, the amygdala is involved in associate fear learning [20]. The hypothalamus regulates the autonomic nervous system via hormone production and release [21]. Moreover, hippocampus secondary affects and regulates blood pressure [22], heart rate, hunger, thirst, sexual arousal, and circadian rhythm (sleep/wake cycle) [23]. The mammillary bodies play a role in memory [24]. The nucleus accumbens is involved in mediation and regulation of reward and satisfaction [25] [26] as well as addiction [27].

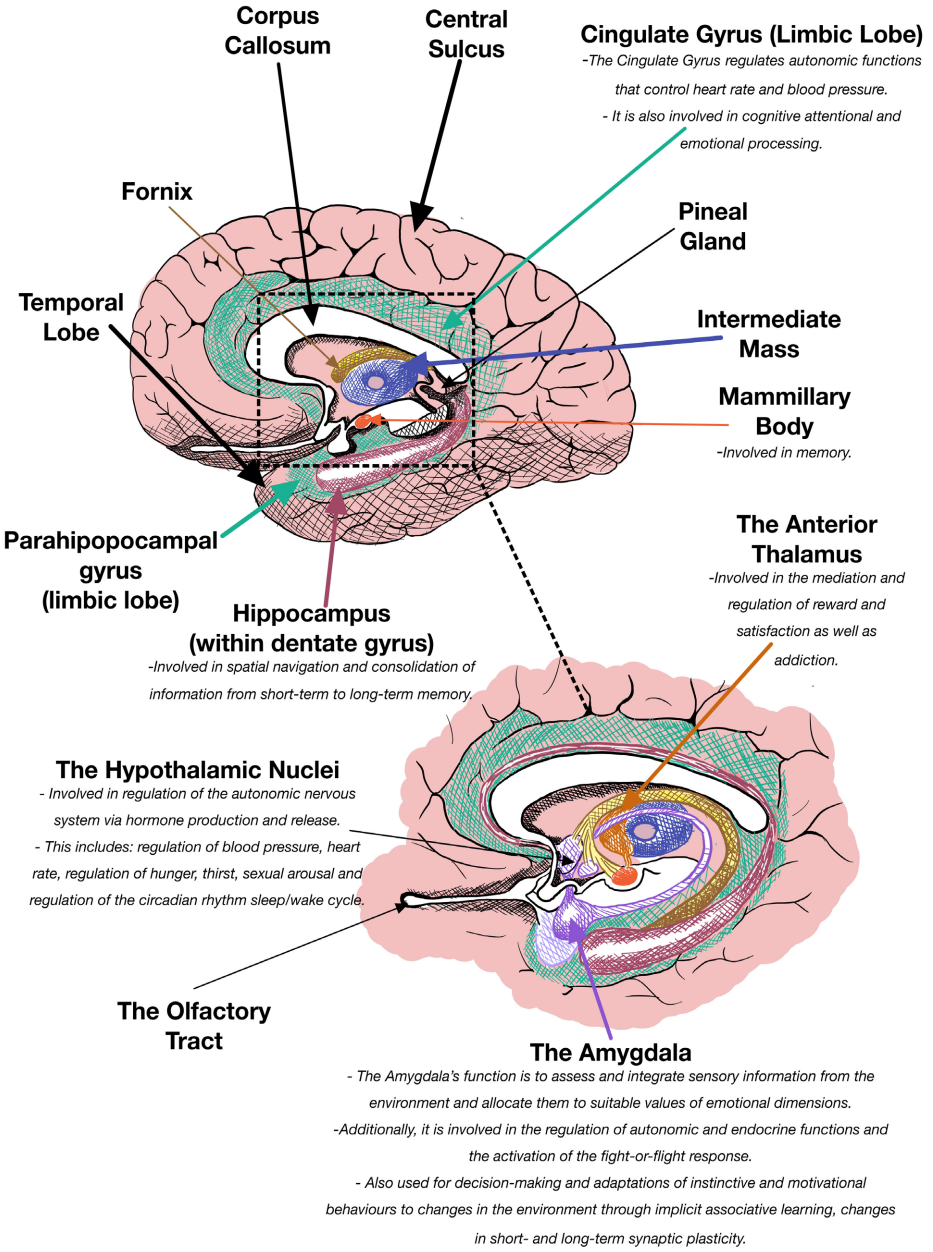

Figure 1. Schematic illustration of the major anatomical structure of limbic system and their functions.

Disruption of limbic structures has huge clinical implications and presents with a variety of neuropsychiatric disorders including Parkinson disease [28], epilepsy [16], dementia [29], post-traumatic stress disorder [30], anxiety disorders [31], schizophrenia, affective disorders [27] [32], attention deficit and hyperactivity disorder [33], Kluver-Bucy syndrome [34], and Korsakoff's psychosis [35].

4. Limbic Encephalitis

The term limbic encephalitis was first used by the British neurophysiologist Corsellis *et al.* (1968) [36] who found inflammatory changes in the medial temporal lobes and limbic structures of patients with progressive memory loss after being diagnosed with lung cancer. Nonetheless, the first description of limbic encephalitis was penned by Brierley and colleagues in 1960 [37]. Whilst limbic dysfunction is the single most consistent finding in autoimmune encephalitis, varying degrees of involvement are seen within the neocortex, striatum, hindbrain, spine, and peripheral nervous system [10] [38].

4.1. Anti-HU Antibodies-Associated Limbic Encephalitis

Hu proteins are RNA-binding proteins that play important roles in neuronal differentiation and plasticity [39] [40]. Anti-Hu or anti-neuronal nuclear antibody 1 (ANNA1) antibodies are autoantibodies, which react with nuclear and cytoplasmic proteins of neurons throughout the central nervous system. Anti-Hu antibody-associated encephalitis is strongly associated with small cell lung carcinoma. This syndrome presents with symptoms of limbic encephalitis, cerebellar degeneration, brainstem encephalitis, dorsal sensory neuronopathy, motor neuron disease and gastroparesis [5] [9] [11] [41]. Patients will also present with symptoms of short-term memory loss, confusional states, Wernicke-Korsakoff's-like symptomatology, and seizure [42]. In a cohort of 27 patients with Anti-Hu-associated limbic encephalitis, Budharm (2022) [43] and colleagues reported local motor seizures as the most common manifestation of this syndrome, followed by ictal expressive speech difficulties.

4.2. Anti-Ri Antibodies-Associated Encephalitis

Ri proteins (similarly to Hu proteins) are RNA-binding proteins mediating neuronal differentiation and plasticity [39] [40]. Anti-Ri antibody or anti-neuronal nuclear antibody 2 (ANNA2) is associated with breast adenocarcinomas and small cell carcinoma of the lung. Clinically it manifests with syndromes of opsoclonus/ataxia, cerebellar degeneration, limbic or brainstem encephalitis, ophthalmoplegia, laryngeal dystonia, and gastroparesis [44] [45].

4.3. Anti-Ma Antibodies-Associated Limbic Encephalitis

The functions of the proteins encoded by paraneoplastic genes are not clear, although they may play a role in apoptosis [46]. Most patients with anti-Ma encephalitis present with eye movement abnormalities and vertical gaze paresis. Other

common symptoms include short-term memory deficit, excessive daytime sleepiness, diplopia, dysarthria, ataxia, parkinsonism or hypokinesia, and narcolepsy [47] [48]. A few cases of a significant unexplained weight gain in the context of hypothalamic obesity have also been reported with anti-Ma encephalitis [49]. Initial cases of anti-Ma limbic encephalitis were reported to be more common in young men with testicular tumours [50]. However, this condition has also been associated with a variety of gynaecological cancers in women. Furthermore, most patients present with neuropsychiatric symptoms before the identification of their malignancy [47]. Anti-Ma antibodies-associated encephalitis has a better prognosis compared to anti-HU encephalitis [50].

4.4. Anti-Voltage-Gated Potassium Channels-Complex Limbic Encephalitis

The neuronal activity is the basis for normal brain function. Altered activity can result in neurological disease like epilepsy, insomnia, hallucinations, schizophrenia, different forms of headache, autism, and even death [51]. Vital for normal brain function is the correct formation of action potentials in neurons and chemo-electrical communication among neuronal cells. Molecular actuators include voltage-gated potassium channels VGKC and ligand-gated ionotropic receptors like the excitatory glutamate or the inhibitory glycine receptors. Both activation, and inhibition, of molecular targets may lead to disharmonies in the concert of brain function [52].

Potassium channels reside in cell membranes, regulating transportation of K^+ ions efflux from and influx into cells. They play crucial roles in both excitable and non-excitable cells and can be found in all species, except for some parasites [53] [54]. They are present in all cell types including neurons and muscle cells. Potassium channels are highly selective, displaying up to 1000-fold preference for K^+ ions over smaller ions such as Na^+ and Li^+ [55]. Depending on the functioning principle and based on the primary structure of a channel-forming subunit, potassium channels are subdivided into Ca^{2+}-activated channels, two-pore domain, and voltage-gated channels. VGKC form the most diverse group, represented by 12 families [56]. They play a key role in a variety of cellular processes, including the functioning of excitable cells, regulation of apoptosis, cell growth and differentiation, the release of neurotransmitters and hormones, maintenance of cardiac activity, and so on [57]. Mutations in the genes of VGKC can lead to hereditary disorders [58], including deafness, epilepsy [59], and certain forms of arrhythmias [60]. They are also involved in the pathogenesis of multiple sclerosis, the pain syndrome [61], as well as benign and malignant tumours [62].

The VGKC-complex is a cluster of proteins that are strongly connected in situ and after extraction in mild detergent. Two major targets of the autoantibodies are leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein 2 (CASPR2) [63] [64]. Anti-voltage gated-complex antibodies were initially described in patients with Isaac's syndrome [65]. Subsequently they were isolated in individuals suffering from limbic encephalitis [66].

4.5. Anti-LGI1 Antibody-Associated Limbic Encephalitis

Leucine, isoleucine, and valine stimulate protein synthesis in muscle and make up about one third of muscle protein [67]. Leucine also suppresses food intake, directly impinges on hypothalamic neurons known to regulate food intake, and influences signalling systems that are associated with feeding behaviours [68]. In the human brain the branched-chain amino acids, particularly leucine, play a vital role in glutamate synthesis. Indeed, from 30% to 50% of brain glutamate and glutamine are derived from leucine alone [69]. Leucine-rich glioma inactivated 1 (Lgi1), having a leucine-rich repeat domain, encodes a secreted protein in the CNS [70]. Current evidence proves that Lgi1 is critical to the pruning of glutamatergic synapses in the hippocampus [71] [72]. Consequently, the deletion or mutation in Lgi1 impairs glutamatergic transmission in hippocampus, which is the pathologic basis for autosomal dominant lateral temporal lobe epilepsy [73] [74] [75] [76]. Except for epileptogenesis, Lgi1 plays roles in neuronal and glial growth [77] [78].

Anti-LGI1 antibody-associated limbic encephalitis is characterised by the subacute onset of psychiatric symptoms such as short-term memory impairment, psychosis and affective symptoms, and neurological symptoms as in faciobrachial seizures, orofacial dyskinesia, and headache [51] [63]. Moreover, almost 80% of patients developed faciobrachial dystonic seizures before the onset of amnesic syndrome [79].

4.6. Anti-CASPR2 Antibody-Associated Limbic (Morvan's Syndrome)

Contactins are a cluster of cell adhesion molecules expressed in the brain which play essential roles in the organisation of axonal domains, axonal guidance, neurogenesis, neuronal growth, synapse formation and plasticity, axo-glia interactions, and neural regeneration. Absence of contactins leads to malformed axons and impaired nerve transmission. Contactin mediated protein complex formation is critical for the organisation of the axon in early CNS development [80].

Contactin-associated protein-like 2 (CNTNAP2, also known as CASPR2) is a type I transmembrane cell adhesion molecule, found in the central and peripheral nervous system, where it is highly expressed throughout the brain and spinal cord, particularly in the frontal and temporal lobes, striatum, dorsal thalamus, and specific layers of the cortex [81]. In humans, alterations in the CNTNAP2 gene are associated with a variety of neurological disorders including epilepsy, schizophrenia, autism spectrum disorder [82], intellectual disability, and language delay, but also obesity [83]. Besides that, in humans, autoantibodies that target the extracellular domain of CNTNAP2 are associated with autoimmune epilepsies, cerebellar ataxia, autoimmune encephalitis, neuromyotonia, Morvan's syndrome, and behavioural abnormalities including amnesia, confusion, and neuropsychiatric features [63].

Anti-CASPR2 antibody-associated limbic encephalitis is characterised by neuromyotonia associated with hallucinations, insomnia, delirium, and autonomic disturbances [63]. Morvan's syndrome affects men older than 50 years of age, with the male to female ratio 2:1 [4].

4.7. Anti-NMDA Receptor Antibody-Associated Encephalitis

Glutamate is the most widely utilised excitatory neurotransmitter in the nervous system. The brain glutamate/glutamine cycle is the metabolic pathway that involves the synaptic release of glutamate from neurons, rapid and efficient glutamate uptake by astroglia, conversion of glutamate to glutamine by astrocytic glutamine synthetase, followed by release of glutamine to the interstitium and uptake by the neurons for conversion back to glutamate [69] [84]. This process efficiently prevents excessive accumulation of glutamate in the interstitium that would induce excitotoxic neurodegeneration [85]. The intrasynaptic glutamate level should be kept low to maximise the signal-to-noise ratio upon the release of glutamate from nerve terminals and to decrease the threat of excitotoxicity resulting in excessive glutamatergic stimulation of susceptible neurons [69]. Likewise, glutamate receptors expressed in diverse types of benign and malignant neoplasms play a role as growth factors and are important for cancer development and progression [86]. Expression of glutamate receptors in tumour cells triggers an anti-tumour immune response, which can suppress tumour growth and symptoms [87]. This tumour immune response can break the immune tolerance and different glutamate receptor autoantibodies can attack the neuronal tissue. This antibody-mediated attack on neuronal structures results in a localised inflammatory response [52].

Most of the excitatory neurotransmission in the central nervous system is mediated by glutamate, which activates both pre and postsynaptic glutamate receptors and ionotropic glutamate receptors (iGluRs). iGluRs are ligand-gated cation channels that are divided into three structurally distinct functional classes: the α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, kainate receptors, and N-methyl-D-aspartate (NMDA) receptors [88].

The AMPA receptors are cation-permeable ionotropic glutamate receptors that are expressed throughout the brain [89]. There are four AMPA receptor subunits (GluA1-GluA4) that are encoded by the genes GRIA1-GRIA4 [90]. Upon binding of glutamate, the pore opening allows the influx of Na^+ ions (along with K^+ efflux) to depolarize the postsynaptic compartment; however, depending on the subunit composition and the RNA editing, AMPA receptors also permit Ca^{2+}-influx, which has important consequences for plasticity by engaging Ca^{2+}-dependent signalling events [91]. The AMPA receptors handle most of the fast excitatory synaptic transmission, and their overactivation is potently excitotoxic. AMPA receptors are implicated in synapse formation and stabilization [92]. In addition, several neurological disorders such as ischaemia, traumatic brain injury and Alzheimer's disease involve abnormal AMPA receptor trafficking, which can lead to synaptic dysfunction and neuronal cell death [93] [94].

The NMDA-type glutamate receptors mediate a major part of excitatory neurotransmission in the CNS. Seven NMDA receptor subunits exist that have distinct regional and developmental expression and own a wide range of functional and pharmacological properties. They are widely distributed at all stages of development and are critically involved in normal brain functions, including neuronal development and synaptic plasticity. NMDA receptors are also implicated in the pathophysiology of many neurological and psychiatric disorders, such as ischaemic stroke, traumatic brain injury, Alzheimer's disease, epilepsy, mood disorders, and schizophrenia [95] [96]. Furthermore, evidence indicates that synaptic and extra synaptic NMDA receptors have distinct compositions and couple with different signalling pathways: while synaptic NMDA receptors promote cell survival, extra synaptic NMDA receptors promote cell death [97]. Evidence suggests that severe glutamate release from presynaptic sites triggers a few postsynaptic NMDA receptors, consequently activating excitotoxic neuronal death by allowing excessive Ca^{2+} influx [98] [99] [100] [101]. NMDA receptor overactivity is the proposed underlying mechanism of epilepsy, dementia, and stroke, whilst decreased NMDA receptor activity results in symptoms of schizophrenia [102] [103].

Anti NMDA receptor antibody-associated encephalitis is the most generic form of all autoimmune encephalitis. Moreover, it is most common in women under the age of 50, with the female to male ratio of 4:1 [104]. The disorder can start with "flu-like" symptoms, followed by psychiatric symptoms [4]. Patients affected present with a wide range of symptoms, including anxiety and panic attacks, hostility and aggression, inappropriate sexual behaviours, or psychotic symptoms. Psychiatric symptomatology often fluctuates. Neurological symptoms such as abnormal movements, speech dysfunction, memory deficits, seizures and altered levels of consciousness appear later during the illness [51] [105]. Writhing movements of the face and limbs may be most prominent in the comatose phases of the illness [106], however, seizures may occur in any stage of the illness [107]. Individuals suffering from anti-NMDAR encephalitis usually improve and ultimately recover a decent quality of life [5].

Anti-AMPA antibody-associated limbic encephalitis is an uncommon subtype of autoimmune encephalitis with the subacute onset of psychiatric symptoms, often seen in women with lung, breast and thymic cancer [38] [108].

4.8. Glutamic Acid Decarboxylase (GAD)-Antibody-Associated Limbic Encephalitis

Cortical excitability reflects an equilibrium between excitation and inhibition. In the mammal cortex glutamate is the central excitatory and GABA the key inhibitory neurotransmitter [109]. There are two isoforms of GAD, GAD65 and GAD67, named for their molecular weights in kilodaltons [10] [110]. GAD is expressed in CNS inhibitory neurons and pancreatic b cells. GABAergic inhibitory neurons are involved in regulation and coordination of voluntary movements [101] [111].

GAD-antibody-associated encephalitis is not typically associated with malig-

nancy, however, is linked with other autoimmune conditions such as type 1 diabetes mellitus. It typically causes temporal lobe lesions with the clinical symptoms of limbic encephalitis plus stiff person syndrome with early and prominent development of seizures [10] [110].

4.9. GABAA Antibody-Associated Encephalitis

The $GABA_A$ receptor ($GABA_AR$) is a ligand-gated chloride channel that mediates fast inhibitory synaptic transmission in the CNS. At the synapse, most $GABA_ARs$ contain 2α subunits, 2β subunits, and 1γ subunit. Pharmacologic or genetic alteration of this receptor causes seizures [112] [113] [114].

In anti-$GABA_AR$ encephalitis seizures are the most common clinical manifestation, accompanied by cognitive impairment, decreased level of consciousness, altered behaviour, or movement disorders. Children with anti-$GABA_AR$ encephalitis tend to present with generalized seizures and movement disorders and are less likely to have an underlying tumour than adults. Patients with $GABA_A$ receptor encephalitis usually have distinctive multifocal cortical-subcortical MRI abnormalities [115].

4.10. GABAB Antibody-Associated Limbic Encephalitis

Metabotropic $GABA_B$ receptor is a G protein-coupled receptor, which mediates slow and prolonged inhibitory neurotransmission in the brain, composed of the $GABA_{B1}$ and $GABA_{B2}$ [116].

Anti-$GABA_B$-receptor-antibody-associated limbic encephalitis present with typical symptoms of limbic encephalitis, however early and frequent seizures predominate. This condition is associated with small-cell lung cancer or pulmonary neuroendocrine tumours. The development of $GABA_B$ limbic encephalitis commonly precedes the diagnosis of cancer. The illness responds well to immunotherapy or the removal of the underlying tumours and in general has a good prognosis [107] [117] [118].

4.11. Anti-Glycine Receptor (GlyR)-Antibody-Associated Encephalitis

Glycine is the simplest amino acid, with just an amino group, a carboxyl group and two hydrogen atoms all bound to one carbon atom. Besides being a decisive building block in many proteins, glycine is also a component of the tripeptide glutathione and of the bile acid glycocholic acid. In addition, it is an essential substrate for the synthesis of a variety of biomolecules such as creatine, porphyrins, and purine nucleotides [119].

In addition to its fundamental role in metabolism, glycine is the major inhibitory neurotransmitter in the CNS. Binding of glycine to the glycine receptor (GlyR) causes chloride influx, membrane hyper polarisation, and thus inhibition of postsynaptic neurons [120]. The GlyR chloride channels mediate fast inhibitory neurotransmission in the spinal cord, brain stem, and retina. Moreover,

GlyR are involved in motor reflex circuits of the spinal cord and supply inhibitory synapses to pain sensory neurons. Heritable mutations of human GlyR gene give rise to a rare neurological disorder, hyperekplexia or startle disease, a disorder characterised by neonatal hypertonia and an exaggerated startle reflex in response to sudden, unexpected stimuli [121] [122] [123].

Anti-GlyR encephalitis primarily affects the spinal cord, and its symptomatology resembles strychnine toxicity (increased muscle tone, spasms, and pathologically exaggerated startle response) as well as symptoms of stiff-person syndrome, which may occur with the syndrome of progressive encephalomyelitis with rigidity and myoclonus and hyperekplexia [124].

4.12. Anti-Yo or Purkinje Cell Antibody (PCA)-Associated Encephalitis

The cerebellum is an automatic processing centre that has two primary functions; adjusting the postural muscles of the body, and programming and fine-tuning movements controlled at the conscious and subconscious levels. The cerebellar cortex holds huge, highly branched Purkinje cells. The extensive dendrites of each Purkinje cell receive input from up to 200,000 synapses. Internally, the white matter of the cerebellum forms a branching array that in sectional view resembles a tree, so-called the "arbor vitae" or "tree of life". The cerebellum receives proprioceptive information from the spinal cord and checks all proprioceptive, visual, tactile, balance, and auditory sensations received by the brain [1]. Anti-Yo or PCA-associated encephalitis is caused exactly by the cerebellar degeneration especially by widespread loss of Purkinje cells [125]. The syndrome presents with typical cerebellar symptoms of ataxia, limb movements, eye movements, voice and swallowing problems, and vertigo [5] [126]. This type of autoimmune encephalitis mostly occurs in women suffering from ovarian or breast tumours [127] [128].

4.13. Anti-CRMP-5 Antibodies-Associated Encephalitis

The collapsin response-mediator proteins (CRMPs) are multifunctional proteins highly expressed during brain development but down-regulated in the adult brain. They are involved in axon guidance and neurite outgrowth signalling. Among these, CRMP2 has been identified as a principal factor in axon outgrowth. Another member, CRMP5, limits the growth-promotional properties of CRMP2 by preventing dendrite outgrowth at initial developmental stages [129]. Anti-CRMP-5 antibodies-associated encephalitis presents with cerebellar symptomatology, cognitive dysfunction, choreiform movements, and cranial neuropathies [38] [130].

4.14. Delta/Notch-Like Epidermal Growth Factor-Related Receptor (DNER)-Antibody-Associated Encephalitis

Delta/notch like epidermal growth factor receptor (DNER) is a transmembrane

protein carrying extracellular epidermal growth factor-like repeats and are specifically expressed in somatodendritic regions of cerebellum. Evidence suggests that DNER promotes cancer cell growth, migration, and invasion. The up-regulation expression of DNER occurs in breast cancer as well as in prostate cancer [131] [132]. Anti-DNER-antibody-associated encephalitis has also been associated with cerebellar degeneration of Purkinje neurons and a remarkably elevated risk of Hodgkin lymphoma [133] [134].

5. Antibody Testing

Antibody status is not needed to consider limbic encephalitis as having a definite autoimmune origin because immune-mediated autoimmune (limbic) encephalitis can occur without detectable autoantibodies [135]. Measurements of autoantibodies, however, remains important because the diagnosis of autoimmune limbic encephalitis can be confirmed by their presence in cerebrospinal fluid (CSF) and/or serum [11]. Moreover, their presence clarifies the immunological subgroup of autoimmune encephalitis, with co-morbidities, tumour association and prognosis that might differ. For instance, the onconeuronal antibodies that more frequently occur with autoimmune limbic encephalitis are Hu and Ma2 and patients who have these antibodies always have an underlying cancer. By contrast the neuronal cell-surface antibodies that are more frequently associated with limbic encephalitis are LGI1 receptor, $GABA_B$ receptor and AMPA receptor antibodies. Antibodies against the intracellular antigen GAD occur in a subgroup of young female patients suffering from limbic encephalitis with predominant seizures and no evidence of cancer [135].

The target antigens of autoantibodies can be composed of several subunits, and antibodies against each of the subunits can have a different clinical significance and implications. Furthermore, the antibodies associated with autoimmune encephalitis are IgG antibodies. Detection of IgA or IgM antibodies against any of the antigens has unclear significance [135]. For example, the NMDA receptor is a heterotetramer comprised of two GluN1 subunits and two GluN2/3 subunits. Detection of IgG antibodies against the GluN1 subunit is a signature of the anti-NMDA receptor encephalitis [136]. Moreover, NMDA receptor IgM and IgA responses have been reported in patients with schizophrenia and other psychiatric disease but also in up to 10% of normal controls [137]. Conversely, the types of IgG responses associated with anti-NMDA receptor encephalitis are not found in patients with schizophrenia [138].

Similarly, molecular precision is important for the voltage-gated potassium channel complex (VGKC) antibodies as the target antigen is not the VGKC itself but the proteins LGI1 and contactin-associated protein-like 2 (CASPR2), with well-defined syndromes associated. The VGKC test may still detect patients with LGI1 or CASPR2 immunity, but low titre serum positive results have uncertain clinical significance [139]. Consequently, a low titre serum VGKC result without corresponding evidence of LGI1 or CASPR2 antibodies, preferably in the CSF,

should not be taken as conclusive indication of autoimmune encephalitis [5].

Despite the importance of antibody testing in autoimmune encephalitis, it is not realistic to include antibody status as part of early diagnostic criteria. This is because antibody tests are not readily available and, where accessible, results can take several weeks to obtain. Additionally, over the course of the disease, levels of antibodies decline, but even after recovery most patients still have antibodies in both serum and CSF [11].

6. Cerebrospinal Fluid Testing

Analysis of cerebrospinal fluid plays a central role in diagnosis of all cases of encephalitis. Most patients with autoimmune encephalitis have CSF antibodies and relevant antibodies are found in their CSF [140] [141]. For example, in patients with anti-NMDA receptor encephalitis up to 14% have antibodies in the CSF, but not in the serum [142]. Moreover, the types of antibodies in the CSF can determine the clinical picture [118] as well as correlate with the progress of the illness [142]. Furthermore, antibody testing using serum can lead to false-positive or false-negative results; in contrast, this problem rarely occurs with CSF analysis [135]. CSF analysis of patients suffering from autoimmune limbic encephalitis shows mild-to-moderate lymphocytic pleocytosis (usually less than 100 white blood cells per mm^3) in 60% to 80% of patients, and elevated IgG index or oligoclonal bands in approximately 50% of cases [6] [141] [143].

7. Imaging

Brain magnetic resonance imaging (MRI) in patients with autoimmune encephalitis may be normal or non-specific [5]. Nevertheless, bilateral abnormalities in the medial temporal lobes on T2 signal are quite characteristic MRI findings of autoimmune limbic encephalitis [105] [107] [135] [140]. However, similar MRI findings are found in almost 95% of patients with herpes simplex virus encephalitis [144], as well as in individuals suffering from tuberculosis and syphilis [145]. MRI findings of patients with anti-dipeptidyl-peptidase-like protein 6 (DPPX) or anti-$GABA_A$ antibody-associated encephalitis have fewer distinctive findings [146].

8. Electroencephalography (EEG)

EEG findings of patients suffering from autoimmune limbic encephalitis are rarely specific [135]. Yet, it is useful for excluding subclinical seizures, as well as for prognosis and differential diagnosis [5]. It has been suggested that normal EEG correlates with good prognosis, independent of other prognostic factors [147]. In a methodical analysis of 446 individuals with anti-NMDA receptor encephalitis, 373 EEGs were abnormal. The EEG abnormalities were also associated with hospitalisation into the intensive care unit and length of recovery period [148].

In the cohort of 20 seropositive patients with anti-NMDA receptor antibody-associated encephalitis, anti-Gly-R, anti-CASPR-2, anti-GAD, and amphi-

physin antibody-associated encephalitis and the control group of 21 seronegative epilepsy or encephalopathy patients with similar clinical features, Baysal-Kirac and his team (2015) [149] did not find any significant difference in EEG findings. On the other hand, [140] in the EEG of a group of 22 patients with autoimmune encephalitis, they found focal or generalized slowing and/or epileptiform activity, maximal in the temporal regions, in all 22 patients tested. Schmitt and his team [150] report typical delta brush EEG pattern in patients with anti-NMDA receptor encephalitis. In the most recent study Moise *et al.* (2019) [151] confirmed a signature EEG pattern in anti-NMDA receptor autoimmune encephalitis, termed extreme delta brush, identified as generalized rhythmic delta activity plus fast activity. Finally, periodic, or rhythmic patterns, seizures, and new-onset refractory status epilepticus conferred an increased risk of poor outcome regardless of autoimmune encephalitis subtype [151].

9. Treatment of Autoimmune Encephalitis

Patients with autoimmune encephalitis present with variable clinical manifestations, severity, comorbidities, and immunotherapy responsiveness, and thus treatment should be individualised. There are no established guidelines for treatment, and diverse regimens are currently used based on the patient's clinical status and the clinician's opinion [152] (**Table 1**).

Common first-line immunotherapeutic agents include corticosteroids, intravenous immunoglobulin, and plasma exchange. Corticosteroids are frequently the first choice, followed by intravenous immunoglobulin and plasma exchange [153]. Corticosteroids with either intravenous immunoglobulin or plasma exchange represent the usual choice when a combination of first-line agents are administered [152].

Corticosteroids are used in the treatment of autoimmune encephalitis, acting to broadly inhibit the inflammatory process, although corticoid drugs pose less specificity for the antibody-mediated immune process. Moreover, they are associated with several systemic side effects [152].

Intravenous immunoglobulin is a blood product extracted from the collected pool of plasma from over a thousand donors. Intravenous immunoglobulin provides antibodies to a broad range of pathogens and is used to provide passive immunity for patients with immunodeficiency [154]. High-dose intravenous immunoglobulin (1 - 2 g/kg) provides various anti-inflammatory and immunomodulatory effects by multidirectional mechanisms such as autoantibody neutralisation, inhibition of complements, cytokines, and leukocyte migration [155]. Intravenous immunoglobulin can be used as a monotherapy in the treatment of autoimmune encephalitis, nonetheless, is more often used after or in combination with high-dose steroids, or with plasma exchange, rituximab, or other immunotherapeutic agents. Intravenous immunoglobulin has a better side effect profile than corticosteroids [152].

Plasma exchange effectively removes autoantibodies and other pathologic substances in the plasma. Plasma exchange also alters the immune system by

Table 1. Treatment alternatives used in autoimmune encephalitis as recommended by Shin *et al.*, 2018 [152].

Treatment	Regimen
First-line immunotherapy	
Methylprednisolone	1 g daily, for 3 - 5 days
Intravenous immunoglobulin	2 g/kg over 5 days (400 mg/kg/day)
Plasma exchange	1 session every other day for 5 - 7 days
Second-line immunotherapy	
Rituximab	375 mg/m^2 weekly intravenous infusion for 4 weeks
Cyclophosphamide	750 mg/m^2 monthly for 3 - 6 months
Alternative treatments	
Tocilizumab	Initially 4 mg/kg, followed by an increase to 8 mg/kg monthly based on clinical response
Low-dose interleukin-2 (aldesleukin)	1.5 million IU/day, 4 subcutaneous injections with 3-week interval
Steroid-sparing agents used for maintenance therapy	
Azathioprine	Initially 1 - 1.5 mg/kg once daily or divided twice daily, target 2 - 3 mg/kg/day
Mycophenolate mofetil	Initially 500 mg twice daily, target 1000 mg twice daily.

changing lymphocyte numbers and their distribution, T-suppressor cell function, and T-helper cell phenotypes [156]. Steroids alone are frequently insufficient to ameliorate autoantibody-mediated immune processes, and direct removal or neutralisation of autoantibodies from the circulation by plasma exchange and intravenous immunoglobulin may show a synergistic effect [152].

When first-line immunotherapy is insufficient, secondary immunomodulatory agents are typically used. Rituximab and cyclophosphamide are the most used second-line agents in autoimmune encephalitis treatment [152]. Rituximab is a partially humanized monoclonal antibody directed against CD20, a glycoprotein primarily found on the surface of B cells, initially approved for the treatment of non-Hodgkin B-cell lymphomas. It is widely used to treat various autoimmune disorders and appears to be effective in several autoimmune CNS and peripheral nervous system disorders [157]. In the United Kingdom, Rituximab is licenced for rheumatoid arthritis (1 g, then 1 g after 2 weeks by intravenous injection), non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, granulomatosis with polyangiitis, and microscopic polyangiitis as well as pemphigus vulgaris [158].

Cyclophosphamide is a widely used chemotherapeutic agent as well as an immunosuppressant for life-threatening or severe rheumatologic and renal diseases such as antineutrophil cytoplasmic antibody -associated vasculitis, lupus

nephritis, and other systemic vasculidites [159] [154]. Its recommended dose for adults for oral use is 1 - 1.5 mg/kg daily, and by intravenous injection 0.5 - 1 g every 2 weeks, then reduced to 0.5 - 1 g every month, frequency adjusted according to clinical response and haematological monitoring [158]. Cyclophosphamide is a less preferable agent than rituximab because of its potentially serious side effects such as myelosuppression, infertility, haemorrhagic, cystitis and an increased risk of malignancy, which lower the priority of its use [152].

10. Conclusions

Autoimmune encephalitides are caused by humoral or cellular responses against specific neuronal antigens. The clinical picture of these syndromes includes limbic encephalitis, Morvan's syndrome, psychosis, or abnormal movements and can occur preferentially as paraneoplastic or nonparaneoplastic syndromes depending on the type of autoantibody.

Limbic encephalitis represents a cluster of autoimmune disorders, with inflammation in the medial temporal lobe characterised by subacute onset of psychiatric symptoms such as short-term memory impairment, psychosis and affective symptoms and neurological symptoms as in faciobrachial and grand mal seizures. Limbic encephalitis and in general autoimmune encephalitides are not easy to diagnose as most patients initially present with psychiatric symptomatology rather than neurological symptomatology (neurological indicators include facial twitching, seizures, confusion, and cognitive decline). Furthermore, immunological and laboratory testing are not easily accessible and, where available, take a long time to determine the diagnosis. Few psychiatrists consider the autoimmune nature of the neuropsychiatric presentation, and it is vital to consider limbic encephalitis in all patients with new-onset psychosis or mania.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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