Autoimmune Encephalitis: Clinical Features, Pathophysiology, and Treatment

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Autoimmune encephalitis represents a group of disorders characterized by various immunologic mechanisms, clinical manifestations, and therapeutic outcomes. They can be associated with paraneoplastic syndromes or nonneoplastic autoimmune processes. Autoimmune encephalitis is usually associated with antibodies that can acutely or subacutely affect any part of the central or peripheral nervous system including neuromuscular junctions and muscles. Antibody-associated encephalitis can be divided into two main categories: (1) encephalopathy associated with antibodies against intracellular antigens and (2) encephalopathy associated with antibodies directed against the neuronal surface and synaptic antigens [1, 2]. The discovery of various antibodies related to autoimmune encephalitis has given us a new insight into pathogenic mechanisms and treatment of these syndromes. That is important since many patients with autoimmune encephalopathy are children and young adults, and they may respond well to immunosuppressive treatment if diagnosed without delay. In this chapter, we review the epidemiology, pathophysiology, clinical characteristics, diagnosis, and treatment of different syndromes associated with autoimmune encephalitis.

History

In 1934, Greenfield initially described two cases of subacute cerebellar degeneration occurring with carcinoma outside the nervous system [3]. Thirteen years later in 1947, Denny-Brown reported two patients with primary sensory neuropathy and muscular changes associated with bronchial carcinoma [4].

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In 1954, Henson et al. [5] published a series of 19 cases with various types of carcinomatous neuropathy and myopathy. Eight of these patients had proximal atrophic weakness of limbs and involvement of ocular and bulbar muscles. Four patients also exhibited myasthenic features with a favorable response to neostigmine in some cases. Later in 1956, Chartan et al. [6] described episodes of severe mental disturbance in three male patients with bronchial carcinoma. In all of those, the mental disorder either preceded or overshadowed the presence of cancer.

In 1968, Corsellis et al. [7] reported autoimmune limbic encephalitis associated with small-cell lung cancer. For years, it was believed that "limbic encephalitis" was almost always associated with a form of neoplasia mainly lung, thymic, or testicular tumors. In 2001, it was shown that voltage-gated potassium channels (VGKC) were associated with reversible limbic encephalitis [8]. Four years later, other antibodies to the cell surface or synaptic proteins were detected in six patients with subacute limbic encephalitis and involvement of additional brain regions [9]. Further studies of those patients with immunotherapy-responsive encephalitis resulted in the characterization of the antigen as the NR1 subunit of the N-methyl-D-aspartic acid receptor (NMDA receptor) and the definition of its clinical characteristics [10–12], since many other neuronal cell surface antigens have been detected and introduced in patients with autoimmune encephalitis.

Epidemiology

The California Encephalitis Project was established in 1998 to identify the etiologic agents and to study epidemiology and clinical characteristics of encephalitis. In 2009, they reported ten cases of NMDA receptor antibodies and concluded that unlike classic paraneoplastic encephalitis, anti-NMDA receptor encephalitis affects younger patients [13]. Since, an increasing number of cases have been reported to the California Encephalitis Project, making NMDA receptor antibodies a significant cause of encephalitis among young patients. Between 2007 and 2011, 761 cases of encephalitis of uncertain etiology in individuals aged ≤30 years were reported to the California Encephalitis Project. Of these, 32 patients were tested positive for anti-NMDAR encephalitis; however, viral encephalitis was diagnosed in only 42 patients [14]. Although anti-NMDAR encephalitis was initially thought to affect young women, often with teratomas, it can affect men and children, with or without any identifiable tumor [15]. Overall, 75% of patients with anti-NMDAR encephalitis can significantly recover when diagnosed promptly [10].

Among paraneoplastic syndrome, Lambert-Eaton myasthenic syndrome, which affects approximately 3% of patients with small-cell lung cancer, and myasthenia gravis, which affects 15% of patients with thymoma, are common [16]. Up to 9% of patients with small-cell lung cancer have at least one form of paraneoplastic syndrome (commonly Lambert-Eaton myasthenic syndrome, sensory neuronopathy, or limbic encephalitis) [16]. γ-Aminobutyric acid (GABA-B) receptor antibodies are also responsible for paraneoplastic limbic encephalitis in patients with small-cell lung cancer [17].

Pathophysiology and Clinical Presentation

Antibodies in autoimmune encephalitis can target intracellular antigens or antigens on neuronal surface/synaptic space. Among those, antibodies which target intracellular antigens are usually associated with paraneoplastic syndromes and a poor prognosis. Antibodies to intracellular antigens include anti-Hu (also known as anti-neuronal nuclear antibody, type 1, ANNA-1), anti-Ma2 (also called anti-Ta), collapsin-responsive mediator protein-3, protein-4, and protein-5 (CRMP3–5), anti-amphiphysin, anti-Yo, anti-Ri, adenylate kinase 5, and BR serine/threonine kinase (BRSK2) antibodies. Table 8.1 summarizes the antibodies to intracellular antigens and their clinical presentation.

Antibodies to neuronal surface/synaptic antigens can also be associated with cancer; however, they are more responsive to immunotherapy. Antibodies to neuronal surface/synaptic antigens are often related to limbic encephalitis. In this group, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis and anti-leucine-rich glioma-inactivated 1 (LGI1) comprise 85% of patients [1]. Anti-NMDA receptor encephalitis has become one of the most frequently recognized autoimmune encephalitides since its discovery. The disease is more frequent among women (80%) and adults younger than 45 years old [39]. Almost half of the patients initially present with a headache and a viral-like process, followed by psychiatric manifestations, altered mental status, in addition to language and memory dysfunction [15, 40]. Seizure is frequent among pediatric patients [39]. More than two-third of the patients suffer from seizures [39]. Table 8.2 summarizes the antibodies to intracellular antigens, their associated syndromes.

More than half of patients with autoimmune encephalitis present with symptoms of limbic encephalopathy including memory deficits, altered mental status, seizures, and neuropsychiatric syndrome. Refractory seizures and status epilepticus have also been reported [59, 60, 68]. Other common features of autoimmune encephalitis include headache, tremor, language difficulties, ataxia, and sleep disorders.

Diagnostic Approach

The diagnosis of autoimmune encephalitis can be challenging because symptoms usually precede the diagnosis of cancer or resemble other neurological or psychological disorders. An international panel of experts has identified diagnostic criteria for paraneoplastic neurological syndromes (Table 8.3) [69].

Patients with clinical presentations of encephalitis should have a full workup including neuroimaging, cerebrospinal fluid (CSF) examination, electroencephalography (EEG), pertinent laboratory and serological studies, and, in some cases, electromyography (EMG). Many other conditions (Table 8.4) are more frequent than autoimmune etiologies of encephalopathies. They should be considered and excluded.

Magnetic resonance imaging (MRI) of the brain is neither sensitive nor specific for the diagnosis of autoimmune encephalitis. However, it is essential to exclude

Table 8.1 Summary of antibodies to intracellular antigens, their mechanisms, and related syndromes

Antibody	Associated tumor	Affected areas	Clinical syndromes
Type 1 antineuronal nuclear antibody (ANNA-1/anti-Hu)	Adults: [18–20] Small-cell lung cancer Other tumors (rare) No cancer (15%) Pediatrics: No cancer (six out of eight cases) [21]	Multifocal, central, and peripheral nervous systems [18–20]	Sensory neuropathy – dorsal root ganglia involvement [22] Limbic encephalitis [22] Brain stem encephalitis and paraneoplastic cerebellar degeneration [23, 24]
Type 2 antineuronal nuclear antibody (ANNA-2/anti-Ri)	Breast, adnexal tumor [25]	Central nervous system neuronal nuclei [25]	Opsoclonus, ataxia [25] Ophthalmoplegia [26]
Purkinje cell cytoplasmic antibody type 1 (PCA-1/anti-Yo)	Ovarian, uterus, adnexal, or breast tumor [27]	Cerebellum – Purkinje cell cytoplasmic antigens [27]	Paraneoplastic cerebellar degeneration [23]
Anti-Ma proteins (Ma1, Ma2)	Testicular cancer (more common in germ cell tumors) [28]	Limbic system, cerebellum, brain stem [28, 29]	Limbic encephalitis (differs from classic limbic encephalitis) [29] Brain stem encephalopathy and myelopathy [29] Ophthalmoplegia, atypical parkinsonism, hypokinetic syndrome [29] Progressive muscular atrophy (a case report) [30]
Anti-amphiphysin	Breast, small-cell lung, ovarian cancer [31, 32]	A nerve terminal protein with a putative role in endocytosis [33]	Stiff-man syndrome [31] Sensory neuronopathy, encephalomyelitis, limbic encephalitis, Lambert-Eaton myasthenic syndrome [32]
Anti-CV2/CRMP5	Thymoma, small-cell lung cancer [34] Renal cell carcinoma and lymphoma [35]	Central and peripheral neurons, including synapses [34]	Basal ganglia abnormalities [35] Cranial, peripheral, and autonomic neuropathy [34] Cerebellar ataxia, dementia, and neuromuscular junction disorders [34]
Others (only a few cases reported): Anti-CRMP3–4 [36] Anti-adenylate kinase 5 [37] Anti-BRSK2 [38]	CRMP3–4: thymoma Anti-adenylate kinase 5: no cancer detected Anti-BRSK2: small-cell lung cancer	Limbic system	Limbic encephalitis (progressive short-term memory deficits, confusion, seizures, and psychosis)

Table 8.2 Summary of antibodies to neural surface, their clinical syndrome, and associated tumors

Antigens	Clinical syndrome	Associated tumor	Miscellaneous
N-methyl-D-aspartate receptor (NMDAR)	Prodromal syndrome (a headache, fever, or viral-like symptoms) Psychiatric disorders (anxiety, bizarre behavior, hallucinations, delusions, etc.) Amnesia Seizure Altered mental status Movement disorders Catatonia Autonomic Instability (hyperthermia, fluctuations of blood pressure, tachycardia, bradycardia) [10, 12, 15, 41–43]	Ovarian teratoma (10–50%, age dependent) Other rare tumors: Testicular germ cell tumor [1] Teratoma of the mediastinum, small-cell lung cancer [10] Hodgkin's lymphoma [44] Neuroblastoma [45]	Also reported in children less than one year old Four times more frequent among women
Leucine-rich glioma-inactivated 1 (LGI1)	Seizures (faciobrachial dystonic) Myoclonus Memory and cognitive deficits Rapid eye movement, sleep behavior disorders [46–49] Chorea [50]	Thymoma Small-cell lung cancer (only 20% are associated with a tumor)	Extracellularly secreted LGI1 links two epilepsy-related receptors (ADAM22 and ADAM23) [51] This syndrome was previously attributed to voltage-gated potassium channels [52]
A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor	Limbic encephalitis: progressive short-term memory deficits, confusion, and seizures Psychosis with bipolar features [53]	Two-thirds of patients: lung, thymoma, breast, ovarian teratoma [53]	Relapse is common
Contactin-associated protein-like 2 (CASPR2)	Encephalitis Peripheral nerve hyperexcitability [54] Morvan syndrome (neuromyotonia, pain, hyperhidrosis, weight loss, severe insomnia, and hallucinations) [55]	Lung, thymoma (<20%)	Can be mistaken for a motor neuron disease

(continued)

Table 8.2 (continued)

Antigens	Clinical syndrome	Associated tumor	Miscellaneous
Gamma-aminobutyric acid A (GABA-A) receptor	Refractory status epilepticus or epilepsia partialis (reported as 100%) [56]	Thymoma (rare) [56]	Diffuse fluid-attenuated inversion recovery (FLAIR) and T2 signal abnormalities [56]
Gamma-aminobutyric acid B (GABA-B) receptor	Limbic encephalitis: progressive short-term memory deficits, confusion, and seizures Ataxia Opsoclonus-myoclonus syndrome [57]	Small-cell lung cancer (50%) [57]	
IgLON5	Unique non-rapid eye movement (REM) and REM parasomnia Obstructive sleep apnea Gait instability followed by dysarthria, dysphagia, ataxia, or chorea [58]	Not paraneoplastic	Pathological features may suggest a tauopathy [58]
Voltage-gated potassium channel (VGKC)	Sleep disturbances, severe insomnia Limbic encephalitis Morvan syndrome Seizure, status epilepsticus [59, 60]	Thymoma, prostate adenothymoma, prostate adenocarcinoma, colon adenocarcinoma, and melanoma [61]	Sleep disorders are diagnostic hallmark [61]
Glycine receptor (GlyR) α1 subunit	Progressive encephalomyelitis with rigidity and myoclonus (PERM) [61] Atypical stiff-person syndrome Seizure Behavioral changes [62]	Thymoma (10%) [63]	Only a few cases reported
Dipeptidyl-peptidase-like protein-6 (DDPX)	Agitation, confusion, myoclonus, tremor, and seizures [64] Weight loss, psychosis, depression, movement disturbances [65]	B-cell neoplasms (10%) [65]	
Metabotropic glutamate receptor 5 (mGluR5)	Limbic encephalitis Headache Involuntary movements [66, 67]	Hodgkin's lymphoma [66]	Only a few cases reported

Table 8.3 Diagnostic criteria for paraneoplastic neurological syndromes

Criteria for *definite* paraneoplastic neurological syndromes
1. A classical syndrome and cancer that develops within 5 years of the diagnosis of the neurological disorder
2. A nonclassical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission
3. A nonclassical syndrome with onconeural antibodies (well characterized or not) and cancer that develops within 5 years of the diagnosis of the neurological disorder
4. A neurological syndrome (classical or not) with well-characterized onconeural antibodies (anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin) and no cancer
Criteria for *possible* paraneoplastic neurological syndromes
1. A classical syndrome, no onconeural antibodies, no cancer but at high risk to have an underlying tumor
2. A neurological syndrome (classical or not) with partially characterized onconeural antibodies and no cancer
3. A nonclassical neurological syndrome, no onconeural antibodies, and cancer present within 2 years of diagnosis

Table 8.4 Differential diagnosis of autoimmune encephalitis

Viral encephalitis, e.g., human herpesvirus 6 (HHV-6), human immunodeficiency virus (HIV), herpes simplex virus (HSV), varicella zoster virus (VZV)	Creutzfeldt-Jakob disease
Primary CNS tumor or metastatic disease	Whipple disease
Ischemic and hemorrhagic cerebrovascular disease	Wernicke encephalopathy
Psychiatric disorders	Chronic CNS infections with atypical bacteria, e.g., *Treponema pallidum*, *Listeria*, tuberculosis
Toxic-metabolic encephalopathy	Other neuroinflammatory diseases, e.g., lupus cerebritis, Behcet's disease, primary angiitis of the central nervous system (PACNS)
Multiple sclerosis	Nonconvulsive status epilepticus
Rapidly progressive dementia	Motor neuron disease

other conditions such as ischemic infarction or tumors. Among patients with encephalitis, signal hyperintensities on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images can be seen in the mesiotemporal lobe, cortical and subcortical regions, or brain stem. Contrast enhancement can be variable, and leptomeningeal enhancement has been reported [70]. The extent of abnormal findings on the MRI is different for each syndrome. For instance, MRI in GABA-A receptor encephalitis often shows multifocal and widespread FLAIR and T2 signal abnormalities [56]. Encephalitic syndromes associated with LGI1 and AMPA receptor antibodies also always cause FLAIR hyperintensity in the mesiotemporal lobe. In a study on 50 patients with paraneoplastic limbic encephalitis, researchers observed that 57% of patients with MRI studies had signal abnormalities in the limbic system [20]. There is also a report of cortical ribboning similar to that seen in Creutzfeldt-Jakob disease

(CJD) among patients with voltage-gated potassium channel (VGKC) autoantibody-associated encephalopathy [71]. Brain MRI is often normal or shows transient FLAIR hyperintensity with or without contrast enhancement in anti-NMDAR encephalitis [10, 72].

Several autoimmune encephalitis syndromes are associated with seizure or status epilepticus [59, 60]. Diffuse slowing or epileptiform abnormalities in the temporal lobe on EEG are the most common findings in patients with encephalitis. EEG is also important to exclude other etiologies for encephalopathy such as subclinical seizures.

Although CSF examination can be normal especially in the initial phase, a mild elevation of protein (<100 mg/dL) and lymphocytic pleocytosis or oligoclonal bands can be an indicator of autoimmune encephalitis [10, 13, 15, 17, 46, 73]. More than 90% of patients with antibodies against NMDA, AMPA, and GABA-B receptors have pleocytosis or oligoclonal bands on CSF examination [10, 53, 56, 57]. CSF analysis is also essential to exclude other etiologies of encephalopathy including infectious and neoplastic causes.

Pertinent antibody testing should be performed in both serum and CSF. Antibodies to cell surface/ synaptic proteins can be detected primarily in CSF. In a multiinstitutional observational study, detection of NMDA receptor antibodies was compared in 250 paired serum and CSF samples. It showed that the screening test is significantly more sensitive in CSF than serum (100% vs. 85%) [39]. A positive serum antibody testing, when CSF is negative for the antibody, raises the possibility of a false positive diagnosis. Although many tests for autoimmune encephalitis are commercially available, a number of autoimmune encephalitis cases can be caused by other, still unavailable or unknown antibodies. Therefore, a negative test result does not rule out autoimmune encephalitis.

All patients with autoimmune encephalitis should be screened for the presence of a tumor. The detected antibody type can also guide the type and extent of screening. On the other hand, detection of a tumor could also assist in the diagnosis of paraneoplastic encephalitis variants and guide the antibody screening plan.

Treatment and Outcome

Autoimmune encephalitis is often associated with a favorable outcome after tumor removal and antineoplastic treatment (if applicable), as well as immunotherapy. In general, steroids, intravenous immunoglobulin, and plasmapheresis are the first line of immunotherapy especially when a tumor is detected and treated [9, 39]. Rituximab and cyclophosphamide comprise the second-line immunotherapy when the first-line treatment fails. Although seizures must be addressed aggressively during the acute phase of the disease, patients often do not require long-term antiepileptic medication.

In a large multiinstitutional observational study, over 500 patients with anti-NMDA receptor encephalitis were treated and monitored up to 2 years. Out of 501 patients, 94% received first-line immunotherapy (steroids, intravenous immunoglobulin, plasmapheresis) or tumor removal, resulting in improvement within

4 weeks in 53% of patients. More than half of patients who failed first-line therapy received second-line immunotherapy (rituximab, cyclophosphamide), resulting in better outcome than those who did not. During the first 24 months, almost 80% of patients reached a good outcome, where relapses occurred in approximately 12% of the patients. About 6% of patients died [39].

Predictors of poor outcome in anti-NMDA receptor encephalitis are a delay in diagnosis and treatment, the need for intensive care, high titer of antibody in CSF and serum, and the presence of teratoma [39, 74]. The overall prognosis for patients with autoimmune encephalitis is variable. Some patients have a complete recovery, while others die or develop a permanent neurologic disability.

Summary

Autoimmune encephalitis has different immunologic mechanisms, clinical manifestations, and therapeutic outcomes. It can be divided into two categories: antibodies against intracellular antigens or antibodies against neuronal surface/synaptic antigens. More than half of patients with autoimmune encephalitis present with symptoms of limbic encephalopathy including memory deficits, altered mental status, seizures, and neuropsychiatric syndrome. Patients with the clinical presentation of encephalitis should have a complete workup including neuroimaging, EEG, lumbar puncture, and serologic testing. Other etiologies of encephalitis are more common and should be excluded. Patients often respond favorably to immunotherapy. Delay in diagnosis and treatment has been associated with a worse prognosis.

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