Autoimmune Encephalitides

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KEYWORDS
- Autoimmune
- Encephalitides
- Hashimoto encephalopathy
- Central nervous system vasculitis

KEY POINTS
- Autoimmune encephalitis is a severe inflammatory disorder of the brain with diverse causes and a complex differential diagnosis including central nervous system vasculitis, and autoimmune encephalitis associated with serum and intrathecal antibodies to intracellular and surface neuronal antigens against constituents of the limbic system neuropil.
- This association has led to a reconsideration of several neuropsychiatric and neurocognitive disorders as having shared mechanisms of origin.
- The successful use of serum and intrathecal antibodies to diagnose affected patients, and their subsequent improvement with effective treatment, has resulted in few biopsy and postmortem examinations.
- In those available, there can be variable infiltrating inflammatory T cells with cytotoxic granules in close apposition to neurons, analogous to microscopic vasculitis.
- One particular type of autoimmune encephalitis is associated with Hashimoto thyroiditis and uniquely associated with true central nervous system vasculitis.

INTRODUCTION

According to Dalmau,¹ myasthenia gravis and Lambert-Eaton myasthenic syndrome are 2 prototypical B-cell peripheral nervous system disorders with targeted antibodies to acetylcholine receptors and voltage-gated calcium channels resulting from disturbed B-cell immunity. In the central nervous system (CNS), paraneoplastic disorders were analogously associated with onconeural antibodies, cross-reactive with tumor nuclear and cytoplasmic neuronal antigens, and mediated by cytotoxic T-cells. In solving the mystery of the large group of undiagnosed neuropsychiatric disorders leading to autoimmune encephalitis (AE) and limbic

Disclosure: The author has nothing to disclose.
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Neurol Clin 37 (2019) 359–381
https://doi.org/10.1016/j.ncl.2019.01.015
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encephalitis (LE), investigators returned to the laboratory to study patterns of newly recognized autoantibodies that recognized surface antigen (SAg) and intracellular antigen (IAg) of the brain neuropil. The successful use of serum and intrathecal antibodies to diagnose affected patients, and their subsequent improvement with effective treatment, resulted in few CNS tissue biopsy and postmortem examinations. However, in those available, the associated histopathology appeared to result from infiltrating inflammatory T-cells, with cytotoxic granules in close apposition to neurons, analogous but distinct from microscopic vasculitis. With the ease of screening the serum and cerebrospinal fluid (CSF) from a panel of pathogenic autoantibodies, and obtaining detailed morphologic and metabolic images of the brain specific for the disorders, AE is included in the differential diagnosis of adult primary angiitis of the CNS (PACNS) and childhood PACNS (cPACNS). This article reviews the historical background, epidemiology, clinical presentation, laboratory evaluation, histopathology, diagnosis, and management of autoimmune encephalitides relevant to CNS vasculitis, in particular Hashimoto encephalopathy (HE).

BACKGROUND

Corsellis and colleagues coined LE, noting a relation to bronchial cancer in 3 patients in the sixth to eighth decades of life. All 3 cases had subacute temporal lobe seizures, neuropsychiatric disturbances, and memory disturbances for 2 years before death. Postmortem examination revealed inflammatory lesions in limbic gray-matter sections of the brain, notably in medial temporal lobe structures, including the hippocampal gyrus. Case 2 had an undifferentiated nonmetastatic lung carcinoma removed 6 months after onset of neurologic symptoms, whereas 2 others had unsuspected cancer at postmortem examination. Case 1 had a bronchial carcinoma restricted to a mediastinal lymph node without a primary lesion, whereas case 3 had an unsuspected oat cell carcinoma infiltrating the main bronchi of both lungs and adjacent mediastinal nodes. Attention turned away from LE and toward neurologic autoimmune paraneoplastic syndromes with the discovery of several neuronal target antigens including Hu (ANNA-1), responsible for paraneoplastic encephalomyelitis in association with small cell lung cancer (SCLC); Ri (ANNA-2) responsible for paraneoplastic cerebellar degeneration in association with breast cancer; and PCA-1 responsible for paraneoplastic cerebellar degeneration in association with gynecologic tumors. Other autoantibodies included anti-MA1 and MA2 and testicular cancer, and the collapsin response mediator protein-5 (CRMP5/Cv2) in association with thymoma. Each with an intracellular target antigen, the resultant histopathology of these antibodies consisted of infiltrative cytotoxic (CD8+) T-cell destruction of neurons, with variable immunoglobulin G (IgG) and complement deposits in the CNS, with fewer helper (CD4+) T-cells, and generally absent B-cells. The role of infiltrating CD8+ T-cells in cell death was suggested by its close apposition to neurons.

Bien and colleagues revisited noncancerous cases of LE in its relation to temporal lobe epilepsy, whereas the interface of strictly paraneoplastic and autoimmune mechanisms was highlighted by recognition of patients with stiff person syndrome (SPS) in association with glutamic acid decarboxylase (GAD) antibodies; and neurologic syndromes associated with voltage-gated potassium channel (VGKC)–complex antibodies. Nonparaneoplastic CNS autoimmunity was investigated in a patient with SPS, epilepsy, and type-1 diabetes (T1D), and increased titers of oligoclonal CSF
IgG,17 in whom serum and CSF produced identical intense staining of all gray-matter regions. GAD65 was an important autoantigen in T1D, being highly expressed in the cytoplasm of pancreatic β cells. However, only patients with very high titers of GAD were associated with LE; they typically presented with recent-onset temporal lobe epilepsy (TLE) and intrathecal secretion defining a form of nonparaneoplastic LE. Other patients within the SPS spectrum harbored antibodies against other proteins of the GABAergic synapse associated with lymphoma, and malignant tumors of the breast, colon, lung, and thymus.18

The clinical phenotypes associated with autoantibodies to VGKC complex ranging from peripheral nerve hyperexcitability (PNH) to Morvan syndrome (MoS) and LE and autoimmune epilepsy19,20 were described in 2 patients with reversible LE.21 By 2010, Graus and colleagues22 had classified neuronal antibodies associated with syndromes resulting from CNS neuronal dysfunction into 2 groups according to the location of the target antigen. One group of well-characterized autoantibodies recognized onconeural IAg antigens, including Ri, Yo, Hu, Ma2, CRMP5/Cv2, and GAD, that were useful in the designation of a specific paraneoplastic neurologic disorder. Bien and colleagues23 described qualitative and quantitative immunopathologic features of biopsy or postmortem brain tissue in 17 cases of AE associated with IAg (Hu, Ma2, GAD) or SAg (VGKC-C and N-methyl-D-aspartate receptor [NMDAR]). Their studies noted higher CD8+/CD3+ ratio and more frequent appositions of granzyme-B (GrB) (+) cytotoxic T-cells to neurons, with associated cell loss in the IAg-onconeural group compared with those in the SAg group. The exceptions were GAD cases that showed less intense inflammation and low CD8/CD3 ratios compared with the IAg-onconeural cases. A role for T-cell–mediated neuronal cytotoxicity was found in LE associated with IAg-directed autoantibodies, whereas a complement-mediated humoral immune mechanism was suggested in VDKC-complex encephalitis. There was apparent absence of both mechanisms in NMDA receptor encephalitis.

Bauer and Bien24 suggested that neurodegeneration in brains of patients with antibodies against IAg was not simply induced by antibody reactivity with the target antigen but rather by the inflammatory T-cells. To be pathogenic, the imputed antibody had to first transit the blood-brain barrier (BBB) and the cell membrane of the target cell to a location where it could bind the pathogenic IAg. Depending on protein conformation and folding, the antigenic site might be readily accessible before inactivation and ensuing irreparable cell damage. A major concern in managing these disorders has not only been prompt treatment of the tumor but commencement of effective immunotherapy targeting mainly cytotoxic T-cells.25 Vasculitis is not a recognized mechanism of injury in intraneuronal antibodies, either in life or at postmortem examination. The exception is the dubious association of extralimbic AE in association with increased serum GAD antibody levels suggested by Najjar and colleagues. A 31-year-old man had new onset of tonic-clonic seizures in association with an enhancing right anterior frontal lobe lesion on brain MRI and irregularity of the distal frontal right middle cerebral artery branches on cerebral angiography. Brain biopsy showed perivascular and intramural inflammation associated with microglia and histiocytic nodules. Serum GAD antibodies tested 6 months after treatment with oral corticosteroids and high-dose intravenous immunoglobulin (IVIg) therapy were increased 20-fold.

The past decade has witnessed the emergence of serum autoantibodies against SAg and synaptic-enriched regions leading to LE that spares the cytoplasm and nuclei of neurons.26–29 Supportive of LE or AE, these new antibodies share the property of strong immunolabeling of areas of dense dendritic network and synaptic-enriched regions in the neuropil of hippocampus. The clinical phenotype associated with novel neuropil antibodies includes dominant behavioral and psychiatric symptoms and
seizures but with inconstant features of cognition and memory, and brain MRI and 2-deoxy-2-[fluorine-18] fluoro-D-glucose (18F-FDG) PET abnormalities that defined a neuronal tropism for structures associated with the medial temporal lobe.

In retrospect, a role for autoimmune dysfunction in neuropsychiatric illness had been sought since the 1930s, when autoantibodies were first reported in a schizophrenia patient. Since then, there have been reports of specific autoimmune responses to self-antigens in psychosis, affective disorders, and other neurobehavioral and neurocognitive disturbances endogenous to the limbic system of the temporal lobe, which includes hippocampal connections to other brain regions. The hippocampus is a highly plastic, stress-sensitive region that plays a central role in mood disorders and the consolidation and transformation of discrete short-term memories and long-term cortical storage. In particular, normal regulation of mood depends on the integrity of brain circuits, including the orbitofrontal-amygdala network, which supports emotions and moods, whereas the hippocampal-cingulate system supports the encoding of memory using all major neurotransmitters, including glutamate, γ-aminobutyric acid, acetylcholine, noradrenalin, and serotonin. Maintenance of the delicate balance of intact cell signaling and neurotransmitter balance seems to be most important in optimal hippocampal functioning. Animal models of major depressive disorder support a role for antidepressant medications as neuroprotective agents because of their effect on the induction of neuronal sprouting, whereas neurogenesis seems to be linked to the enhanced expression of brain-derived nerve growth factor associated with developmental stresses such as early-life maternal separation. Long-term treatment with antidepressant medications is thought to act on monoamine systems neurotransmitter systems that increase cyclic adenosine monophosphate (cAMP)–dependent phosphorylation, and the upregulation of cAMP response element–binding protein (CREB) messenger RNA levels, dysfunction of which has also been implicated in MDD. MRI fused with 18F-FDG-PET and volumetric analysis have been used to study hippocampal morphology and metabolism revealing reduced hippocampal volume, all of which seem to predict vulnerability to neuropsychiatric disturbances. The mechanisms by which genetic vulnerability, early disturbed CNS neurodevelopment, infection, trauma, and neuroinflammation confer a vulnerability to mood disorders and neurocognitive disturbances are not well understood.

AUTOIMMUNE LIMBIC ENCEPHALITIDES

Three autoantibodies found in children and adults with LE target intracellular GAD65, and surface antigens of the NMDAR and VGKC complex. Classically, the associated symptoms, which evolve over days to weeks, include short-term memory loss, sleep disturbances, seizures, irritability, depression, hallucinations, and personality change.

**Anti–Glutamic Acid Decarboxylase 65 Encephalitis**

Autoimmunity targeting the 65-kDa isoform of GAD65 encompass diverse autoimmune disorders such as T1D and rare neurologic disorders including LE, TLE, cerebellar ataxia, and large and small fiber peripheral and autonomic neuropathy. A review of adult-onset SPS showed a prevalence estimate of 1 in 1.25 million with a predominance of women, and average age of onset of 40 years. The frequency of high titers of anti-GAD antibodies defined a radioimmunoassay (RIA) value greater than 1000 IU/mL in TLE of unknown origin is 21% of cases, with the highest titers related to TLE. Affected patients are typically women with T1D, early-onset epilepsy,
and concomitant hypothyroidism, psoriatic arthritis, and Celiac disease, a third of whom reported onset of LE as the predominant feature, with supportive findings of amygdala and hippocampus signal intensities on brain MRI, and medial temporal hypometabolism on FDG brain PET. The levels of anti-GAD ranged from 1207 to 87,510 IU/mL, with absent oligoclonal bands (OCBs), and a ratio of serum/CSF GAD antibody levels greater than 1 suggesting intrathecal synthesis. Malter and colleagues estimated the prevalence of GAD antibodies in LE to be 17%, noting a subgroup of patients with TLE who had very high titers equivalent to those with SPS, medial temporal inflammation on MRI, and concomitant LE. In the TLE cohort, GAD antibody encephalitis proved to be as common as VGKC-complex antibodies but differed in younger age, female sex, presentation of first seizure, CSF OCBs, and intrathecal autoantibody synthesis. Patients with high levels of GAD antibodies, and classic or other neurologic syndromes not typically associated with GAD antibodies were at higher risk for an underlying cancer.

Gagnon and Savard reviewed the clinical experience of 58 cases of GAD65-antibody LE beginning with the first reported case and inclusively through 2016, in 7 observational studies, 3 case series, and 21 published case reports, providing a useful summary of the literature of anti-GAD65–associated LE. Diabetes alone, generally T1D, was noted in 50% of cases, in association with thyroiditis, diabetes, celiac disease, psoriasis, and common variable immune deficiency respectively in 73%, 18%, 9%, and 9%. Cancer was noted in 6 (10%) cases, including 4 SCLC and 2 malignant thymomas, generally in men of mean age 61 years (range, 38–70 years). The commonest presenting clinical features were seizures in 56 (97%) cases, most commonly refractory status epilepticus; cognitive impairment in 38 (59%), mainly affecting memory, language, executive function, and attention; psychiatric symptoms in 16 (28%) cases, most commonly depression, behavior, perception, and anxiety. The most common seizure presentation was refractory status epilepticus.

Low titers of anti-GAD65 antibodies, generally less than 20 nmol/L, occur in T1D and in the general population, whereas cases of anti-GAD65–associated neurologic disorders, including LE, are seen in the hundreds of nanomoles per liter. GAD65 is located predominantly in nerve terminals anchored to the cytoplasm-facing side of synaptic vesicles where it thought to synthesize GABA for neurotransmission supplementary to basal levels. The classification of high titers of anti-GAD65 autoantibodies has been problematic in being grouped with onconeural autoantibodies.

The dominant clinical phenotype of seizures, neurocognitive disturbances, and neuropsychiatric disturbances in most patients with anti-GAD autoantibody–associated LE is explained by the frequent involvement of the medial temporal lobes; an inflammatory CSF with intrathecal secretion of the anti-GAD65 autoantibody, and OCBs. Bien and colleagues described a 24-year-old woman with frequent temporal lobe seizures, nonparaneoplastic LE, and a serum anti-GAD65 antibody titer of 1:32,000, in whom T2/fluid-attenuated inversion recovery (FLAIR) MRI evolved over a period of 8 months, showing right hippocampal swelling and signal increase to sclerosis and atrophy on MRI commensurate with clinical progression. Among 58 literature patients, out of 58 (78%) patient MRIs were abnormal, with specific involvement of the temporal lobes in 34 (59%), and multifocal abnormalities in 9 (16%); 7 patient MRIs were normal. The results of electroencephalography (EEG), available in 35 cases, showed epileptiform discharges in 27 (77%) and focal temporal involvement in 19 (70%). Lumbar CSF was studied in 41 cases, showed pleocytosis in 11 (27%) with white blood cell (WBC) counts ranging from 7 to 114 cells/µL, and present OCBs in one-half of cases. There were significantly increased titers of anti-GAD65...
antibodies in both serum and CSF in 35 patients, and in either serum (in 18) or CSF alone in 3.

Bien and colleagues\textsuperscript{23,45} summarized the histopathologic features of selective resection of the sclerotic hippocampus in a patient, which included neuronal loss and astrogliosis and a strong accumulation of inflammatory cells in the resected hippocampus. There was marked invasion of the hippocampus by lymphocytes, which were mainly CD8+ T-cells with the cytotoxic effector molecule GrB, in addition to CD20+ B-cells and CD138+ plasma cells. The pattern of pyramidal cell loss was severe in sectors CA4 and CA3, with selective sparing of CA1 and CA2. Surviving neurons were positive for major histocompatibility complex class I, fulfilling the prerequisite for attack by CD8+ T-cells. The investigators\textsuperscript{23} quantitated the number of parenchymal T-, B-, and plasma cells; macrophages; and glial cells in 3 cases of anti-GAD65 autoantibody LE, which included a previously reported case,\textsuperscript{40} differentiating them from the IAg-onconeural cases (Ma2 in 3 cases; Hu in 4 cases); SAg types associated with VGKC complex (4 cases) and NMDA receptor (3 cases); and Rasmussen encephalitis (22 cases) and neurodegeneration controls (25 cases). The percentage of CD8 T cells in the IAg-GAD cases was intermediate (54%) between the IAg-onconeural and SAg cases. The CD8+/CD3+ ratio of the SAg cases was significantly different from the Rasmussen encephalitis controls. Apposition of multiple GrB+ lymphocytes to single neurons was consistent with a specific cytotoxic T-cell attack in case GAD/3. Bien and colleagues\textsuperscript{23} noted diffuse cytoplasmic IgG detected by anti–human IgG in both neurons and astrocytes in all cases similar to that of controls, which they attributed to leakiness of damaged neuronal membranes. Staining of C9neo indicating complement activation was negative in the IAg-GAD cases.

The diagnosis of anti-GAD LE should be considered in patients with a clinical syndrome of temporal lobe seizures, cognitive and psychiatric disturbances, and brain MRI abnormalities on T2FLAIR MRI implicating the medial temporal lobes; CSF pleocytosis, present OCB; and an EEG revealing temporal lobe epileptic or slow-wave activity in association with high levels of anti-GAD65 autoantibodies on RIA. In the case series summarized by Gagnon and Savard,\textsuperscript{43} full recovery was noted in 8% of patients who were treated with corticosteroids alone, with IVIg, or in combination with plasma exchange (PE), as well as another who received no immunosuppressant therapy and recovered. Death occurred in 8% of patients, several of whom had an associated cancer. Sustained improvement was noted 43% of cases with follow-up of 8 years.

There are unsubstantiated cases of biopsy-proven seronegative encephalitis reported by Najjar and colleagues\textsuperscript{46,47} in association with isolated neuropsychiatric disorders with a questionable relationship to prototypical AE.

**Anti–N-Methyl-D-aspartate Receptor Encephalitis**

Dalmau and Bataller\textsuperscript{48} identified a new CNS antigen as NR1/NR2B12 heteromers of the NMDAR with predominantly neuropsychiatric symptoms from a cohort of 526 cases of noninfectious LE with antibodies against CNS proteins. The anti-NMDA antibody seems to play a critical role in synaptic plasticity and memory. Although anti-NMDA receptor encephalitis is not by definition associated with cancer, 59% of patients had a tumor, most commonly benign-appearing cystic mature or immature teratoma tumors of the ovary. All showed serum or CSF antibodies to the NMDAR. A year later, the same investigators\textsuperscript{26} described a case series of 100 patients with antibodies against NR1-NR2 heteromers of the NMDAR as measured by enzyme-linked immunosorbent assay (ELISA), 91 of whom were women, all with psychiatric symptoms or memory complaints. Seizures were seen in 76 patients; 88 were unresponsive
or had altered consciousness, 86 had dyskinesias, 69 had autonomic instability, and 66 showed hypoventilation. Three-quarters presented initially to a psychiatric service.

Given its characteristic disease course, it is assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin have anti-NMDAR encephalitis, representing about 1% of all young patients’ admissions to intensive care units (ICUs). A French study noted a frequency of anti-NMDAR encephalitis of 2% in febrile encephalitis, which may be an underestimate because it excluded children. A multicenter, population-based, prospective study showed that anti-NMDAR encephalitis accounted for 4% of case of encephalitis in the United Kingdom, making it the most common cause of AE after acute demyelinating encephalomyelitis (ADEM) in children.

Clinically, anti-NMDAR encephalitis commences with nonspecific prodromal symptoms of headache, fever, nausea, or viral-infection–like illness, but over days to weeks, seizures and neurocognitive and neurobehavioral complaints emerge, including memory loss and frank neuropsychiatric manifestations of insomnia, mania, anxiety, depression, and paranoia. There can be movement disorders with orolingual-facial dyskinesia, autonomic manifestations, central hypoventilation, tachycardia, and bradycardia. The eventual outcome is favorable in up to three-quarters of all patients, who recover and have mild deficits with immunotherapy, whereas one-quarter have severe persistent deficits or die. Relapses in 25% to 30% of cases are partly attributed to lack of treatment, whereas 12% of treated cases relapsed in the first 2 years in one long-term outcome cohort analysis.

Most patients with anti-NMDAR encephalitis have intrathecal synthesis of antibodies and numerous CD 138+ antibody–secreting plasma cells in perivascular, interstitial, and Virchow-Robin spaces with complement-fixing IgG and IgG3 subtypes, as well as B- and T-cells in perivascular regions. Complement-mediated mechanisms in anti-NMDA receptor encephalitis studied in cultured rat hippocampal neurons tested for complement fixation show complement binding in vitro, although not in the brains of affected patients.

Testing for NMDAR antibodies is recommended in patients who manifest encephalitic signs, psychiatric symptoms, seizures, and CSF inflammation, after exclusion of viral and bacterial causes of infection regardless of neuroradiologic investigation because the disorder may be associated with normal MRI findings in up to 50% of cases. The remaining one-half include nonspecific changes and abnormal T2/FLAIR MRI hyperintensities in the mesial temporal lobe, cerebral or cerebellar cortex, basal ganglia, or brainstem. FDG brain PET shows hypermetabolism or hypometabolism in the affected regions. Up to 25% of patients have electrographic seizures. CSF analysis can show moderate lymphocytic pleocytosis, increased protein content, increased IgG index, and CSF-specific OCBs, which are typically negative at first testing, but can become positive later with disease progression in up to one-half of cases.

The histopathologic aspects of NMDAR encephalitis were studied in 14 cases, including 9 at postmortem examination and 5 in brain biopsy tissue. Dalmau and colleagues described 12 women with prominent psychiatric symptoms, amnesia, seizures, dyskinesia, autonomic dysfunction, and altered consciousness. All had serum/CSF antibodies that immunolabeled the neuropil of hippocampus/forebrain, in particular the cell surface of hippocampal neurons, and reacted with NR2B, and to a lesser extent NR2A, subunits of the NMDA receptor. NR2B binds glutamate and forms heteromers (NR1/NR2B or NR1/NR2A/NR2B) that are preferentially expressed in the adult hippocampus/forebrain. Expression of functional heteromers, and no single subunits, was required for antibody binding. The CSF and serum of all
12 patients showed a distinctive pattern of reactivity with the neuropil of rat hippocampus, and the immunolabeling predominantly occurred with the cell membrane of neurons and was intense in the molecular layer of the hippocampus. Three patients, aged 14, 24, and 35 years (cases 2, 6, 10) died, including 1 (case 10) previously reported, 3 to 6 months after symptom presentation. MRI showed T2/FLAIR hyperintensities in the medial temporal lobes (case 2), hyperintensity of the parietal sulci and enhancement of overlying meninges (case 6), and a third (case 10) showed normal findings. CSF in all 3 showed pleocytosis varying from 115 (case 10) to 219 WBCs (case 6) with minimally increased or normal protein content, and positive OCBs. Immunofluorescence microscopy experiments showed colocalization of antigens reacting with patient antisera and antibodies against NR2B, and colocalization of these antibodies in patients’ tumor samples and in brain. Postmortem examination showed extensive gliosis, rare T-cell infiltrates, and neuronal degeneration predominantly involving, but not restricted to, the hippocampus in all 3. Microglial nodules and neuronophagia were rarely seen. In all cases, these findings predominated in the hippocampus, where there was intense IgG immunostaining.

The main epitope targeted by the antibodies is the extracellular N-terminal domain of the NR1 subunit. Patients’ antibodies decrease the numbers of cell-surface NMDAR and clusters in postsynaptic dendrites, an effect that is reversed by antibody removal. Tüztün and colleagues extended the immunopathologic analysis of cases 6 and 10 reported previously by Dalmau and colleagues, noting that lymphocytic infiltrates were uncommon, being rarely noted in the perivascular and leptomeningeal regions, and scarcely distributed in brain parenchyma. CD20+ B-cells and CD79a plasma cells were identified in the perivascular space, including 1% cytotoxic T-cells and absence of GrB+, Fas, and Fas ligand–positive cells. IgG, including deposits, was noted in all areas of the CNS but most intensely in the hippocampus. Using HEK293 cells expressing NR1/NR2B, the NMDAR IgG were mainly IgG1 but included IgG2 and IgG3 types.

Camdessanche and colleagues reported the postmortem findings of a brain biopsy specimen from an 18-year-old woman with NMDAR encephalitis who presented with subacute mood changes and facial jerks. Brain MRI showed foci of T2 hyperintensities in the right frontal lobe, and CSF showed 21 WBCs and OCBs. The frontal lobe showed perivascular cuffing of CD20+ B-cells and a few CD138+ plasma cells, with few CD3+ T-cells or CD68+ macrophages scattered throughout gray and white matter and in perivascular spaces. Retrospective screening for anti-NMDAR antibodies was performed on a CSF sample that was positive at a dilution of 1:10, both in the neuropil of the rat hippocampus and in transfected HEK293 cells.

Martinez-Hernandez and colleagues described 2 male patients, aged 7 and 59 years, and 3 female patients aged 5, 24, and 35 years, the last 2 with ovarian teratomas and anti-NMDAR encephalitis, who presented with subacute short-term memory deficits, psychiatric disturbances, seizures, movement disorders, and dysautonomia ranging from 22 days to 4 months. CSF showed increased protein levels ranging from 94 to 219 mg/dL with OCBs, and brain MRI showed increased FLAIR signal in medial temporal lobes (case 1), parietal cortex (case 2), and left temporal cortex (case 3), in the insula and anterior temporal lobes with atrophy in another (case 5). Brain MRI was normal in case 4. Treatment with combined immunotherapy in 1 patient who underwent a brain biopsy was effective, whereas the others died. One patient who died underwent earlier brain biopsy, and the remaining 3 patients were studied at postmortem examination. Patients’ antibodies were able to fix complement on cultures of rat hippocampal neuron but this was not detected in any of the brain regions of...
3 patients, or in biopsies of 2 patients, all with anti-NMDAR encephalitis. The main histologic findings were an abundance of infiltrating CD138+ plasma cells and plasmablasts in perivascular regions capping blood vessels, Virchow-Robin spaces, and lining the meningeal-brain surface in proximity to the CSF.

Bien and colleagues examined brain biopsy tissue from 2 women and 1 man, aged 17 to 22 years with NMDAR encephalitis, all 3 with encephalopathy lasting 2 months to 12 months, none with an associated tumor. Two were treated with immunotherapy before frontal (2 patients) or temporal lobe cortical biopsy. Serial MRI in 1 patient did not show hippocampal atrophy. Histopathology of the tissue specimens showed low density of T cells, in the range of neurodegeneration controls. The ratio of perivascular CD8+/CD3+ was slightly increased, and there were cytotoxic granules in some parenchymal T cells, but no apposition of CD8++ T-cells to single neurons. Diffuse cytoplasmic IgG was evident in both neurons and astrocytes and C9neo deposition was present in the cytoplasm and on the surface of hippocampal CA4, dentate, and cortical neurons. The neocortex of NMDAR antibody-positive patients showed almost no inflammation, and no clear signs of neuronal loss. Even though NMDA receptor antibodies seemed to be involved in the clinical disease process, there was no evidence to suggest a classic mechanism of cytotoxic T-cell or humoral immune-mediated neuronal cell death. The possibility that a more active inflammatory infiltrate or antibody deposition could be found at an earlier disease stage in both the hippocampus and cortex could not be excluded, although it was striking that MRI evidence of inflammation in the hippocampus was rare.

Collectively, the histopathologic findings were consistent with a selective and reversible decrease in NMDAR surface density and synaptic localization that correlated with patients’ antibody titers. The mechanism of this decrease was selective antibody-mediated capping and internalization of surface NMDARs, which was supported by the experimental finding of Hughes and colleagues who studied Fab fragments prepared from patients’ antibodies that did not decrease surface receptor density. Subsequent cross-linking with anti-Fab antibodies recapitulated the decrease caused by intact patient NMDA receptor antibodies. These cellular mechanisms seem to be the cause of the specific titer-dependent and reversible loss of NMDARs. The loss of the subtype of glutamate receptors that eliminates NMDAR-mediated synaptic function may underlie the learning, memory, and other behavioral deficits observed in affected patients.

Suggested criteria for the definite diagnosis of anti-NMDAR LE include the presence of IgG anti-GluN1 antibodies in a suspected patient with subacute onset of psychiatric behavior or cognitive disturbances, seizures, movement disorder, and autonomic dysfunction; abnormal EEG that shows focal or diffuse slowing or epileptic activity; and CSF pleocytosis or OCBs. Prompt diagnosis of anti-NMDAR encephalitis leads to improvement typically after removal and treatment of an offending cancer, or in the absence thereof. The demonstration of copious infiltrates of antibody-secreting cells in the CNS of affected patients provides an explanation for the intrathecal synthesis of antibodies, and implications for treatment used to arrest and reverse the disorder using IVIg, corticosteroids, cyclophosphamide, or rituximab.

It is now assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin would have anti-NMDAR encephalitis, representing about 1% of all young patients’ admissions to ICU. A French study noted a frequency of anti-NMDAR encephalitis of 2% in febrile encephalitis, which could be an underestimate because of the exclusion of children. A multicenter population-based prospective study showed that anti-NMDAR encephalitis accounted for 4%
of case of encephalitis in the United Kingdom, making it the most common cause of AE after ADEM in children.51

**Anti–Voltage-gated Potassium Channel Complex Encephalitis**

About the same time that MoS was described, anti–VGKC complex antibodies were determined using RIA in patients with noninfectious AE.19 Although the disorder was generally termed LE, the term limbic encephalopathy was also used because more patients were found to be seropositive without evidence of classic features of hyperintense signal in the medial temporal lobes on brain MRI, and CSF inflammation.19 Autoantibodies against the VGKC complex detected by RIA in the sera of patients with AE did not bind directly to VGKC-complex channel proteins proper, but instead to synaptic and axonal neuronal proteins that coprecipitated with detergent-solubilized VGKC.64,65

Attention has focused on identifying the principal autoantigens in the VGKC complex and expanding the spectrum of corresponding phenotypes. Initial reports66,67 suggested that patients’ antibodies were bound to the VGKCs Kv1.1 and Kv1.2. Subsequent studies showed that leucine-rich glioma-inactivated protein 1 (LG11), and contactin-associated protein–like 2 (CASPR2) were the main autoantigens64,65 and associated with transiently expressed axonal glycoprotein (TAG1), postsynaptic density protein-1 (PDZ), and the ankyrin-spectrin protein in both the PNS and CNS. Antibodies against contactin-2 usually occur in association with those targeting LGI1 or Caspr2 and were identified in other disorders, raising doubts about their importance. There is a diversity and overlap of neurologic phenotypes associated with VGKC complex IgG in the serum and CSF, and distinct immunoglobulin-subtype specificity. The commonest presentation of VGKC-complex autoantibodies is LE in the CNS, and neuromyotonia or MoS in the periphery.

In the United Kingdom, where the incidence of encephalitis is estimated at 5.23 cases per 100,000 population per year based on admissions to the National Health Service between 2005 and 2009, Granerod and colleagues68 estimated the incidence of encephalitis as 4.32 cases/100,000/y. A capture-recapture model estimated the incidence of encephalitis to be 8.66 cases/100,000/y. Two percent of patients (n = 216) had more than 1 encephalitis admission during the study period, and the incidence did not change (4.20 cases/100,000/y) when subsequent admissions of these patients were excluded from the analysis. By using data restricted to the primary diagnostic field, the overall mean incidence was 2.75 cases/100,000/y (95% confidence interval, 2.39–3.10 cases/100,000/y). The results of multivariable analyses showed that, compared with 2005 to 2006, incidences in all subsequent years were slightly higher but with little evidence of a trend (P = .19). The incidence rate was highest among patients less than 1 year of age and in those greater than 65 years of age. A retrospective study that reviewed antibodies to VGKC, LGI1, and CASPR2 in 46 children with severe acute encephalitis identified only 1 affected child (2.2%) among 46 children.69

Among 64 patients with VGKC-complex encephalitis,70 the clinical features included neuropsychiatric features, disorientation, confusion, or amnesia in 100% of patients; tonic-clonic seizures in 92%; delusions in 21%; hallucinations in 17%; agitation in 6%; pain in 4.7%; and peripheral neuropathy in 1.6% of cases. Neurocognitive complaints, psychiatric symptoms, and seizures typical evolve over days to weeks, occasionally acutely, but more often insidiously over months before coming to medical attention. Flanagan and colleagues71 studied the finding of an apparent dementia in 72 affected patients. Responsiveness to immunosuppressant and immunomodulatory
therapy was predicted by seropositivity for neuronal VGKC-complex antibody more than calcium channel or neuronal acetylcholine receptor \( (P = .01) \). Up to 40% of patients may also manifest frontal lobe and frank psychiatric features. Parthasarathi and colleagues\(^7^2\) described a 58-year-old man with panic attacks and psychogenic non-epileptic seizures who later developed delusions and hallucinations followed by confusion. He was found to have VGKC-complex antibodies and was treated with immunomodulatory therapy leading to near-complete recovery. Bettcher and colleagues\(^7^3\) delineated cognitive strengths and weaknesses among 12 patients with VGKC-complex encephalitis, noting mild to moderate impairment in memory and executive functions, with variable impairments in language and sparing of visuospatial skills that correlated with MRI findings of T2/FLAIR hyperintensities in medial temporal lobe (10 out of 10) and basal ganglia (2 out of 10). Serial cognitive examination revealed heterogeneity in cognitive function.

Seizures occur in 90% of cases and are most commonly focal, with infrequent generalization, manifesting typical medial temporal lobe signature with hand and orofacial automatisms. Three seizure semiologies, ictal bradycardia, piloerection, and fasciobrachial dystonic seizures (FBDS), show a strong association to LE associated with LGI1 antibodies. FBDSs consist of brief frequent episodes of abnormal unilateral and bilateral movements of the arms, sometimes the ipsilateral muscles of the face, and more rarely the leg. Video EEG shows an epileptic origin of these myocloniclike movements; however, regular EEG with scalp electrodes often misses an interictal focus. If FBDSs are recognized early, and serum LGI1 antibodies are detected, immunotherapy prevents progression to frank LE, which in one study arose after a median delay of 36 days. Kalachikov and colleagues\(^7^4\) described autosomal dominant lateral temporal epilepsy (ADLTE) characterized by partial seizures and preceding auditory signs in the LGI1/epitempin gene expressed on chromosome 10q24. Mutations in this gene introduce premature stop codons and prevent production of full-length protein from the affected allele. Although LGI1 haploinsufficiency causes ADLTE, the underlying molecular mechanism that results in abnormal brain excitability has instead been attributed to dysregulation of synaptic \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) in hippocampal neurons in the epileptic LGI1 knockout mouse.\(^7^5\) Fukata and colleagues\(^7^6\) proposed that extracellularly secreted LGI1 linking 2 epilepsy-related brain receptors, a disintegrin and metalloproteinase domain 22 (ADAM22) and ADAM23, organize a transsynaptic protein complex that includes presynaptic potassium channels and postsynaptic AMPA receptor scaffolds. The lack of LGI1 disrupts this synaptic protein connection and selectively reduces AMPA receptor–mediated synaptic transmission in the hippocampus.

Younger\(^7^7\) described new-onset FBDS and memory disturbances in association with distal large and painful small fiber peripheral neuropathy and dysautonomia without systemic malignancy in a patient with extrathecal VGKC-complex antibody production. Epidermal nerve fiber studies confirmed small fiber neuropathy in association with abnormal autonomic laboratory testing.

Neuropathic pain as a manifestation of VGKC-complex autoimmunity was noted in 316 (4%) of 1992 patients evaluated neurologically at a tertiary referral center\(^7^8\) and was typically subacute in onset, nociceptive, regional, or diffuse. In cases suspected of peripheral neuropathy with mild subjective loss of temperature and pain attributed to small fiber dysfunction, electrodiagnostic studies show variable minor reduction of sural sensory nerve action potential amplitudes with motor hyperexcitability. The VGKC-complex antibody titers were often low (0.02–0.1 nM) and antibodies to GLI1 or CASPR2 were present in 28% overall, with the latter most common (7%).
Autonomic involvement was noted in 29% of the cohort studied by Klein and colleagues, and in 3 (60%) of the patients described by Lahoria and colleagues. Hypothermia was described in association with VGKC-complex antibody–associated LE in 4 patients, 1 of whom had concomitant neuropathic pain, and, in the absence thereof, the others were conjectured to have otherwise disturbed hypothalamic thermoregulatory mechanisms as the cause for dysautonomia.

LGI1 is a secreted synaptic protein that associates with and regulates Kv1.1 and Kv1.2, as well as AMPA. Caspr2 is a transmembrane axonal protein of the neurexin IV superfamily that localizes to the juxtaparanode of myelinated axons, and its extracellular domain interacts with contactin-2, where it connects with the cytoskeleton via protein 4.1B. Caspr2, contactin-2, and protein 4.1B are all necessary to concentrate Kv1.1 and Kv1.2 channels in the juxtaparanode. Lai and colleagues studied proteins associated with Kv1.1 and Kv1.2, noting that VGKCs themselves were the autoantibody targets, explaining the diversity of symptoms among patients with these antibodies. LGI1 is primarily a CNS protein, and LGI1 antibodies are associated with LE, seizures, and hyponatremia. LGI1 antibodies cause reversible CNS synaptic dysfunction by several mechanisms. The antibodies may prevent binding of LGI1 to the receptors that it regulates, or they might act on the LGI1-ADAM protein complex. Alternatively, LGI1 antibodies could disrupt currents mediated by Kv1.1 and Kv1.2, and/or impair AMPAR function, either indirectly by blocking LGI1-mediated regulation of these proteins or directly by disrupting the entire protein complex. The identification of LGI1 as a major target of so-called VGKC antibodies clarifies several aspects of the associated disorder.

Caspr2 antibodies are associated with AE, PNH, and MoS. Peripheral nervous system manifestations may precede or follow those of the CNS by up to several years. Some affected patients have an associated thymic tumor, but most do not. Mutations in the human gene encoding Caspr2 (CNTNAP2) are associated with autism, epilepsy, Tourette syndrome, cortical dysplasia, obsessive-compulsive disorder, Pitt-Hopkins syndrome, and other mental disabilities. Mice with a caspr2 deletion show analogous behavioral defects and symptoms. Note that common variants of the CNTNAP2 gene in healthy individuals are associated with abnormal language processing and are a risk factor for autism. Caspr2 antibodies act by disrupting axonal potassium currents. Factors such as differences in time to establishment of intrathecal antibody synthesis or in the structure of tight, septatelike junctions of myelinating cells around the axons may explain this variability. The VGKC-complex antibody levels broadly differ between the different syndromes, with highest levels in LE and FBDS, moderate levels in MoS, and lowest levels (often <400 pM) in PNH.

The high proportion of VGKC-complex IgG-seropositive patients whose serum samples lack LGI1 IgG and CASPR2 IgG specificities suggests that other VGKC-complex molecular targets remain to be discovered. Only about 4% to 5.5% of unselected cases were seropositive by RIA with confirmatory retesting using 125I-α-dendrotoxin alone (radioligand for Kv1.1, Kv1.2, and Kv1.6 channels), making the test unreliable as a screen for LE without further subtyping for LGI1 and CASPR2-IgG. So selected, 26% to 28% of seropositive VGKC sera revealed reactivity with LGI1 and/or CASPR2-IgG, with a significant association between LGI1-IgG positivity and cognitive impairment and seizures (\(P<.05\)), and CASPR2-IgG positivity and peripheral motor excitability (\(P = .004\)); however, neither autoantibody was pathognomonic for a specific neurologic presentation. There has been concern for screening of unselected sera for VGKC-complex antibodies by RIA. It can be argued that VGKC-complex RIA antibody test should be used as initial screening to select positive samples that could then be confirmed by LGI1 or CASPR2-IgG antibody subtyping;
however, the latter may also be positive in selected VGKC-complex antibody-negative sera by RIA. Paterson and colleagues noted positive VGKC-complex antibody values (>400 pM; >0.4 nM) that were likely to be relevant in LE and related syndromes, as well as low-positive values (<400 pM; 0.1–0.4 nM) in 32 out of 44 cases considered to be nonautoimmune, 4 (13%) cases of which were found to have a definite or probable paraneoplastic neurologic disorder, neuromyotonia, or MoS. Ances and colleagues noted that the RIA used in the clinical analysis of VGKC-complex antibodies identified a limited number of subunits (Kv1.1, Kv1.2, and Kv1.6) but that it was reasonable to speculate that antibodies to other subunits, K channel families, and VGKC ion channels might also associate with LE.

Neuroimaging studies in VGKC-complex antibody-associated LE show highly variable results. Both mesial temporal lobe hypometabolism on FDG brain PET and hypermetabolism have been described. In a patient with VGKC-complex LE who did not definitively show structure abnormalities on serial brain MRI over time despite ongoing temporal lobe seizures captured on video-EEG, FDG brain PET fused with gadolinium-enhanced MRI later showed bitemporal hypometabolism. Baumgartner and colleagues identified 9 out of 18 (50%) patients positive for nonparaneoplastic antibodies against neuronal surface antigens (VGKC or NMDA-R), 2 of whom displayed mesiotemporal hypermetabolism on FDG brain PET, with 4 others who were rated normal, and 3 who displayed hypermetabolism outside the mesiotemporal region. The fraction of abnormal scans using MRI was lower (10 out of 16; 62.3%) than for FDG brain PET (14 out of 18; 77.7%).

CSF results were equally variable in VGKC-complex autoimmunity. Jarius and colleagues performed 29 lumbar punctures in 17 patients with VGKC-complex LE, noting normal findings in up to 53% of CSF specimens. There were no significant differences between the CSF findings and the titers of serum VGKC-complex autoantibodies. Slight pleocytosis, mainly consisting of lymphocytes and monocytes, and increased total protein concentrations were present in 41% and 47%, respectively. A disturbance of the integrity of the BBB was found in 6 (35%) patients based on an abnormal CSF/serum humoral immune response. Absence of CSF-specific OCB, considered a marker of autochthonous antibody synthesis within the CNS in all patients, suggested an extrathecal origin of VGKC-complex autoantibodies. Vincent and colleagues reported the CSF findings in 10 patients, all with VGKC-complex antibody-associated LE, noting mild lymphocytosis and mild or moderately increased protein content in one-half. OCBs were noted in 1 patient, whereas 6 other OCBs were identical to serum. VGKC-complex antibody assays on matched serum and CSF showed antibodies levels of the latter present in 4 patients that varied between less than 1% and 10% of the serum, and less than 10% in 1 patient with the lowest serum value. These findings were consistent with extrathecal synthesis of VGKC-complex antibodies.

Irani and Vincent estimated features of peripheral neuropathy in 1.6% of VGKC-complex antibody-positive LE cases. Lahoria and colleagues described 5 patients with painful polynuropathy, all positive for VGKC-complex autoantibodies (range, 0.08–1.18 nM), 2 of whom had antigens positive for CASPR2 and LGI1-IgG, both at low VGKC-complex antibody titers (respectively 0.08 and 0.16 nM/L). Electrodiagnostic studies showed length-dependent sensorimotor polyneuropathy that was concordant with abnormal indices of axonal degeneration or demyelination in 4 nerves, and the latter with quantitative analysis of semithin sections in 2. All 5 showed absence of inflammatory cell infiltration. By comparison, the symptoms of small fiber neuropathy, which arise from dysfunction in nociception, temperature, and autonomic modalities, are most adequately assessed by epidermal nerve fiber density in a 3-mm punch
biopsy of skin from the lateral calf and thigh, and a combination of cardiovagal, sudomotor, and adrenergic function tests in comparison with controls.

Eight patients with VGKC-complex LE were studied histopathologically, including stereotactic brain biopsy in 3,19,23 at epilepsy surgery in 1 case,23 and at postmortem examination in 4 patients.23,82–84 Vincent and colleagues19 described a 56-year-old man with 7-month history of confusion and memory impairment who developed partial focal seizures, anxiety, and delusions. CSF showed mild pleocytosis and brain MRI showed unilateral left medial temporal lobe signal change with focal slow activity on EEG. The serum VGKC antibody titer was 2224 pM (normal, 0–100 pM; >400 pM highly increased). Histopathology of a stereotactic biopsy of the left amygdala showed positive staining for perivascular and parenchymal CD45+ lymphocyte infiltrates, astrogliosis, and CD68+ microglial activation. He was received a course of intravenous dexamethasone with a slight beneficial response but persistent memory deficits. Follow-up brain MRI showed evolution of bilateral hippocampus atrophy and signal changes.

Dunstan and Winer87 reported a 78-year-old man with a 2-week history of confusion, cognitive impairment, and hyponatremia. Brain MRI showed increased signal in the right medial temporal lobe with subcortical white matter changes. CSF was normal. Assay for VGKC antibodies was 1637 pM by RIA. He received anticonvulsants but deteriorated because of sepsis and died. Postmortem examination showed no evidence of a malignancy. The brain showed severe neuronal loss with multiple reactive astrocytes, macrophages, and scattered T cells in the right amygdala nucleus and adjacent hippocampus.

Park and colleagues88 described a 65-year-old woman with a 3-month history of amnesia, disorientation, memory loss, and partial complex seizures. Brain MRI was normal and CSF showed 17 WBCs. EEG showed mild diffuse slowing. She later developed hyponatremia, and serum VGKC-complex antibodies were 1.73 nmol/L (normal, <0.02 nmol/L) by RIA. Whole-body FDG-PET showed mediastinal adenopathy. She was treated with intravenous corticosteroids for 5 weeks without improvement and later died. General autopsy limited to the chest showed no malignancy. Postmortem examination of the brain showed mild focal perivascular T-cell lymphocyte cuffing and infiltrates of overlying meninges and parenchyma of the cingulate gyrus, hippocampus, amygdala and midbrain.

Khan and colleagues89 reported a 56-year old man with a 4-month history of confusion, disorientation, and seizures. A serum VGKC antibody titer was 3327 pM by RIA and there was hyponatremia. Brain MRI showed left hippocampal atrophy on T2/FLAIR images. General postmortem examination showed no malignancy. Examination of the brain showed pathologic changes in both hippocampi and right amygdala regions comprising pyramidal neuronal cell loss in the CA4 region, marked activation of CD68+ microglia, and reactive GFAP+ astrocytosis extending to the subiculum, less so near the joining of the parahippocampal gyrus. There were perivascular infiltrates of CD20+ B-cells and a few CD4+ T-cells, especially in the right hippocampus.

Bien and colleagues23 summarized the histopathologic findings in the brain of 4 cases, 3 men and 1 woman, aged 33 to 68 years, with LE (3 patients) and multifocal encephalitis (1 patient), ranging from 5 to 9 months. Serum VGKC antibody titers were 167, 288, 958, and 2224 pM respectively. Serial MRI showed an evolution from hippocampal swelling with T2/FLAIR signal increase to frank hippocampal atrophy and increased signal intensities. Histopathologic examinations, including quantitative immunocytochemical studies, showed variably intense inflammation and overall lower CD8/CD3 ratios, although there were GrB+ T-cells present in the lesions without
opposition to neurons or release of FrB, therefore T-cell cytotoxicity was not a major contributor. Immunoglobulin and complement deposition on neurons was a prominent finding, and terminal deoxynucleotidyl transferase dUTP nick and labeling (TUNEL) reaction in the same area showed acute neuron cell death, suggesting antibody and complement-mediated neuronal cell damage in these patients. The investigators noted that IgG4 rather than IgG1 antibodies dominated in the sera of patients with VGKC-complex LE.

Suspected patients with new onset and rapid progression of memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system, bilateral medial temporal lobe abnormalities on T2/FLAIR MRI, and CSF pleocytosis combined with TLE or slow-wave activity on EEG should be screened for VGKC-complex antibodies, with detection of LGI1 and CSFPR2 by RIA. The diagnosis of VGKC-complex LE can be established in suspected cases when serologic studies are combined with clinical, neuroradiologic, and CSF inflammatory parameters and a reasonable exclusion of alternative diagnoses. If so, immunomodulatory and immunosuppressive therapy should begin. Less than one-half of affected patients fail to improve with first-line therapy using IVIg, PE, or corticosteroids, needing to advance to second-line agents, including cyclophosphamide and rituximab.

Bataller and colleagues noted that treatment responsiveness of LE was especially favorable among patients with antibodies to the VGKC complex, with overall improvement in two-thirds or more of patients. However, a favorable response to therapy was not limited to patients with VGKC-complex antibodies but extended to novel-cell-membrane antigens expressed in the hippocampus. The salutary effect of immunotherapy in the management of seizures in VGKC-complex antibody-associated LE is well supported by the autoimmune basis of FBDS.

HASHIMOTO THYROIDITIS AND ENCEPHALOPATHY

For nearly half a decade, investigators have pursued the association of Hashimoto thyroiditis (HT) and a reversible encephalopathy with clinicopathologic resemblance to CNS vasculitis. In 1966, the British neurologist Brain and colleagues described HE in a 40-year-old man with 12 ictal and strokelike episodes of confusion and agitation 1 year after onset of treated hypothyroidism. The cerebral disorder remitted completely after 19 months commensurate with a decline in high serum thyroid-antibody levels. Treatment with prednisone and an anticoagulant for 3 months was ineffective. His neurologic symptoms remitted while he was taking only levothyroxine. The investigators concluded that the likeliest explanation for this protracted and stuttering brain disorder was localized cerebral edema caused by antibody-mediated autoimmunity. Jellinek and Ball extended the results of Brain and colleagues, describing the original patient, who, at age 62 years, died 12 years later of an unrelated cause. Postmortem examination showed virtually no remaining thyroid tissue and atheromatous cerebrovascular changes with splenic atrophy. The investigators postulated that underlying autoimmunity was the cause of HT, HE, and splenic atrophy. A half decade later, Rowland and colleagues characterized the clinicopathologic aspects of HE, beginning with the patient described by Brain and colleagues and ending in 2002, adding a case of their own. The diagnosis of HE, as described by Rowland and colleagues, which rested on the presence of HT (Fig. 1) with measurably high titers of thyroid peroxidase (TPO) or antithyroglobulin (Tg) antibodies, clinical encephalopathy, and absence of CSF evidence of bacterial or viral infection, has served as the standard for future case selection.
Clinical Presentation

In the series of Rowland and colleagues,\textsuperscript{94} the mean age at onset of symptoms of HE was 44 years (range, 9–78 years). In addition to encephalopathy as required, strokelike signs presented in 23 (27%) cases, seizure in 56 (66%), myoclonus in 32 (38%), and visual hallucination or paranoid delusion in 31 (36%). The course was relapsing and remitting in 51 (60%) cases.

Laboratory Findings

In the series of Rowland and colleagues,\textsuperscript{94} both Tg and microsomal or TPO antibodies were found together in 60 (71%) cases, with 1 antibody of the 2 normal in 20 (24%) cases. There was no relationship between the neurologic symptoms and signs and the type or serum concentration of antithyroid antibodies. Altogether, 30 (35%) cases were subclinically hypothyroid, 19 (22%) were euthyroid, and 17 (20%) were overtly hypothyroid. Fourteen (16%) cases had an increased erythrocyte sedimentation rate or antinuclear antibodies, and 3 had a concomitant connective tissue disease. An increased CSF protein level was noted in 66 (78%) patients, with abnormal findings in neuroimaging in 40 out of 82 (49%) or EEG in 80 out of 82 (98%) patients. A goiter was detected in 24 out of 39 (62%) patients. \textsuperscript{18}F-FDG-PET of the brain fused with MRI may show signal abnormality in the hippocampus with hypometabolism in the mesial temporal lobes. Nuclear medicine cerebral perfusion with single-photon emission computed tomography may disclose regions of hypoperfusion that overlap with areas of hypometabolism, suggesting concomitant disruption of the BBB.

Immunopathogenic Mechanisms

Unlike the close relationship between antithyroid antibodies and HT, in HE neither high titers of antithyroid antibodies nor the presence of subclinical or overt hypothyroidism seems to account for the observed encephalopathy.\textsuperscript{94} The neurologic findings in euthyroid patients are similar to those in patients with subclinical or overt hypothyroidism.

Ochi and colleagues\textsuperscript{95} provided a link between HT autoimmunity and the CNS using human brain proteome map and two-dimensional electrophoresis to screen brain
proteins reactive to serum antithyroid antibodies. The investigators\textsuperscript{95} identified $\alpha$-enolase, a candidate marker for HE-related disorder, encoded on 1p36.23. Kishitani and colleagues\textsuperscript{96} extended the findings of Ochi and colleagues,\textsuperscript{95} noting anti–NH$_2$ terminal of $\alpha$-enolase antibodies in sera of 24\% of patients with HE and limbic abnormalities on MRI showing abnormal signal in unilateral or bilateral medial temporal lobes, and diffuse slow-wave activity with epileptogenic discharges. These findings suggested that LE associated with anti–NH$_2$ terminal of $\alpha$-enolase antibodies may be an etiopathogenic factor of HE in some cases. Graus and colleagues\textsuperscript{3} proposed HE as a recognizable autoimmune encephalopathy after exclusion of other syndromes associated with well-defined autoantibodies. It is still unclear whether antithyroid antibodies represent an immune epiphenomenon in a subset of patients with encephalopathy or are associated with pathogenic mechanisms of the disorder.

According to Rowland and colleagues,\textsuperscript{94} one subgroup of patients with HE present with strokelike episodes. Inoue and colleagues\textsuperscript{97} described a patient with progressive parkinsonism and normal cognitive and intellectual performance. Slow background activity on EEG was the only sign of encephalopathy, which normalized after treatment with corticosteroids. Younger\textsuperscript{98} described a patient with hemiparkinsonism in a strokelike onset. $^{18}$F-FDG-PET metabolic imaging showed severe hypometabolism within the posterior aspect of the left putamen, suggesting focal vascular injury, with superimposed left temporal and left parietal hypometabolism and mild volume loss relative to the rest of the brain (Fig. 2).

Fig. 2. HE. PET imaging from the vertex to foramen magnum following injection of 10-mCi $^{18}$F-FDG (left) shows severely reduced metabolic activity in the posterior half of the left putamen, with correlative morphologic changes (right) with fusion to gadolinium-enhanced MRI.
A vasculitic pathogenesis seems to be equally likely in some cases of HE based on the tendency for increased autoimmunity in HT. In addition, the available histopathology in HE supports an inflammatory vasculopathy, so noted in 1 postmortem case that showed lymphocytic infiltration of brainstem veins, and in brain biopsy tissue from another case categorized as isolated angiitis caused by lymphocytic infiltration of the walls of arterioles and veins. Brain biopsy tissue of a second living patient showed perivascular cuffs of lymphocytic cells. It is noteworthy that patients with HE and circulating $\alpha$-enolase antibodies are at risk for heightened autoimmune activity and a tendency for systemic and invasive autoimmune disorders, including systemic vasculitis.

**Treatment**

The significance of corticosteroid sensitivity in HE is widely accepted as a criterion for the diagnosis. However, as Rowland and colleagues suggested, it would be unwise to define any condition by response to any particular therapy, especially if not replacing a specific deficit or directing it at a particular target. Patients with HE improve in association with, but not necessarily because of, corticosteroid therapy. Moreover, those that respond to corticosteroids have no distinguishing clinical characteristics nor receive treatment in other fashions for a meaningful comparison.

**SUMMARY**

There has been a rapid expansion in knowledge of AE neurologic and neuropsychiatric disorders. Three well-described disorders targeting antigens on the surface or in the cells of the temporal lobe neuropil manifest limbic and extralimbic dysfunction. Patients with HT may develop a rare autoimmune encephalopathy. Recognition of these cases has shifted clinical paradigms and led to new insights into the mechanisms of AE. Patients with available histopathology show variable humoral and cell-mediated autoimmune mechanisms, with cytotoxic T-cell inflammation targeting neuropil antigens, making them more similar than not, to primary CNS vasculitis. However, one important difference is the more favorable outcome in autoimmune encephalopathy and HE compared with primary CNS vasculitis, making their recognition essential in choosing appropriate immunotherapy to achieve long-lasting remission.

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