Autoimmune Encephalitides

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Abstract

Autoimmune encephalitis is a severe inflammatory disorder of the brain with diverse causes and a complex differential diagnosis. A recent advance in the past decade has led to the identification of new syndromes and biological markers that have transformed the approach to diagnosis and management of autoimmune encephalitis. Limbic encephalitis, the commonest form of autoimmune encephalitis, combines common presentations of cognitive, psychiatric, and epileptic disorders and has until recently been considered paraneoplastic or postinfectious in origin. The autoimmune encephalitides are clinically and histopathologically associated with serum and intrathecal antibodies to intracellular and surface neuronal antigens, and constituents of the limbic system neuropil. This has led to a reconsideration of a number of neuropsychiatric and neurocognitive disorders as having shared mechanisms of origin. This chapter reviews their historical background, clinical presentation, laboratory evaluation, histopathology, diagnosis and management.

Keywords: Autoimmune; Encephalitis; Hashimoto; Encephalopathy

Abbreviations: LE: Limbic encephalitis; ANNA-2: Anti-Neuronal Nuclear Antibody type 2; POMA: Paraneoplastic Opsoclonus Myoclonus Ataxia; SMN: Subacute Motor Neuronopathy; CSF: Cerebrospinal Fluid; PCA-1: Purkinje cell antibody type-1; PCD: Paraneoplastic Cerebellar Degeneration; SCLC: Small-Cell Lung Cancer; ANNA-1: Anti-Neuronal Nuclear Antibody type-1; PEM: Paraneoplastic Encephalomyelitis; DRG: Dorsal Root Ganglia; SPS: Stiff-Person Syndrome; GAD: Glutamic Acid Decarboxylase; VGKC: Voltage-Gated Potassium Channel; MHC: Main Histocompatibility Complex; TLE: Temporal Lobe Epilepsy; PNH: Peripheral Nerve Hyperexcitabiity; MoS: Morvan's Syndrome; BBB: Blood-Brain Barrier; NMDA: N-methyl-D-aspartate; AMPA: Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MRI: Magnetic Resonance Imaging; EEG: Electroencephalography; FBDS: Fasciobrachial Dystonic Seizures; ADLTE: Autosomal Dominant Lateral Temporal Epilepsy; LTP: Long-Term Potentiation; BDNF: Brain-Derived Neurotrophic Factor;

Historical Perspective

Corsellis, et al. [1] coined the term limbic encephalitis (LE) in 1968, noting a relation to bronchial cancer in three patients in the sixth to eighth decade of life, and showing close clinicopathologic similarity to cases described by Brierley, et al. [2] six years earlier. All three cases had subacute temporal lobe seizures, neuropsychiatric, and memory disturbances for two years before death. Postmortem examination revealed inflammatory lesions in limbic grey matter sections of the brain, notably in medial temporal lobe structures of the uncus and amygdala nuclei, and in the hippocampal, cingulum and dentate gyri. Case 2 had an undifferentiated non-metastatic lung carcinoma removed six months after onset of neurological symptoms, while two others had clinically unsuspected cancer at postmortem examination. Case 1 had a bronchial carcinoma restricted to a mediastinal lymph node without a primary lesion, while

Case 3 had an unsuspected oat cell carcinoma infiltrating the main bronchi of both lungs and adjacent mediastinal nodes. A decade earlier, Henson, et al. [3] described a patient with subacute cerebellar degeneration and concomitant features of subacute motor neuronopathy prior to discovery of occult breast carcinoma. Postmortem examination showed spinal cord anterior horn cell loss accompanied by focal lymphocytic inflammation, crescentic anterolateral cord demyelination sparing pyramidal tracts, and Wallerian motor nerve degeneration in the legs. The target antigen, Ri or anti-neuronal nuclear antibody type 2 (ANNA-2), named for the patient in whom it was identified, became synonymous with paraneoplastic opsoclonus myoclonus ataxia (POMA) syndrome and breast cancer. Younger, et al. [4] extended that association in recognizing its occurrence in a patient with subacute motor neuronopathy (SMN). That patient's antiserum and cerebrospinal fluid (CSF) recognized a 55 kD antigen present in tumor nuclei and the nuclear neuronal antigen Nova1 [5] expressed in the developing subcortical brain and ventral spinal cord motor system of humans and rodents [6,7], and to Nova2, expressed in rostral neocortex [8].

A second intracellular onconeuronal serum and CSF autoantibody termed Yo or Purkinje cell antibody type-1 (PCA-1) was recognized by Greenlee & Brashear [9] and later by Giometto, et al. [10] as the cause of paraneoplastic cerebellar degeneration (PCD) demonstrating reactivity of to both ovarian carcinoma nuclei and cerebellar Purkinje cell neurons. At the same time, the investigations of Posner, et al. [11,12] focused on small-cell lung cancer (SCLC)and series of patients with a spectrum of encephalitic disorders, ranging from pure limbic encephalopathy to a diffuse and lethal encephalomyelopathy, frequently accompanied by dorsal root ganglionopathy. These patients shared a common feature, harboring high-titer autoantibodies, termed Hu or anti-neuronal nuclear antibody type-1 (ANNA-1) [11-14] against a family of neuron-specific RNA binding proteins, termed HuB, HuC, and HuD [15,16]. In the same year, 1991, Szabo, et al. [17] described the paraneoplastic encephalomyelitis (PEM) antigen, and Dalmau, et al. [18] described the clinical findings of 71 patients with anti-Hu and SCLC-associated PEM/sensory neuronopathy (PEM/PSN).

According to Darnell [19] the reason why some patients presented with what appeared to be the same autoantibody but quite different disease symptoms was unknown, but the achievements in SCLC-associated PEM sketched a model for the pathogenesis of paraneoplastic encephalitis [16,20]. In this model, the SCLC triggered the neurological disorder by immune-mediated action at a distance. The hypothesis was that the normal neuron-specific nature of expression of the HuB-D proteins related to its ability to trigger an antitumor immune response to nascent lung cancer cells. In some patients, the tumor immune response was then linked to immune recognition of neurons normally expressing the Hu proteins, leading to neurological symptoms.

Other syndromes associated with paraneoplastic encephalitis were elucidated by Dalmau, et al. [21,22] in their descriptions of anti-MA1 and MA2 and testicular cancer; and the collapsin response mediator protein-5 (CRMP5/Cv2) in association with thymoma [23]. Each with an intracellular target antigen, the resultant histopathology of these antibodies generally consisted of infiltrative cytotoxic (CD8+) T-cell destruction of neurons, with variable IgG and complement deposits in the CNS and dorsal root ganglia (DRG) (in the anti-Hu cases), and fewer helper (CD4+) T-cells, and generally absent B-cells. Bernal, et al. [24] and Blumenthal, et al. [25] illustrated the role of infiltrating CD8+ T-cells in cell death by showing their close opposition to neurons.

In 2000, Bien, et al. [26] & Mori, et al. [27] described several patients with non-paraneoplastic LE. The interface of strictly paraneoplastic and autoimmune mechanisms was subsequently highlighted in the characterization of patients with stiff-person syndrome (SPS) associated with antibodies to glutamic acid decarboxylase (GAD); and the clinical neurological syndromes associated with voltage-gated potassium channel (VGKC)-complex antibodies.

The formulation of the relation of GAD antibodies to SPS has been especially instructive in understanding how far the science of autoimmune neurologic disorder has advanced. In 1988, Solimena, et al. [28] investigated the existence of non-paraneoplastic CNS autoimmunity in a patient with SPS, epilepsy and type-1 diabetes (T1D, and increased titers of oligoclonal CSF IgG. Both the serum and CSF produced identical intense staining of all gray-matter regions.GAD65 was thence an important autoantigen in T1D, being highly expressed in the cytoplasm of pancreatic β cells. GADderived peptides were presentable by main histocompatibility complex (MHC) class I molecules and recognized by CD8+ T-cells on the surface of β cells [29]. Activation of CD8+ GAD specific T-cells further differentiated into memory cells suggesting a pathogenic role in T1D [30]. However, only patients with very high titers of GAD were associated with LE [31], and they typically presented with recent-onset temporal lobe epilepsy (TLE) and intrathecal secretion, defining a form of non-paraneoplastic LE. Other patients

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within the SPS spectrum harbored antibodies against other proteins of the GABA ergic synapse, including amphiphysin and gephyrin, which were found to associate with lymphoma, and malignant tumors of the breast, colon, lung, and thymus [32].

Contemporaneously, the clinical phenotypes associated with autoantibodies to VGKC-complex ranged from peripheral nerve hyperexcitabiity (PNH), to Morvan's syndrome (MoS), and LE and autoimmune epilepsy [33,34]. VGKC-complex antibodies were detected in a patient with MoS [35] and subsequently described in 2 patients with LE [36]. Both patients were negative for typical paraneoplastic antibodies and with near-complete recovery, including one with recurrent thymoma after plasma exchange, while the other patient recovered spontaneously without specific immunotherapy. The immunoprecipitation of VGKC-complexes linked a number of clinical syndromes that might otherwise have remained separate.

By 2010, Graus, et al. [37] classified neuronal antibodies associated with syndromes resulting from CNS neuronal dysfunction into two groups according to the location of the target antigen. One group of well-characterized autoantibodies that recognized intracellular neuronal antigens included Ri, Yo, Hu, Ma2, CRMP5/Cv2 and GAD. These so called onconeural antibodies were useful in the designation of a specific paraneoplastic neurological disorder [38-40]. Bien, et al. [41] described qualitative and quantitative immunopathologic features of biopsy or postmortem brain tissue in 17 cases of autoimmune encephalitis (AE) associated with intracellular (IAg) (Hu, Ma2, GAD) or surface antigens (SAg) (VGKC-C and NMDA). Their studies noted higher CD8+/CD3+ ratio and more frequent appositions of granzyme-B-positive (GrB)(+) cytotoxic T-cells to neurons, with associated cell loss in the IAg-onconeural group compared to those in the SAg group. The exceptions were GAD cases that showed less intense inflammation and relatively low CD8/CD3 ratios compared to the IAg-onconeural cases. A role for T-cell-mediated neuronal cytotoxicity was found in encephalitides with antibodies against IAg, 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 & Bien [42] 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, they pointed out, the imputed antibody first had to transit the blood-brain barrier (BBB) and then the cell membrane of the target cell to a location where it could bind the pathogenic intracellular antigen. Depending uponprotein conformation and folding, the antigenic site might be readily accessible before inactivation and ensuing irreparable cell damage. It is difficult to imagine that an intracellular antibody could easily overcome each of these obstacles. Although there have not been in vivo studies revealing neuronal cell death due to infiltration with onconeural antibodies against putative IAg, in vitro studies have shown somewhatcontradictory results, with earlier studies demonstrating accessed cultured neurons without damage [43] and later ones demonstrating induction of cell death after antibody uptake [44]. 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 [45]. Vasculitis has not been a recognized mechanism of injury in intraneuronal antibodies, either in life or at postmortem examination.

The past decade witnessed the emergency of serum autoantibodies against SAg and synaptic-enriched regions leading to LE that spared the cytoplasm and nuclei of neurons, such as those against GluN1 or GluN2/3 synaptic subunits of N-methyl-D-aspartate (NMDA) [46] and glycine receptors [47]; and to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [48]. Several novel neuropil antigens that localized to the cell surface of neurons and dendritesco-localized with synaptophysin and spinophilin [49].

Supportive of LE or AE, these new antibodies shared the property of strong immunolabeling of areas of dense dendritic network and synaptic-enriched regions in the neuropil of hippocampus, sparing most neuronal cell bodies. The clinical phenotype associated with the novel neuropil antibodies included dominant behavioral and psychiatric symptoms and seizures. With inconstant features of cognition and memory, brain-magnetic resonance imaging (MRI)and 2-deoxy-2-[fluorine-18] fluoro-D-glucose (18F-FDG PET) abnormalities were less frequently restricted to the medial temporal lobe than in patients with classical paraneoplastic and VGKC-complex antibodies.

A role for the autoimmune dysfunction in neuropsychiatric illness has been sought since the 1930s when autoantibodies were first reported in a schizophrenia patient [50]. Since that time, there have been reports of specific autoimmune responses to self-antigens in psychosis, affective disorders, and other neurobehavioral abnormalities [51,52]. Clinical

neurologists, neuroscientists and psychiatrists, all have a stake in the emerging link between autoimmunity and resulting neurologic and psychiatric disorders in AE [53].

Autoimmune Encephalitides

One autoantibody associated with LE targetsan IAg (GAD65 receptor) and three target neuronal SAg (NMDA receptor, VGKC-complex, and AMPA receptor). Classically, symptoms associated with them evolve over days to weeks and include neurocognitive and neurobehavioral manifestations as diverse as short-term memory loss, sleep disturbances, seizures, irritability, depression, hallucinations, and personality change, implicating inflammatory involvement of the limbic system, which includes the medial temporal lobes, frontobasal and cingular regions.

Anti-Gad65 Encephalitis

Background

Autoimmunity targeting the 65 kilo Dalton (kDa) isoform of GAD65 encompass diverse autoimmune disorders such as T1D and rare neurologic disorders including LE, temporal lobe epilepsy (TLE), cerebellar ataxia, and large and small fiber peripheral and autonomic neuropathy [54].

Epidemiology

A review of adult-onset SPS showed a prevalence estimate of 1 in 1,250,000 [55] with a predominance of women, and average age of onset of 40 years [56]. The frequency of high titers of anti-GAD antibodies defined an RIA value >1000 IU/ml in TLE of unknown origin is 21% [57] of cases, with the highest titers related to TLE. Affected patients were 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 OCB, and aratio of serum/CSF GAD antibody levels>1 suggesting intrathecal synthesis. Malter, et al. [58] 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 equally common to VGKC-complex antibodies but differed in younger age, female sex, and presentation of first seizure, CSF oligoclonal bands, and intrathecal autoantibody synthesis.

A recent retrospective analysis of patients with paraneoplastic neurologic syndromes from 1995 to 2013 (58) defined by the criteria of Graus, et al. [59] detected high GAD antibody levels (>2000 U/mL) by RIA in 15 patients. Six patients (40%) presented with encephalitis (5 typical LE); 6 PCA, 2 SPS, 1 POMA, 1 PEM, and 1 with a syndrome of vertigo, ataxia, axial rigidity and dysautonomia. Sixpatients had lung cancer (4 SCLC), 4 neuroendocrine tumors (2 pancreas and 2 thymic carcinoids), 2 thymoma, 2 breast cancer, and 1 patient had non-Hodgkin lymphoma. Cancer preceded the neurological diagnosis by a median delay of 3 months. In 3 tumors so studied (2 pancreatic and 1 thymic carcinoma), all expressed GAD65 antigenicity. In a comparison to 106 patients with non-paraneoplastic neurological syndromes, the latter group had encephalitis in 16% (none LE); with nearly equal prevalence of PCD and SPS (67%), and 18% isolated epilepsy. Patients with high levels of GAD antibodies, and classic or other neurological syndromes not typically associated with GAD antibodies, were at higher risk for an underlying cancer.

Clinical Aspects

Gangnon & Savard [60] reviewed the clinical experience of 58 cases of GAD65-antibody LE beginning with the first reported case [61] inclusively through 2016,in 7 observational studies, 3 case series, and 21 published case reports [31,49,62-88]. They provide a useful summary of the literature of anti-GAD65 associated LE. Among the 58 cases, there were 21 children and 37 adults, 59% of whom were female, with a median pediatric age of 10 years (range 1-17 years) and mean adult age of 39 years (range 19-70 years). 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. Less common clinical manifestations included fever, dysautonomia, cerebellar incoordination and headache respectively in 8 (12%), 7 (12%), 4 (7%), and 3 (5%) cases. The most common seizure presentation was

refractory status epilepticus. Mild muscular rigidity [62] and SPS [71] were diagnosed in 2 cases, as well as myoclonus [68,73,74] and facial cramps [62] in 4 others.

Cellular and Synaptic Antibody Effects

The structural biology of GAD autoantigen has been previously reviewed [89]. Low titers of anti-GAD65 antibodies, generally <20 nmol/L occur in T1D and in the general population, while cases of anti-GAD65-associated neurological disorders including LE are seen in the hundreds of nmol/L. Two GAD isoforms with distinct localizations and functions, GAD65 and GAD67, are expressed in presynaptic CNS GABAergic neurons, and in pancreatic ⍰ ⍰ cells. Glutamic acid decarboxylase converts L-glutamate to GABA using pridoxal-5'-phosphate (PLP) as a cofactor. GABA is the commonest inhibitory neurotransmitter in the CNS and the ligand for the inhibitory voltage-gated chloride channel GABAA, and G-protein coupled GABAB receptors. GAD67 commonly coexists with GAD65 antibodies in patients with neurologic autoimmunity. However GAD67 is rarely an autoantigen in isolation, found predominantly in the cytoplasm where it produces basal levels of GABA; whereas GAD65 is located predominantly in nerve terminals anchored to the cytoplasm-facing side of synaptic vesicles where it believed to synthesize GABA for neurotransmission supplementary to basal levels. The classification of high titers of anti-GAD65 autoantibodies has bene problematic in being grouped with onconeural autoantibodies directed at an IAg [41] since they are not consistently paraneoplastic in origin.

Laboratory Investigations

Adominant clinical phenotype of seizures, neurocognitive and neuropsychiatric disturbances in most patients with anti-GAD-autoantibody associated LE has been explained by the frequent involvement of the medial temporal lobes; an inflammatory CSF with intrathecal secretion of the anti-GAD65 autoantibody, and oligoclonal bands. Bien, et al. [90] described a 24-year-old woman with frequent temporal lobe seizures, non-paraneoplastic LE, and a serum anti-GAD65 antibody titer of 1:32,000, in whom T2/FLAIR MRI evolved over a period of 8 months, demonstrating right hippocampal swelling and signal increase to sclerosis and atrophy on MRI commensurate with clinical progression. The same authors [41] extended their findings to two other patients age 18 and 31 years, with a respective duration of disease of 127 and 115 months, manifesting refractory temporal lobe seizures and LE. The latter patient showed similar evolution of medial temporal atrophy in the context of T2/FLAIR hyperintensities during the disease course. The remaining patient who had unilateral encephalitic T2-hypersignal in the left amygdala was found at the time of epilepsy surgery to have a normal MRI without medial temporal brain atrophy despite a 10-year disease history.

Among 58 literature patients [60], 45/58 (78%) patient MRIs were abnormal with specific involvement of the temporal lobes in 34 (59%), and multifocal abnormalities in 9 (16%); and 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 so studied in 41 cases, showed pleocytosis in 11 (27%) with white blood cell (WBC) counts ranging from 7 to 114 cells/ul; and present oligoclonal bands in one-half of cases. Hyponatremia was identified in 3 cases. There were significantly elevated titers of anti-GAD65 antibodies in both serum and CSF in 35 patients; and in either serum (in 18) or CSF alone in 3. Concurrent antibodies were reported in 11 cases, including those to GABAA in 5 cases, and VGKC-complex or GABAB in 3 cases. Antibodies to NMDA receptor and AMPAR, and on coneural antibodies were all absent.

FDG brain PET imaging and MRI were complementary in 50% of cases [49]. Combining both MRI and PET, all patients had temporal lobe abnormalities. EEG may be useful in classifying the seizure type and directing the use of anticonvulsants especially when clinical seizures lack motor convulsions.

Histopathologic Correlation

The clinicopathologic features of anti-GAD antibody LE were described in a woman [90] who presented with frequent complex temporal lobe seizures at age 23. Over 8 months there was an evolution of right hippocampal swelling and signal increase on T2/FLAIR MRI to sclerosis and atrophy. At the time of epilepsy brain surgery CSF showed 10 WBC and oligoclonal bands. Right-sided selective amygdalohippocampectomy of the sclerotic hippocampus showed strong encephalitic features. High-dose corticosteroid therapy administered over several months resulted in seizure-free status until she was weaned off them 2.4 years later when she developed Cushing syndrome. She lapsed into a series of temporal lobe seizures and memory impairment accompanied by temporal left hippocampal swelling for which long-term corticosteroid and azathioprine therapy was started with slow clinical improvement. At follow-up 3.7 years later, she was still experiencing frequent partial temporal lobe seizures with memory deficits.

Bien and colleagues [41,90] summarized the histopathologic features of selective amygdalohippocampectomy of the sclerotic hippocampus in this patient that 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 that 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 2. Surviving neurons were positive for MHC class I, fulfilling the prerequisite for attack by CD8+ T-cells.

Bien, et al. [41] quantitated the number of parenchymal T-, B-, and plasma cells, macrophages and glial cells in 3 cases of anti-GAD65 autoantibody LE. Their analysis which included one previously reported case [90], differentiated anti-GAD65 cases from others with IAg-onconeural autoantibodies (Ma2 in 3 cases; Hu in 4 cases); SAg autoantibodies targeting VGKC-complex (4 cases) and NMDA receptor (3 cases), compared to cases of 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. That ratio was lower than in the parenchyma confirming thatCD8+ T-cells migrated into the parenchyma more readilythan CD4+ T cells. Apposition of multiple GrB+ lymphocytes to single neurons, consistent with a specific cytotoxic T-cell attack in case GAD/3 [90]. Bien, et al. [41] 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 indicative of complement activation was negative in the IAg GAD cases. CD68+ cells comprised 0.2% in the IAg-GAD cases.

The finding of a reduced CD8+/CD3+ ratio of the IAg-GAD cases, all without concomitant tumor, was lower than the IAg-onconeural group. It was also within the highest ratios of the SAg group of NMDAR cases compatible with the hypothesis that T-cells were a necessary aspect for neuronal loss and hippocampal atrophy in the 2 GAD-associated LE (in GAD cases 2 and 3).Notwithstanding, the absence of an underlying malignancy could contribute to the long duration of disease and overall less intense inflammation.

As noted by Bien, et al. [41], the pathogenic role of GAD antibodies has not been certain because of the different associated clinical syndromes (SPS, cerebellar ataxia, TLE and LE). Multiple antibodies against IAg and SAg may explain the relatively low CD8+/CD3+ and GrB+/CD3+ ratios in the IAg-GAD cases.

Diagnosis and Treatment

The diagnosis of anti-GAD LE is justified in patients with a clinical syndrome of temporal lobe seizures, and cognitive and psychiatric disturbances, brain MRI abnormalities on T2FLAIR MRI implicating the medial temporal lobes; CSF pleocytosis and OCB; and EEG revealing temporal lobe epileptic or slow-wave activity, in association with high levels of anti-GAD65 autoantibodies by RIA. Most cases will fail to disclose an underlying malignancy.

In the series of 58 literature cases summarized by Gangnon & Savard [60] follow-up was available in 53 cases. Full recovery was noted in 4 (8%) cases, 3 of whom received corticosteroids alone, with intravenous (IV) immunoglobulins, or in combination with PE; a fourth case received no immunosuppressant therapy and recovered. Death occurred in 4 (8%) cases, 3 of whom had an associated cancer. Sustained improvement was noted in 23 (43%) cases with follow-up of 96 months. A favorable outcome was noted in 45% of cases with positive CSF GAD65 antibodies compared to 56% of those with antibodies only in serum.

Anti-Nmda Receptor Encephalitis

Background: In 2007, Dalmau, et al. [91] 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 receptor antibody appears 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 teratomas tumors of the ovary. All showed serum or CSF antibodies to the NMDA receptor.

A year later, the same investigators [46] described a case series of 100 patients with antibodies against NR1-NR2 heteromers of the NMDA receptor as measured by enzyme-linked immunosorbant assay (ELISA), 91 of whom were women, all with psychiatric symptoms or memory complaints. In addition, 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.

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Epidemiology

Given its characteristic disease course, it is now assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin would have anti-NMDA receptor encephalitis [92] representing about 1% of all young patients' admissions to intensive care units (ICU). A French study [93] noted a frequency of anti-NMDA receptor encephalitis of 2% in febrile encephalitis that may be an underestimate because it excluded children. A multicenter, population-based, prospective study showed that anti-NMDA receptor encephalitis accounted for 4% of case of encephalitis in the United Kingdom (UK) making it the most common cause of AE after acute demyelinating encephalomyelitis (ADEM) in children [94].

Clinical Aspects

Clinically, anti-NMDA receptor encephalitis commences with nonspecific prodromal symptoms of headache, fever, nausea, or viral-infection like illness [95], but over days to weeks, seizures, neurocognitive and neurobehavioral complaints emerge including memory loss and frank neuropsychiatric manifestations of insomnia, mania, anxiety, depression, and paranoia [96,97]. There can be movement disorders with oro-lingual-facial dyskinesia, autonomic manifestations, central hypoventilation, tachycardia and bradycardia [91,97]. Autoantibodies targeting the NMDA receptor occur with herpes simplex virus encephalitis (HSVE) [98]. Chorea was noted 10 days to 6 weeks after HSVE [92]. The eventual outcome of all patients was favorable in three-quarters who recovered or had mild deficits with immunotherapy, whereas one-quarter had severe persistent deficits or died. Relapses so noted in 25% to 30% of cases [99], were partly attributed to lack of treatment, while 12% of treated cases relapsed in the first two years in one long-term outcome cohort analysis [100].

Cellular and Synaptic Antibody Effects

Human embryonic kidney cells 293 (HEK293) ectopically expressing single or assembled NR1-NR2 subunits have been used to determine the epitope targeted by the anti-NMDA receptor, the extracellular N-terminal domain of the NR1 subunit. By quantitative analysis of the NMDA receptor in neuronal cell culture, there was a decrease in the numbers of cell-surface NMDA receptor, and NMDA receptor clusters in postsynaptic dendrites. Most patients with anti-NMDA receptor 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 [101] showed complement binding in vitro and in neural tissue of teratoma tumors, although not in the brains of affected patients.

Laboratory Investigations

Testing for NMDA receptor 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 since the disorder may be associated with normal MRI findings in up to 50% of cases. The remaining one-half may include non-specific changes and abnormal T2/FLAIR MRIhyperintensities in the mesial temporal lobe, cerebral or cerebellar cortex, basal ganglia or brainstem. There is typically no abnormal enhancement or hemorrhage. FDG brain PET may show hyper- or hypometabolism in the affected regions [102]. Up to 25% of patients have electrographic seizures (100). CSF analysis can show moderate lymphocytic pleocytosis, increased protein content, elevated IgG index, and CSF-specific oligoclonal bands [103] which were typically negative at first testing, but can become positive later with disease progression in up to one-half of cases [99].

Histopathologic Correlation

The histopathologic aspects of NMDA receptor encephalitis were studied in 14cases [41,46,101,104-107] including 9 at postmortem examination [101,104,107] and 5 in brain biopsy tissue [41,101,107]. Dalmau, et al. [104] 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, not single subunits, is 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 patient sage 14, 24 and 35 years of age (Cases 2, 6, 10) died, including one (Case 10) previously reported [105], 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 three showed pleocytosis varying from 115 (Case 10) to 219 WBC (Case 6) with minimally increased or normal protein content, and positive oligoclonal bands. Immunofluorescence microscopy experiments demonstrated co-localization of antigens reacting with patient antisera and antibodies against NR2B, and co-localization 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 three. Microglial nodules and neuronophagia were rarely seen. In all cases, these findings predominated in the hippocampus but also affected other areas of the brain, brainstem, and spinal cord. There was intense IgG immunostaining of the hippocampi resembling rodent-staining of NMDA receptor in brain sections without complement immunostaining. Subsequent studies by the same author [46] employing HEK293 cells determined that the main epitope targeted by the antibodies was the extracellular N-terminal domain of the NR1 subunit. Patients' antibodies decreased the numbers of cell-surface NMDA receptor and clusters in postsynaptic dendrites, an effect that reversed by antibody removal. Tüzün, et al. [106] extended the immunopathological analysis of Cases 6 and 10 reported previously by Dalmau, et al. [104] noting that lymphocytic infiltrates were uncommon, and were rarely noted in the perivascular and leptomeningeal regions or scarcely distributed in the 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 were noted in all areas of the CNS but most intense in the hippocampus, basal forebrain, and cervical spinal cord. Using HEK293 cells expressing NR1/NR2B, the NMDA receptor IgG were mainly IgG1, but included IgG2 and IgG3 types. Tumor samples exhibited NR1/NR2-expressing tumor cells in varying amounts.

Camdessanché, et al. [107] reported the postmortem findings of a brain biopsy specimen from an 18-year-old woman with NMDA receptor 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 WBC and oligoclonal bands. A frontal lobe showed that showed perivascular cuffing of CD20+ B-cells and a few CD138+ plasma cells, with few CD3+ T-cells or CD68+ macrophages scattered throughout grey and white matter and in perivascular spaces. Retrospective screening for anti-NMDA receptor 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, et al. [101] described 2 men, age 7 and 59 years, and three women age 5, 24 and 35 years, the latter two with ovarian teratomas, and anti-NMDA receptor 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 protein elevation ranging from 94 to 219 mg/dL with oligoclonal bands; and brain MRI showed increased FLAIR signal in medial temporal lobes (Case 1), parietal cortex (Case 2), left temporal cortex (Case 3), and 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 one patient who underwent a brain biopsy was effective, while the others died. One patient who died underwent earlier brain biopsy, and the remaining three patients were studied at postmortem examination. Patients' antibodies were able to fix complement on cultures of rat hippocampal neuron but were not detected in any of the brain regions of 3 patients, or in biopsies of 2 patients, all with anti-NMDAR encephalitis. The main histological findings were an abundance of infiltrating CD138+ plasma cells and plasmablasts in perivascular regions cuffing blood vessels, Virchow-Robin spaces, and lining the meningeal-brain surface in proximity to the CSF. Using cultures of rat hippocampal neurons, the patients' antibodies were able to fix complement but deposits of IgG were absent, nor was there complement immunostaining at postmortem examination or in brain tissue biopsies. In contrast to brain, tumor neural tissue showed complement immunoreactivity.

Bien, et al. [41] examined brain biopsy tissue from 2 women and 1 man, age 17 to 22 years with NMDAR encephalitis, all three 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 one 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 elevated, and there were cytotoxic granules in some parenchymal T-cells, but no opposition 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 NMDA receptor antibody-positive patients showedalmost no inflammation, and no

clear signs of neuronal loss. Even though NMDA receptor antibodies appeared to be involved in the clinical disease process, there was no evidence to suggest a classical 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 NMDA receptor 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 NMDA receptors. This was supported by the experimental finding of Hughes, et al. [108] 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 appear to be the cause of the specific titer-dependent and reversible loss of NMDA receptors. The loss of the subtype of glutamate receptors that eliminates NMDA receptor-mediated synaptic function may underlie the learning, memory and other behavioral deficits observed in affected patients.

Diagnosis and Treatment

Suggested criteria for the definite diagnosis of anti-NMDA receptor encephalitis [109] includes 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; and abnormal EEG that shows focal or diffuse slowing or epileptic activity; and CSF pleocytosis or oligoclonal bands.

Prompt diagnosis of anti-NMDA receptor 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 disorderemployingIV immunoglobulins, corticosteroids, cyclophosphamide, or rituximab.

Given its characteristic disease course, it is now assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin would have anti-NMDA receptor encephalitis [92] representing about 1% of all young patients' admissions to ICU. A French study [93] noted a frequency of anti-NMDA receptor encephalitis in 2% in febrile encephalitis that could be an underestimate because of the exclusion of children. A multicenter population-based prospective study showed that anti-NMDA receptor encephalitis accounted for 4% of case of encephalitis in the UK, making it the most common cause of AE after ADEM in children [94].

Anti-Vgkc-Complex Encephalitis

Background

About the same time that MoS was described, anti-VGKC-complex antibodies were determined using by Buckley [36], Schott [110], Thieben [111] & Vincent, et al. [33] using RIA in patients with noninfectious AE. While the disorder was generally termed LE, the term limbic encephalopathy was also used as more patients were found to be seropositive without evidence of classical features of hyperintense signal intensities in the medial temporal lobes on brain MRI, and CSF inflammation [33,112].

Alteration of trans-synaptic scaffolding systems in AE that affects neuronal cell adhesion moleculesare crucial for proper synapse formation and adhesion, plasticity, and function. In both developing and mature neurons, these molecules serve to recruit and anchor pre- and postsynaptic proteins to appropriate synaptic localizations, allowing for normal synaptic transmission. Autoantibodies against the VGKC-complex detected by RIA in the sera of patients with AE do not bind directly to VGKC-complex channel proteins proper, but instead to synaptic and axonal neuronal proteins that coprecipitate with detergent-solubilized VGKC [113,114].

Attention has focused on identifying the principal autoantigens in the VGKC-complex and expanding the spectrum of corresponding phenotypes. Initial reports [115,116] suggested that patient antibodies were bound to the VGKC Kv1.1 and Kv1.2. Subsequent studies showed that leucine-rich glioma-inactivated protein 1 (LGI1) LGI1, and contactin-associated protein-like2 (Caspr2) were the main autoantigens [113,114,117] associated with transiently expressed axonal glycoprotein (TAG1), post synaptic density protein-Drosophila disc large tumor suppressor-zonula occludens-1 protein (PDZ), and ankyrin-spectrin protein, in both the peripheral and CNS. Antibodies against contactin-2 usually occur in association with those targeting LGI1 or Caspr2 were identified in other disorders [118] raising doubts about

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their importance. There is a diversity and overlap of neurological phenotypes associated with VGKC-complex-IgG in the serum and CSF, and distinct Ig-subtype specificity. The commonest presentation of VGKC-complex autoantibodies is LE in the CNS, and neuromyotonia or MoS in the periphery [119].

Epidemiology

In the UK, where the incidence of encephalitis is estimated at 5.23 cases/100,000/year based upon admissions to the National Health Service between 2005 and 2009, Granerod, et al. [120] estimated the incidence of encephalitis as 4.32 cases/100,000 population/year. A capture–recapture model estimated the incidence of encephalitis to be 8.66 cases/100,000/year. Two percent of patients (n = 216) had >1 encephalitis admission during the study period; and the incidence did not change (4.20 cases/100,000/year) 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/year (95% CI 2.39 cases–3.10/100,000/year). The results of multivariable analyses showed that compared with 2005–2006, incidence in all subsequent years was slightly higher but with little evidence of a trend (p = 0.19). The incidence rate was highest among patients <1 year of age, and in those >65 years of age. A retrospective study that reviewed antibodies to VGKC, LGI1 and Caspr2 in 46 children with severe acute encephalitis identified only one affected child (2.2%) among 46 children [121].

Clinical Aspects

Among 64 patients with VGKC-complex encephalitis [122] the clinical features overall 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 [111,33,99] typically evolved over days to weeks, occasionally acutely, but more often insidiously over months before coming to medical attention.

The finding of an apparent dementia in 72 affected patients was studied by Flanagan and colleagues [123]. 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, et al. [112] 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 treated with immuno-modulatory therapy leading to near complete recovery. Bettcher, et al. [124] delineated cognitive strengths and weaknesses among 12 subjects 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 (10/10) and basal ganglia (2/10). Serial cognitive examination revealed heterogeneity in cognitive function.

Seizures that occur in up to 90% of cases are most commonly focal in nature, 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 associations to LE associated with LGI1 antibodies. FBDS consist of brief frequent episodes abnormal unilateral and bilateral movements of the arms, sometimes the ipsilateral muscles of the face, and more rarely the leg. Video electroencephalography shows an epileptic origin of these myoclonic-like movements however regular EEG with scalp electrodes often misses an interictal focus. If FBDS 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 [125].

Kalachikov, et al. [126] 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 prevents production of full-length protein from the affected allele. Although LGI1 haploin sufficiency causes ADLT, the underlying molecular mechanism that results in abnormal brain excitability has instead been attributed to dysregulation of synaptic AMPA receptors in hippocampal neurons in the epileptic LGI1 knock-out mouse [127]. Fukata, et al. [128] proposed that extra cellularly secreted LGI1 linking two 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

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selectively reduces AMPA receptor-mediated synaptic transmission in the hippocampus.

Younger [129] described new-onset FBDS and memory disturbances in association with distal large and painful small fiber peripheral neuropathy, 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. Sleep disorders were noted in a group of patients with antibodies to VGKCs, without further specification of the target antigen [130]. Affected patients with LE may develop myoclonic movements resembling Creutzfeldt-Jakob disease [113,131].

Neuropathic pain as a manifestation of VGKC-complex autoimmunity was noted in 316 (4%) of 1,992 patients evaluated neurologically at a tertiary referral center [132] that was typically sub-acute in onset, nociceptive, regional, or diffuse. In those 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 hyper excitability. 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%). Bennett & Vincent [133] conjecture that VGKC-complex antibodies lead to enhanced excitability of the somatosensory system noting that Caspr2 is an adhesion molecule that forms a complex with Kv1.1 and 1.2 in the juxtaparanodal region of the node of Ranvier capable of modulating intermodal resting potential. Its effects could also operate on the soma of C-fiber nociceptors that express VGKC currents, blockade of which could enhance neuronal excitability. Analogously, voltage-gated sodium channels were deemed responsible for the generation and conduction of action potentials in the peripheral nociceptive neuronal pathway where NaV 1.7, NaV 1.8, and NaV 1.9 sodium channels (encoded by SCN9A, SCN10A, and SCN11A) are preferentially expressed [134].

Autonomic involvement was noted in 29% of the cohort studied by Klein, et al. [132], and in 3 (60%) of the patients described by Lahoria, et al. [135]. Hypothermia was described in association with VGKC-complex antibody-associated LE in 4 patients [37], Patient 1 of whom had concomitant neuropathic patient, and in the absence thereof in the others who were conjectured to have otherwise disturbed hypothalamic thermoregulatory mechanisms as the cause for dysautonomia.

Cellular and Synaptic Antibody Effects: LGI1 is a secreted synaptic protein that associates with, and regulates Kv1.1 and Kv1.2, as well as AMPA [128]. Caspr2 is a transmembrane axonal protein of the neurexin IV super family that localizes to the juxtaparanode of myelinated axons, and its extracellular domain interacts with contactin-2 [136] where it connects with the cytoskeleton via protein 4.1B. Caspr2, contactin-2 and protein 4.1B, all of which are necessary to concentrate Kv1.1 and Kv1.2 channels in the juxtaparanode. Lai and colleagues [113,117] 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 AMPA receptor function, either indirectly by blocking LGI1-mediated regulation of these proteins or directly by disrupting the entire protein complex. A study involving application of serum from a patient with LGI1 antibodies to a hippocampal slice preparation showed effects similar to application of a Kv1.1 and Kv1.2 antagonist [137]. 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 autoimmune encephalitis, peripheral nerve hyperexcitability, and MoS. Peripheral nervous system manifestations may precede or follow those of the CNS by up to several years. Some affected patients may 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 [138-140]. Mice with a Caspr2 deletion show analogous behavioral defects and symptoms [141]. Interestingly, common variants of the CNTNAP2 gene in healthy individuals are associated with abnormal language processing and are a risk factor for autism [142]. 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, septate-like junctions of myelinating cells around the axonsmay explain this variability. The VGKC–complex antibody levels also broadly differ between the different syndromes, with highest levels in

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LE and FBDS, moderate levels inMoS, and lowest levels (often <400 pM) in PNH.

Laboratory Investigation: 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) [119,143,144], making the test unreliable as a screen for LE without further subtyping for LGI1 and Caspr2-IgG. So selected, 26% [3] to 28% [19] 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) [3], 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. Graus & Gorman [145] argued that the VGKC-complex RIA antibody test could be used as initial screening to select positive samples that could then be confirmed by LGI1 or Caspr2-IgG antibody subtyping, however the latter were also positive in selected VGKC-complex antibody-negative sera by RIA [144,146]. Paterson, et al. [147] 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 32/44 cases considered to be non-autoimmune, 4 (13%) cases of which were found to have a definite or probable paraneoplastic neurologic disorder, neuromyotonia or MoS. Ances, et al. [49] 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 [33].

Cerebral imaging studies in VGKC-complex antibody associated LE show highly variable results. Both mesial temporal lobe hypometabolism on FDG brain PET [148,149] and hypermetabolism have been described [150]. In a patient with VGKC-complex LE [149] who did not definitively demonstrate 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, et al. [150] identified 9/18 (50%) patients positive for non-paraneoplastic antibodies against neuronal surface antigens (VGKC or NMDA-R), 2 of whom displayed mesiotemporal hypermetabolism on FDG brain PET, with 4 others were rated normal, and 3 displayed hypermetabolism outside the mesiotemporal region. The fraction of abnormal scans employing MRI was lower (10/16; 62.3%) than FDG brain PET (14/18; 77.7%).

CSF results were equally variable in VGKC-complex autoimmunity. Jarius, et al. [151] 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 elevated total protein concentrations were present in 41% and 47%, respectively. A disturbance of the integrity of BBB was found in 6 (35%) patients based upon 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 [151] suggested an extrathecal origin of VGKC-complex autoantibodies. Vincent, et al. [33] reported the CSF findings in 10 patients, all with VGKC-complex antibody-associated LE, noting mild lymphocytosis and mild or moderately raised protein content in one-half. OCB were noted in 1 patient, while 6 other OCB 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 <1 and 10% of the serum, and beneath 10% in one patient with the lowest serum value.

Ten positive sera retested for binding to rat brain sections revealed 5 that were strongly seropositive by RIA and immunohistochemistry directed mainly against Kv1.1 and Kv1.2 subtypes of VGKC present in the molecular layer of the dentate gyrus of the hippocampus as previously shown by others [36,152,153]. These findings were consistent with extrathecal synthesis of VGKC-complex antibodies. It is of interest that NM brain SPECT imaging in the present patient [125] showed perfusion defects similar to 2 reported patients with FBDS and LGI1-antibody LE [125] that might explain passage of extrathecally-derived VGKC-complex antibodies across a disrupted BBB.

Irani & Vincent [122] estimated features of peripheral neuropathy in 1.6% of VGKC-complex antibody-positive LE cases. Lahoria, et al. [135] described five patients with painful polyneuropathy, all positive for VGKC-complex autoantibodies (range 0.08 to 1.18 nM), two 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

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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 [154], are most adequately assessed by epidermal nerve fiber density in a 3 mm punch biopsy of skin from the later calf and thigh [155], and a combination of cardiovagal, sudomotor and adrenergic functions tests [156] with comparison to controls.

Histopathologic Correlation

Eight patients with VGKC-complex LE were studied histopathologically, including stereotactic brain biopsy in 3 [33,41] at epilepsy surgery in 1 case [41], and at postmortem examination in 4 patients [41,157-159]. Vincent, et al. [33] described a 56-year-old man with7-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 0-100pM; >400 pM highly elevated). Histopathology of a stereotactic biopsy of the left amygdala showed positive staining for perivascular and parenchymal CD45+ lymphocyte infiltrates, astrogliosis, and CD68+ microgial activation. He was received a course of intravenous dexamethasone with a slight beneficial response with persistent memory deficits. Follow-up brain MRI showed evolution of bilateral hippocampus atrophy and signal changes.

Dunstan, et al. [157] 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. Cerebrospinal fluid was normal. Assay for VGKC antibodies were 1637 pM by RIA. He received anticonvulsants but deteriorated due to 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, et al. [158] 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 WBC. 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, and amygdala and midbrain.

Khan, et al. [159] reported a 56-year old man with a 4 month history of confusion, disorientation and seizures. A serum VGKC antibody titer was 3,327 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 pathological changes in both hippocampi and right amygdala regions comprised of 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 parahippocampus gyrus. There were perivascular infiltrates of CD20+ B-cells and a few CD4+ T-cells especially in the right hippocampus.

Bien, et al. [41] summarized the histopathologic findings in the brain of 4 cases, 3 men and 1 woman, age 33 to 68 years, with LE (3 patients) and multifocal encephalitis in another, 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 examination 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 GrB, 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 labelling (TUNEL) reaction in the same area demonstrated acute neuron cell death suggesting antibody and complement mediated neuronal cell damage in these patients. The authors [41] noted that IgG4 rather than IgG1 antibodies dominated in the sera of those with VGKC-complex LE. In light of the finding that immunoprecipitated dendrotoxin-labelled VGKC-complexes directed at GGI1, Caspr2 or other undefined components of the VGKC-complex [113,99], it is notable that one of the 3 cases with C9neo deposition was LGI1 seropositive, while the second was negative for both LGI1 and Caspr2. A third case that showed extensive C9neo deposition on neural somata and neuronal death was serologically indeterminate.

Diagnosis and Treatment

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 activityon 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 serological 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 employing IV immunoglobulins, plasma exchange, or corticosteroids, needing to advance to second-line agents including cyclophosphamide and rituximab.

Bataller, et al. [160] 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 (nCMAg) expressed in the hippocampus. If the autoantigens were unknown but found to be highly enriched in neuronal cells membranes of the hippocampus, these antibodies were likewise associated with a favorable outcome emphasizing the usefulness of immunohistochemistry with PFA-fixed tissue and cultures of live hippocampus rat neurons in the analysis of highly-suspected patients with LE. The salutary effect of immunotherapy in the management of seizures in VGKC-complex antibody-associated LE are well supported by the autoimmune basis of FBDS [161].

AMPA Encephalitis

Background

In 2009, Lai, et al. [161] characterized antibodies to GluR1 and 2 in 10 patients with LE that was often paraneoplastic yet treatment responsive with a tendency to relapse with an antibody-mediated pathogenesis in which the patients' antibodies altered the synaptic localization and number of AMPA receptors (AMPAR). Further studies by the same authors [162] in a larger cohort highlighted the presence of prominent neuropsychiatric features.

Epidemiology

This is a rare disorder and probably underreported with few cases and no large series from which to draw reliable population incidence estimates.

Clinical Aspects

Among 10 patients with AMPA encephalitis described by Lai, et al. [161], the median age of nine affected women and one man was 60 years (age range 38-78 years),who presented with subacute confusion, disorientation, short-term memory loss, and personality change. Four patients developed seizures. Neurological examinations were consistent with limbic encephalopathy. The clinical presentation among 22 additional patients [163] the most frequent presentation was also LE in 10 patients, however in ten patients, other symptoms heralded or accompanied LE including, seizures, behavioral change, psychosis, spasticity, optic neuropathy, sensory neuropathy, ataxia, behavioral change, aphasia, hemiparesis, involuntary movements, and autonomic dysfunction.

Cellular and Synaptic Antibody Effects

Antibodies to the ionotropic AMPAR target SAg of the GluA1 or Glu2 subunits, important in fast excitatory input to the brain [164]. Lai, et al. [161] employed immunoprecipitation to identify the primary antigens that manifested distinctive protein bands of about 100 kDA which when analyzed by mass spectrometry showed sequences derived from the GluR1/2 subunits of the AMPAR. Western blot analysis confirmed that the band precipitated by patients' antibodies contained both GluR1 and GluR2 subunits. Such antibodies were present in paired serum and CSF samples, and all had intrathecal synthesis. All affected patients' serum or CSF samples show intense neuropil staining on brain tissue immunohistochemistry and react with HEK cells co-expressing GluA1/2 subunits of AMPA receptor. Manifesting tumors expressed the same subunits by immunohistochemistry. Antibody binding to the receptor, with capping and internalization led to a decrease in synaptic AMPAR activity. Removal of antibodies from neuronal cultures restored receptor numbers and localization of AMPAR clusters [162]. Located in hippocampus and outer cortex, olfactory regions, lateral septum, basal ganglia, and amygdala [165], AMPAR trafficking plays a role in long-term potentiation (LTP) important in long-lasting increase in signal transmission between neurons forming the substrate for memory and learning. Brain-derived neurotrophic factor (BDNF) activates the kinase, mechanistic target of rapamycin

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(mTOR) that regulates GluR1 expression required for memory formation. A consequence of blocking of AMPARs is interruption of the learning process [165]. The disorder was paraneoplastic in association with thymoma, SCLC, and breast cancer [162], so noted in seven patients, including 5 diagnosed by the time of initial episode of LE, and 2 patients at first relapse of LE. Other cancers in addition included ovarian teratoma and thymus carcinoid tumors [163].

Laboratory Investigation

In 11 of 12 patients described by Höfrberger, et al. [162] who presented with LE, MRI showed unilateral (2 cases) or bilateral (9 cases) medial temporal increased T2/FLAIR signal abnormalities. EEG showed epileptiform activity in 5 patients, focal temporal slowing in 1, and diffuse slowing in 3 patients. CSF was abnormal due to pleocytosis in 5 patients or increased protein in 2 patients, with both together in 1; and normal 4 patients. Additional neuronal antibodies were found in six patients, including 3 each targeting the IAg-onconeural antibodies CRMP5 and amphiphysin; and SAg determinants on the GABAB receptor and NMDA receptor; the majority with associated tumors. In nearly all cases, the resulting clinical phenotypes were determined by the associated antibody-immune response rather than that of the AMPAR antibody syndrome.

Histopathologic Correlation

Two patients (Autopsy Case 5 and 9) died and underwent postmortem examination [162]. The first patient, a44-year-old woman with rapidly progressive change of behavior and confusion had an enlarged mediastinum, and serological studies demonstrating CV2/CRMP5 onconeural antibodies. She died of other causes. At postmortem examination, there was a thymoma. Neuropathological findings in the brain were consistent with LE including perivascular and interstitial inflammatory infiltrates, microglial proliferation, and astrocytosis that largely predominated in the hippocampi. Some of the interstitial infiltrates surrounded neurons, forming neuronophagic nodules, and were predominantly composed of CD8+ T-cells that expressed TIA-1. Autopsy Case 9, a 59 year-old woman with progressive memory loss and behavioral change died of other causes after clinical recovery of LE of other causes was free of systemic cancer. Neuropathological studies limited to the hippocampus revealed a pattern of LE that included mild perivascular lymphocytic cuffing and scattered foci of lymphocytes in the parenchyma, predominantly in the CA4 region. Microglial nodules were rarely identified.

Diagnosis and Treatment

This is a rare disorder with few confirmed cases. However, suspected patients present with a subacute onset of and rapid progression of working memory deficits, seizures, and psychiatric symptoms suggesting involvement of the limbic system. Supporting laboratory findings include unilateral or bilateral abnormalities on T2/FLAIR brain MRI involving the medial temporal lobes with CSF pleocytosis and EEG findings of epileptic or focal slow wave activity also involving the temporal lobes. The finding of increased titers of serum and CSF AMPA antibodies with intrathecal synthesis makes the diagnosis certain. There may be associated autoimmune or additional antibodies to IAg and SAg, and a high likelihood of a concomitant neoplasm.

Follow-up for a mean of 72 weeks was available from 21 of 22 cases studied by Höfrberger, et al. [162] who received first-line immunotherapy consisting of corticosteroids, IV immunoglobulins, or plasma exchange, and 5 others who received second-line biological therapies. Thirteen patients underwent oncologic treatments consisting of tumor resection, chemotherapy, and radiation therapy. At last follow-up, 10 patients has a partial favorable response and 6 patients had no response; and 5 patients died of cancer. Clinical relapse occurred in only one patient in the analysis by Höfrberger, et al. [162] but in 5 (50%) of patients reported by Lai, et al. [161]. In virtually all of those patients, the clinical response to treatment was also partial, consistent with a favorable response to immunosuppression, yet eventual neurological deterioration related to a prominent cytotoxic T-cell immunity notably in the setting of cancer.

Conclusion

Autoimmune encephalitis has provided a valuable link between the research and clinical realms, and at the convergence of neuroscience and psychiatry, with many autoantibody syndromes straddling the two worlds, all for the benefit of affected patients. Future research endeavors will be oriented toward understanding basic underlying mechanisms of these conditions, such as the cause, production and distribution of specific autoantibodies in the serum and CSF, and identifying with further precision the underlying autoimmune responses so important in pathogenesis and response to treatment.

Conflict of interests: The author denies any conflict of interest.

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