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Immunologically Mediated Dementias

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Abstract

Although most dementias are due to neurodegenerative or vascular disease, it is important to diagnose immunologically mediated dementias quickly because they can be both rapidly progressive and readily treatable. They usually affect function of limbic and cortical structures, but subcortical involvement can also occur. Because of the variety of symptoms and the rapid course, these dementias present a particular challenge to the clinician and may require evaluation and intervention in the inpatient setting. Diagnostic workup typically reveals evidence of an autoimmune process and, in some cases, cancer. In contrast to the neurodegenerative processes, many of the immunologically mediated dementias respond to immunomodulatory therapy.

Introduction

Most dementias are caused by neurodegenerative disease for which management is largely symptomatic and treatment options are limited. During the past several decades, an increased awareness of immune-mediated processes that compromise brain structures responsible for cognition and behavior has emerged. These diseases can be distinguished from neurodegenerative conditions by the typically subacute presentation, evidence of pathologic antibodies and/or extensive inflammation, an often focal presentation (eg, limbic encephalitis [LE]) and, most importantly, the potential for therapeutic intervention with immunomodulatory agents or treatment of the underlying cancer in the case of paraneoplastic disease [1•].

Immunologically mediated dementias may be divided into two broad categories, those in which 1) specific antigens and antibodies have been identified or 2) no specific antigen or antibody has been identified but there is evidence of cellular inflammation. This distinction is somewhat artificial because there is often overlap, but we make this classification (and have divided this article accordingly) because the etiology may sometimes be important for choosing the most appropriate treatment. This review discusses the clinical features, diagnostic approach, and treatment intervention for the immunologically mediated dementias. Certain autoimmune-mediated conditions that slowly over time can result in cognitive impairment, such as multiple sclerosis, are not included in this review. We begin with the specific antigen/antibody-associated dementias, such as the paraneoplastic diseases, the autoimmune-mediated channelopathies (eg, anti–voltage-gated potassium channel encephalopathy [anti–VGKC-E], anti–glutamic acid decarboxylase [anti-GAD] syndrome), Hashimoto's encephalopathy (HE), gluten sensitivity (GS), dementia, systemic lupus erythematosus (SLE), and Sjögren's encephalopathy. In many of these conditions, the antibodies are known to be pathogenic (eg, many paraneoplastic disorders and channelopathies). However, although antibodies or antigens have been identified for others, they may not be clearly pathogenic (eg, Sjögren's encephalopathy, HE, SLE, celiac sprue). The second part of this article discusses autoimmune

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dementias with no specific antigen/antibody but evidence of cellular inflammation, including Behçet's disease, sarcoidosis, and primary angiitis of the central nervous system (PACNS).

Immune-Mediated Dementia/Encephalopathy Associated With Specific Antigens or Antibodies

Paraneoplastic syndromes

The paraneoplastic syndromes are an inflammatory group of conditions that result in the production of anti-neuronal antibodies in the cerebrospinal fluid (CSF) and serum resulting in focal neurologic symptoms [2,3•]. These antibodies react with the neuronal proteins usually expressed by the patient's tumor and precede the detection of the underlying tumor in about 70% of patients [3•]. Syndromes relating to paraneoplastic disease include LE, cerebellar degeneration, opsoclonus-myoclonus, myelopathy, sensory neuronopathy, or diffuse weakness as in Lambert-Eaton syndrome [3•]. In general, patients with autoantibodies against cell membrane antigens, such as VGKCs and novel cell membrane antigens, have a more favorable response to treatment and prognosis than patients with antibodies against intraneuronal antigens [4].

Some investigators feel that the autoantibody profile is more indicative of the underlying neoplasm than it is predictive of a specific neurologic syndrome because many patients have more than one antibody, making it difficult to know which is responsible for the neurologic symptoms [2]. We also have found, however, that the syndrome can often suggest certain antibodies. For example, if a patient presents with a classic limbic encephalopathy with memory and behavioral features, we might test for anti-Hu, anti-CV2, anti-Ma2, anti-VGKC, and other antibodies as well as certain cancers (Table 1).

The most common paraneoplastic syndrome leading to cognitive and behavioral impairment is LE, in which the antibody response is produced against limbic system structures. A paraneoplastic LE (PLE) may result from antibodies produced from occult cancers [5]. LE also occurs without a known cancer [6,7•,8•]. At the same time, 40% of patients with LE do not have detectable central nervous system (CNS) antibodies [4]. Specific antigen/antibody-associated dementia or encephalopathy syndromes are discussed below.

Anti-Hu antibody—Hu is one of the most common intracellular antigens associated with limbic encephalopathy. Patients with anti-Hu antibodies who present with neurologic symptoms frequently are smokers and usually have small cell lung carcinoma [3•], but less than 5% of patients may never develop cancer [9]. The most common clinical presentation is LE or cerebellar degeneration, but other syndromes can include myelitis, epilepsia partialis continua, nonconvulsive status epilepticus, sensory neuronopathy, and central hypoventilation syndrome [9]. Immediate treatment of the underlying tumor may result in a more favorable prognosis [3•].

Anti-CV2 antibody—Anti-CV2 antibody (also called anti–collapsin response mediated protein 5 [anti-CRMP5]) is produced in thymoma and small cell lung cancer [3•]. Serum studies also may show other paraneoplastic antibodies, such as anti-Hu and anti-Zic [10]. Patients with cognitive symptoms present with an encephalomyelitis that rarely limits itself to the limbic system and results in cognitive and behavioral deficits secondary to involvement of frontostriatal and basal ganglia circuitry [11]. Other presentations include cerebellar degeneration, chorea, uveitis, optic neuritis, myelitis, and peripheral neuropathy [3•].

Anti-Ma2 antibody—Anti-Ma2 antibody is traditionally associated with testis germ-cell tumors but also can be found in older individuals with breast and non–small cell lung and

cancer [12]. It should be suspected in men younger than age 50 presenting with LE. CNS regions affected include the limbic system, diencephalon, and upper brainstem [12]. Patients may present with vertical gaze palsy, limb rigidity, and hypokinesis [9] and can also develop orofacial and jaw dystonia [13]. Sleep abnormalities, including excessive daytime sleepiness, narcolepsy, cataplexy, and rapid-eye-movement sleep disorders, can occur. Treatment consists of orchiectomy in males, immunotherapy (corticosteroids and intravenous immunoglogulin [IVIG]), and chemotherapy, resulting in resolution of neurologic symptoms in about 30% of patients [12].

Anti-NMDAR antibody—A form of LE is anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) antibody–associated encephalopathy from serum antibodies produced against the NR1-NR2 heteromers of the NMDAR [3•,14•]. It is most frequently found in younger women (median age, 23 years; range, 5–76) suffering from ovarian teratoma. Patients often have a prodrome of headache and/or fever followed by psychiatric symptoms (agitation, delusional thoughts, and hallucinations) and/or memory loss. Other findings include dyskinesias, altered consciousness, autonomic instability, and hypoventilation. Serum or CSF antibodies to the NR1-NR2 heteromers are diagnostic, but CSF levels are higher. CSF pleiocytosis and oligoclonal bands are common [14•]. MRI findings include increased T2/fluid-attenuated inversion recovery (FLAIR) signal in the cerebral/cerebellar cortex and meningeal enhancement [9]. Treatment is by tumor resection and immunosuppression [14•].

Anti-AMPAR antibody—LE due to positive anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies in the CSF was recently described in 10 patients. The median age was 60 years, and 90% of the patients were women. Most presented with an LE with the subacute (< 8 weeks) onset of confusion, memory loss, and behavioral changes. Some had seizures. The CSF showed pleocytosis with occasional elevated protein and the presence of oligoclonal bands. FLAIR MRI showed increased medial temporal lobe T2 signal. Seven patients had tumors. Although response to tumor treatment and immunosuppression was excellent, relapse was common [15•].

Anti-Ri antibodies—Anti-Ri (also called anti–neuronal nuclear antibody-2 [anti–ANNA-2]) antibodies most commonly result in opsoclonus-myoclonus (involuntary, arrhythmic, chaotic, multidirectional saccades with horizontal, vertical, and torsional components) along with other neurologic signs and, less commonly, with encephalopathy. Adults typically have breast cancer, ovarian malignancy, and small cell lung cancer [3•,16]. Some other paraneoplastic antibodies less commonly associated with LE are shown in Table 1.

Nonparaneoplastic syndromes

Anti–voltage-gated potassium channel encephalopathy—VGKC-E is an antibody-mediated LE in which anti-VGKC antibodies are directed against plasma membrane potassium channels [6]. VGKCs are responsible for repolarizing the nerve terminal following the action potential [8•,17]. These channels are widely distributed throughout the nervous system and, consequently, autoantibodies against the VGKC cause a variety of neurologic conditions, including neuromyotonia, Morvan syndrome, seizures, dysautonomia, and LE [6,7•,8•].

VGKC-E typically affects patients during middle age (range, 44–79 years) and has an acute-subacute course (< 6 months), but more chronic, prolonged courses (> 6 month) have been described [6,8•]. The most common symptoms of VGKC-E include cognitive impairment, complex-partial/secondary-generalized seizures, hyponatremia, myoclonus, and dyssomnia [7•,8•]. Cognitive dysfunction includes anterograde and retrograde amnesia, confusion, disorientation, and executive dysfunction, and behavioral manifestations include disinhibition,

confabulation, hallucinations, depression, agitation, and personality change [6,8•]. It can present as a rapidly progressive dementia and be mistaken for Creutzfeldt-Jakob disease (CJD) [7•]. The hyponatremia is thought to be secondary to the syndrome of inappropriate secretion of antidiuretic hormone [18]. By definition, patients with VGKC-E have an elevated VGKC antibody (> 100 pM) in the serum or CSF. Brain MRI often shows T2-weighted hyperintensity in the medial temporal lobes or other areas [6,7•]. CSF analysis is usually non-specific, with mild lymphocytosis, increased protein, and occasionally oligoclonal bands [6]. Although many cases of VGKC-E are associated with tumors [7•,19], such as small cell lung cancer and thymoma, most are not [6]. It is not clear if the tumors are related to the antibody expression. Importantly, patients tend to respond dramatically to immunosuppression, but relapses can occur [6].

Hashimoto's encephalopathy—HE is a rare encephalopathy associated with elevated antithyroperoxidase or antithyroglobulin antibodies. The prevalence is estimated at 2.1 in 100,000 subjects [20,21•,22]. The mean age of onset is between 45 and 55 years, and it occurs five times more frequently in women than in men [22]. Patients often have other autoimmune diseases, such as type 1 diabetes mellitus, SLE, and Sjögren's syndrome [23]. Patients may be hypothyroid, hyperthyroid, or euthyroid, but the diagnosis of HE should be made only when a patient has returned to a euthyroid state [22].

It has been suggested that HE has two different types of presentations. The first is a relapsing/remitting course with stroke-like episodes, and the second involves insidious onset of cognitive dysfunction with seizures in an older patient [24]. Seizure disorder can be found in 70% to 80% of patients with HE [22]. About 25% to 30% of patients may have stroke-like episodes consisting of lateralizing motor or sensory deficits in multiple vascular territories [25]. Other symptoms include tremor, ataxia, sleep disturbance, headache, psychosis, visual hallucinations, and myoclonus [22].

Antithyroperoxidase is more frequently elevated than antithyroglobulin antibodies [22,23]. However, because antithyroid antibodies are found in up to 10% of the general population, only high titers in the setting of encephalopathy should be considered clinically relevant, and thus other disorders must first be ruled out. Diagnosis is one of exclusion [26]. CSF lymphocytic pleocytosis and mildly elevated protein are common [22]. The electroencephalogram (EEG) is equally nonspecific, with findings ranging from slow-wave abnormalities to epileptic foci and even periodic epileptiform discharges as seen in CJD [27]. Brain MRI findings vary considerably and include generalized atrophy, periventricular white matter changes, and diffuse increased signal on T2-weighted sequences in the subcortical and cortical white matter [22,23]. Brain biopsy has shown nonspecific changes such as arteriolar mural lymphocytic infiltration, chronic perivascular inflammation, mild gliosis, and perivascular lymphocytic cuffing [22,23]. HE responds dramatically to immunosuppression, such as with high-dose corticosteroids (eg, intravenous methylprednisolone) [24]. Prolonged or repeat immunosuppressive treatment may be needed [21•,22].

Anti–glutamic acid decarboxylase antibody syndrome—Anti-GAD antibodies are associated with neurologic and nonneurologic syndromes (eg, diabetes). Neurologic presentations include stiff-person syndrome, progressive encephalomyelitis with rigidity and myoclonus, ataxia, seizures, oculomotor dysfunction, autonomic instability, and cognitive impairment [28,29]. Symptoms are thought to result from B-cell–mediated autoantibodies produced against the presynaptic epitopes on the enzyme GAD as well as the synaptic membrane protein (located on cytoplasmic side of cell membrane), amphiphysin [29]. Diagnosis is by detection of anti-GAD antibodies, which are present in the serum or CSF in 90% of patients [30]. Therapy may be symptomatic (eg, muscle relaxants for spasms) as well as disease modifying, such as with immunosuppression [29].

Gluten-sensitivity dementia—Gluten sensitivity (GS) is defined by seropositivity for gluten-induced autoantibodies and/or a condition that improves on a gluten-free diet (GFD). GS can cause a dementia syndrome [31]. The GS dementia syndrome is generally accompanied by at least one or all of the following: ataxia, myoclonus, seizures, headaches, and neuropathy [31,32•,33]. Progression can be rapid or slow and may be episodic or continuous [32•]. Manifestations of GS can include dermatitis herpetiformis, aphthous stomatitis, fatigue, osteoporosis, and malabsorptive syndromes. Only 30% of neurologic GS will also have gluten-sensitivity enteropathy (GSE), or celiac disease, an immune-mediated disease caused by gluten ingestion [33–36]. Although neurologic GS might be an epiphenomenon, alteration of symptoms with a GFD and certain studies suggest a causal relationship [33,37–39]. It may co-occur with other autoimmune disorders, most commonly hypothyroidism [34], and certain vasculitides [33,36].

One or all of the following GS antibody titers may be elevated: antigliadin (AG) IgG or IgA, antitissue transglu-taminase (ATTG) IgG or IgA, antiendomysial IgA or IgG. Certain HLA types are risk factors [33]. Antibody testing should be done before a GFD is begun and should include testing for AG IgG, AG IgA, ATTG IgA, and total IgA; if there is IgA deficiency, ATTG IgG should be tested [36]. If titers are positive, the small bowel should be biopsied [36]. The CSF in patients with GS dementia can show nonspecific inflammatory signs, elevated neuron-specific enolase, and elevated AG or ATTG antibodies [32•,39,40]. Brain imaging can show cerebral and/or cerebellar atrophy and/or cerebral calcifications as well as enhancing areas and/or patchy or confluent areas of T2 prolongation in cerebellar and cerebral cortical and subcortical white and gray matter [31–33]. Suspected diagnosis usually merits a trial of a GFD [31–33]. For rapid progression or failure of a GFD, IVIG, plasmapheresis, corticosteroids, or other immunosuppression might be helpful [31,36].

Sjögren's encephalopathy—Sjögren's syndrome is an inflammatory autoimmune condition that primarily affects the exocrine glands, resulting in destruction of the lacrimal and salivary glands. Most patients have an underlying systemic autoimmune disease such as rheumatoid arthritis or SLE, although some patients present with primary Sjögren's syndrome. Neurologic involvement occurs in about 20% of patients with Sjögren's syndrome [41]. Peripheral nervous system involvement, particularly sensory neuropathy, is more common than CNS involvement. Sjögren's encephalopathy is rare and can present as a rapidly progressive dementia, behavioral/frontal lobe disorders, and meningitis, but it also can resemble the relapsing-remitting form of multiple sclerosis [41,42]. Acute or chronic myelopathy, as well as motor neuron disease, can occur [41]. Peripheral neuropathy, including symmetric axonal sensorimotor neuronopathy, mononeuritis multiplex, polyradiculopathy, and cranial neuropathy (most frequently cranial nerves V, VII, and VIII), is another common neurologic manifestation [41]. Sjögren's syndrome has been reported to present with recurrent acute attacks of nonvasculitic autoimmune inflammatory meningoencephalitis with symptoms of fever, chills, headache, myalgias, delirium, and meningeal signs [43]. Brain MRI often shows white matter lesions, and many patients meet radiologic criteria for multiple sclerosis [44]. Diagnosis is often by lip biopsy. Treatment consists of chronic immunomodulatory therapy [44].

Systemic lupus erythematosus—SLE is a multiorgan systemic inflammatory process that occurs primarily in young women and is caused by auto-antibody production and immune complex formation [41]. Although a systemic illness, SLE eventually leads to neurologic and/or neuropsychiatric disease in 60% to 75% of patients. SLE probably attacks the CNS by three different mechanisms: antibodies directed against the brain parenchyma and spinal cord, antibody-mediated thrombosis/noninflammatory vasculopathy and, rarely, immune complex–mediated inflammatory vasculitis [41].

Patients usually present with neurologic disease early in the course of the SLE. One study showed that 60% of neurologic complications were noted 1 year after the diagnosis of SLE [41]. The course of illness has an acute-subacute onset with eventual remission. Common CNS presentations include cognitive dysfunction, mood disorder, psychosis, strokes, or seizures [45]. Brain biopsy may reveal CNS vasculitis, even when brain angiogram is negative [42]. Stroke can account for about 20% of neurologic symptoms in SLE patients and is usually associated with an antibody-mediated hypercoagulable state or cardiogenic embolism [42]. Thus, a common brain MRI finding is focal stroke with hyperintensity on diffusion-weighted imaging (DWI) sequences [46]. Antiphospholipid antibodies can be present and should be measured. However, recent studies have shown little relationship of antiphospholipid antibodies to increased stroke incidence [47]. Other neurologic presentations that result largely from a focal SLE-related vasculopathy include a optic neuropathy, transverse myelitis typically affecting the lumbosacral levels of spinal cord, and neuropathy (cranial neuropathy, symmetrical distal neuropathy, demyelinating neuropathy, mononeuropathy, mononeuritis multiplex, and autonomic neuropathy) [41].

Immune-Mediated Dementia/Encephalopathy Not Associated With Specif c Antigens or Antibodies

Sarcoidosis

Sarcoid is a granulomatous multisystem disease that results in inflammatory responses most commonly in the lungs, eyes, and skin. The highest annual incidence occurs in northern European countries (5–40 cases per 100,000), and it affects black Americans three times as frequently as white Americans. About 25% of patients with sarcoidosis present with neurologic symptoms [48]. The most common presentations include cranial nerve palsies, headache, and ataxia. Neurosarcoid may also affect the intracranial vessels, leading to a granulomatous angiitis of the CNS [49]. Cognitive changes occur in up to 26% of patients, and many cases of rapidly progressive dementia have been described [50]. Contributing factors to cognitive impairment include parenchymal inflammation, hypercalcemia, and elevated intracranial pressure secondary to space-occupying lesions [50].

Behçet's disease

First described by Turkish dermatologist Hulusi Behçet in 1937, Behçet's disease is characterized by uveitis, oral aphthae, and genital ulcerations [51]. The cause is unknown [42]. Neurologic involvement (neuro-Behçet's) varies from as low as 5% (often manifesting with behavioral problems [eg, personality changes]) [52,53] to as high as 50% [42]. Patients can have cognitive impairment with amnesia and a frontal dysexecutive syndrome as evidenced by neuropsychological testing [54]. It has been suggested that parallel cortico-subcortical circuits connecting different parts of the cortex with the caudate and thalamus might account for the cognitive/behavioral profile. In addition to cognitive and behavioral problems, patients can present with pyramidal tract, spinal cord, and sphincter dysfunction [52]. CNS involvement may be parenchymal or nonparenchymal [55]. Behçet's disease may also result in a vasculitis of the vasa vasorum [55]. Brain MRI often reveals focal or diffuse T2-weighted hyperintensities, particularly in the basal ganglia, thalamus, upper brainstem, and mesial temporal structures, and may mimic multiple sclerosis [42,52]. Treatment is with high-dose corticosteroids and long-term immunosuppression [42]. Poor prognostic signs include parenchymal involvement, brainstem lesions, an inflammatory CSF, a primary or secondary progressive course, and/or relapse during steroid tapering [52].

Primary angiitis of the CNS

PACNS is a rare autoimmune disease characterized by a primary vasculitis confined to the CNS that results in multifocal symptoms [56]. Only about 500 cases have been reported worldwide. Patients typically present in middle age with headache, stroke, seizures, myelopathy, and encephalopathy [56]. PACNS may have a fluctuating or stepwise progressive course with ischemic strokes relating to the underlying vasculitis. Similar presentations can be found among patients with CNS vasculitides resulting from giant cell arteritis, polyarteritis nodosa, and Wegener's granulomatosis [56]. In addition, spirochetal, rickettsial, viral, fungal, and bacterial (eg, endocarditis) infections can lead to a secondary CNS vasculitis that resembles PACNS.

Patients may show elevation of inflammatory markers, including C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR). CSF typically shows a mild leukocytic pleocytosis and protein elevation. Brain MRI reveals a variety of abnormalities, including multiple ischemic lesions of varying ages, hemorrhages, leukoencephalopathy, and gadolinium enhancement of the meninges. In rare cases, patients may have mass lesions or isolated myelopathies on MRI [56].

Diagnosis is often by conventional angiography, which shows multifocal narrowing and vessel occlusion of large and medium-sized CNS vessels. Because other conditions may show similar changes on angiography, a leptomeningeal or parenchymal brain biopsy will further confirm the presence of granulomatous inflammation, lymphocytic infiltration, and fibrinoid necrosis, which are characteristic features of PACNS.

Recommended treatment for PACNS is similar to that of the systemic vasculitidies and typically entails a combination of corticosteroids and other immunosuppression as needed. Despite these therapeutic options, there is a 25% reported relapse rate [56].

Diagnostic Workup

The diagnostic workup of the immune-mediated dementias begins with a complete history and physical examination. A detailed history should focus on clues relating to a subacute presentation, cancer risk factors, and autoimmune disease. Various historical points may be more suggestive of one condition over others. For instance, sarcoid should be considered in black Americans with respiratory problems and encephalopathy, whereas Sjögren's encephalopathy should remain high in the differential diagnosis of patients with rheumatoid arthritis, xerostomia, and/or mental status changes.

Given the overlapping clinical phenotype associated with immune-mediated dementias, we suggest broad screen serum laboratory studies for both antibody- and cell-mediated processes (Table 2). Screening laboratories should address rheumatologic causes of dementia (eg, with ESR, CRP, antinuclear antibody [ANA], antineutrophil cytoplasmic antibody [pANCA and cANCA], dsDNA, and anti-Ro/anti-La antibodies). Any of these biomarkers may be positive in SLE, Behçet's disease, or Sjögren's syndrome. Because HE and VGKC-E can present as rapidly progressive dementias mimicking CJD, they should be tested for in all patients with rapid dementia (Table 2). If paraneoplastic conditions are suspected, testing should be conducted for a panel of serum and CSF paraneoplastic antibodies. We generally recommend sending for panels of antibodies, because many of these antibodies can co-occur and some may help diagnose the underlying cancer. A reasonable panel for the more common paraneoplastic causes of LE might include anti-Hu, anti-CV2, anti-Ma, anti-amphiphysin, anti-Zic4, and possibly others. If patients exhibit ataxia, serum anti-Yo and anti-GAD antibodies should be measured.

CSF analysis should be performed for any patient suspected of having an immune-mediated dementia. The typical CSF of these disorders is nonspecific, revealing inflammatory signs of lymphocytic pleocytosis, increased protein levels, an elevated IgG index, and CSF-specific oligoclonal bands. Thus, all CSF should be analyzed for protein, glucose, cell count, IgG index (for a serum–CSF ratio), and oligoclonal bands. If paraneoplastic disease is suspected, CSF can be analyzed for antineuronal antibodies, depending on the syndrome, but particularly anti-NMDAR and anti-AMPAR conditions, in which CSF antibody production is an order of magnitude higher than serum production (Table 2).

We recommend that all patients with a suspected autoimmune encephalopathy undergo MRI with intravenous gadolinium with FLAIR, T1, T2, and DWI and with apparent diffusion coefficient (ADC) sequences. Particular attention should be given to T2 and FLAIR sequences for T2-weighted hyperintensities within the brainstem and mesial temporal lobes that may suggest paraneoplastic or nonparaneoplastic LE. Because the medial temporal lobes can be susceptible to MRI artifact, we recommend acquiring T2 and FLAIR sequences in both the axial and coronal planes. MRI T2-weighted hyperintensities localized to the medial temporal lobes occur in about 80% of patients presenting with PLE [9]. Other possible considerations include ischemic strokes, which can be associated with SLE or HE. Finally, patients with sarcoid may have evidence of thickening and enhancement of the leptomeninges on T1 postgadolinium sequences. There may be other nonspecific findings, such as enhancing or nonenhancing parenchymal or dural lesions [48]. DWI with ADC sequences is helpful in diagnosing other causes of subacute presentations of dementia, such as CJD and strokes.

An EEG should be obtained in any patient experiencing a rapidly progressive dementia to both confirm abnormal slowing as well as screen for cortical irritability and to rule out seizures. The EEG carries particular importance in LE (particularly VGKC-E) and HE, which are commonly associated with seizures [22].

Systemic inflammatory conditions may require further studies to support a given diagnosis. Patients with suspected paraneoplastic disease should undergo body imaging of the chest, abdomen, and pelvis with CT. If the x-ray or CT is negative and paraneoplastic conditions are suspected, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) should be performed. If certain paraneoplastic antibodies are found and the cancer workup is negative, serial imaging and testing every few months is recommended. If sarcoid is in the differential diagnosis, a CT scan or x-ray of the chest is helpful to screen for hilar lymphadenopathy. The diagnosis of Sjögren's disease can be confirmed with a lip biopsy. Finally, the standard workup of PACNS includes a conventional angiogram to screen for characteristic vasculitic beading.

Treatment

One of the major features distinguishing the autoimmune-mediated dementias from the neurodegenerative dementias is their often dramatic responsiveness to treatment.

Whereas immunomodulatory treatment for autoantibodies and steroid administration are generally indicated for the immune-mediated dementias, therapy for some patients starts with removal of the causative agent. For instance, the paraneoplastic syndromes often improve after treatment of the underlying tumor, as in the case of LE associated with anti-Hu, anti-CV2, anti-Ma2, anti-NMDAR, or anti-AMPAR antibodies. Furthermore, GS is most effectively treated by a GFD.

The immune-mediated dementias associated with specific antigens/antibodies, particularly paraneoplastic syndrome, VGKC-E, anti-GAD, celiac disease, and HE, are especially responsive to antibody-reducing therapies such as intravenous corticosteroids, IVIG, or plasmapheresis. When treating initially with corticosteroids, we recommend giving high doses

(eg, 1 g of intravenous methylprednisolone daily for 5 days followed by slow prednisone taper) in a monitored setting. In some conditions, such as VGKC-E, serum antibody levels may be measured to assess therapeutic efficacy. For antibody-mediated conditions, particularly with $CD20^+$ B-cell involvement, agents such as rituximab may be helpful [7•].

Some of the immune-mediated dementias are associated with more systemic disease and require chronic, routine immunosuppressive therapy. Although chronic prednisone is the cornerstone of treatment for Behçet's disease, PACNS, neurosarcoid, SLE, and Sjögren's encephalopathy, other types of immunosuppression are commonly used. Severe or refractory disease may warrant chronic treatment with cyclophosphamide. IVIG or plasmapheresis has been used in SLE and Sjögren's encephalopathy [42] as well as other conditions. For sarcoidosis, prednisone is frequently combined with azathioprine (150 mg/d) and hydroxychloroquine 400 mg/d [57•]. For physicians not familiar or comfortable with immunosuppressive treatment, patients with immune-mediated dementias may be treated with the assistance of rheumatologists or neuroimmunologists.

Conclusions

Although most neurologists have experience diagnosing and treating typical dementias, such as those due to neurodegenerative conditions, including Alzheimer's disease, few neurologists have as much familiarity with autoimmune causes of dementia. Whereas Alzheimer's disease can be managed at a more leisurely pace, the immune-mediated dementias typically require urgent diagnosis and treatment with immunosuppressants or the underlying etiology. Increased awareness of the immune-mediated dementias and their comorbid symptoms should lead to prompt diagnosis and treatment of these fascinating and mysterious conditions.

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Table 1
Paraneoplastic antibodies or syndromes associated with cognitive impairment

Paraneoplastic antibody	Most common associated cancers	Main cognitive symptoms	Other neurologic and other symptoms	Comments
Anti-Hu (ANNA-1)	SCLC	Paraneoplastic encephalitis (may involve cortical, limbic, and brainstem structures)	PCD, autonomic dysfunction, sensory neuronopathy, myelitis	May co-occur with other Abs
Anti-CV2 (anti-CRMP5)	SCLC, thymoma	LE	Paraneoplastic cerebellar degeneration, chorea, uveitis, optic neuritis, peripheral neuropathy	May co-occur with other Abs
Anti-Ma2	Germ-cell tumor (usually testis), non-SCLC	LE, hypothalamus, brainstem symptoms	Paraneoplastic cerebellar degeneration in rare cases	Male predominance
Anti-NMDAR	Teratoma (often ovarian)	Severe psychiatric symptoms, memory loss, decreased consciousness	Seizures, dyskinesias, hypoventilation, autonomic instability	Female predominance; CSF Ab levels higher than serum Ab levels
Anti-VGKC	Thymoma, SCLC	LE, seizures	Neuromyotonia, myoclonus, hyponatremia	Can present as a rapid dementia, such as CJD
Anti-amphiphysin	SCLC, breast	Paraneoplastic encephalomyelitis, LE	Stiff-person syndrome, myelopathy	Anti-Sox Abs also may be present
Anti-Zic4	SCLC	N/A	PCD	Often co-occurs with anti-Hu and anti-CV2 Abs; encephalopathy may occur when other paraneoplastic Abs are present [10]
Anti-AMPAR	Lung, breast, thymus	LE, agitation	Seizures	Female predominance; CSF pleiocytosis; CSF Ab levels higher than serum Ab levels; other autoimmune conditions common
Anti-Ri	Neuroblastoma in children, breast cancer and ovarian malignancies in adults	N/A	Opsoclonus-myoclonus, cerebellar degeneration, brainstem encephalitis	—

Abs—antibodies; AMPAR—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA—anti–neuronal nuclear antibody; CJD—Creutzfeldt-Jakob disease; CRMP5—collapsin response mediated protein 5; CSF—cerebrospinal fluid; LE—limbic encephalitis; N/A—not applicable; NMDAR—*N*-methyl-D-aspartate receptor; PCD—paraneoplastic cerebellar degeneration; SCLC—small cell lung cancer; VGKC—voltage-gated potassium channel.

Table 2
Diagnostic workup of immune-mediated dementias

Disease	Serum studies	CSF studies	Other
Paraneoplastic syndrome	Anti-Hu, anti-CV2, anti-AMPA, anti-NMDA, anti-Ma2, anti-Yo, anti-Ri, anti-Zic4 Abs	Same antibody markers as for serum studies; protein, glucose, cell count, IgG index, OCBs	CT or PET of chest/abdomen/pelvis for neoplasm
Anti–VGKC-E	Anti-VGKC Ab	Protein, glucose, cell count, IgG index, OCBs	Electrolytes for hyponatremia; EEG for seizures; EMG for neuromyotonia
Anti–GAD antibody	Anti-GAD Ab	Anti-GAD Ab, protein, glucose, cell count, IgG index, OCBs	Rule out stiff-person syndrome, diabetes, seizures
Hashimoto's encephalopathy	TSH, free T4, anti-TPO, anti-TG Abs	Protein, glucose, cell count, IgG index, OCBs	Diagnosis of exclusion
Gluten sensitivity (celiac disease)	Anti-gliadin IgG/IgA; anti–tissue transglutaminase IgG/IgA Abs	Protein, glucose, cell count, IgG index, OCBs	Small bowel biopsy; HLA-DQ2, -DQ8, -DQ1
Systemic lupus erythematosus	ANA, anti-dsDNA Ab, anti-Smith Ab, false-positive VDRL	Protein, glucose, cell count, IgG index, OCBs	
Sjögren's encephalopathy	ANA, anti-Ro (SS-A) Ab, anti-La (SS-B) Abs	Protein, glucose, cell count, IgG index, OCBs	Lip biopsy (minor salivary gland) for focus of lymphoid aggregates
Behçet's disease	—	Protein, glucose, cell count, IgG index, OCBs	N/A
Sarcoidosis	ACE level	ACE level, protein, glucose, cell count, IgG index, OCBs	Chest CT or x-ray
Primary angiitis of the CNS	ESR, CRP, pANCA and cANCA (for possible cause of secondary CNS angiitis)	Protein, glucose, cell count, IgG index, OCBs	Conventional angiogram of cerebral vasculature (gold standard); leptomeningeal or parenchymal biopsy if necessary

Abs—antibodies; ACE—angiotensin-converting enzyme; AMPA—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANA—anti-nuclear antibody; cANCA—cytoplasmic antineutrophil cytoplasmic antibody; CNS—central nervous system; CRP—C-reactive protein; CSF—cerebrospinal fluid; EEG—electroencephalogram; EMG—electromyogram; ESR—erythrocyte sedimentation rate; GAD—glutamic acid decarboxylase; N/A—not applicable; NMDA—*N*-methyl-D-aspartate; OCBs—oligoclonal bands; pANCA—perinuclear ANCA; PET—positron emission tomography; T4—thyroxine; TG—thyroglobulin; TPO—thyroid peroxidase; TSH—thyroid-stimulating hormone; VDRL—venereal disease research laboratory (test); VGKC—voltage-gated potassium channel; VGKC-E—VGKC encephalopathy.