Autoimmune Meningitis and Encephalitis

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KEYWORDS

• Autoimmune encephalitis • Autoimmune meningitis • Paraneoplastic disorder
• Limbic encephalitis

KEY POINTS

- Meningeal or parenchymal inflammation often indicates a treatable disorder, and clinicians should consider infectious, neoplastic, and autoimmune diseases in patients with undifferentiated meningitis or encephalitis. Suspicion for autoimmune meningitis or encephalitis is heightened in younger patients with subacute disease onset and/or a personal or family history of autoimmunity.
- Early evaluation of suspected autoimmune encephalitis should include assessment for specific neural autoantibodies, as the identification of a positive antibody often precludes the need for brain biopsy and allows therapeutics to commence.
- Numerous autoimmune processes without associated neural autoantibodies can cause meningitis, encephalitis, or both and may be categorized into histiocytic, fulminant demyelinating, vasculitic, amyloid-related, and systemic rheumatologic disorders. Many require tissue sampling to diagnose.
- Although clinicians should aggressively seek alternative systemic biopsy sites when available, brain biopsy is a high-yield and relatively low-morbidity procedure in the appropriate clinical setting.

INTRODUCTION

Evaluating undifferentiated meningitis or encephalitis is challenging due to their broad differential diagnoses with significant clinical and etiologic overlap. Meningitis denotes inflammation of the meningeal space and typically presents with headache, nuchal rigidity, cerebrospinal fluid (CSF) pleocytosis, or leptomeningeal enhancement on MRI. In contrast, encephalitis signifies inflammation of the brain parenchyma, resulting in focal or multifocal deficits, potentially with corresponding parenchymal imaging abnormalities. These syndromes commonly co-occur as meningoencephalitis and cause a combination of signs and symptoms.

Meningeal inflammation is demonstrated by CSF pleocytosis or intrathecal antibody production, including an elevated immunoglobulin G (IgG) index, independent CSF

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Neurol Clin 40 (2022) 93–112
https://doi.org/10.1016/j.ncl.2021.08.007 **neurologic.theclinics.com**

oligoclonal bands (OCBs), or identification of a specific neural autoantibody. Inflammation of brain parenchyma is demonstrated by tissue pathology or, more commonly, inferred based on the combination of meningeal inflammation and focal deficits, indicating concurrent parenchymal involvement. Importantly, although abnormally elevated CSF protein or parenchymal enhancement on MRI can suggest an inflammatory process, neither one is sufficient evidence in isolation.

Because the presence of inflammation usually indicates a treatable condition, etiologic diagnosis of meningitis and encephalitis becomes especially important and considerations include infections, neoplasms, and autoimmune disorders. Although all 3 categories should be considered in every patient, certain features increase the likelihood of an autoimmune cause. Autoimmune pathology is typically subacute in onset and more common in individuals with a personal or family history of autoimmunity.[1] Younger age, female sex, or postpartum status also raise suspicion.[2] Autoimmune meningitis or encephalitis requires a systematic workup, and this review provides one practical approach tailored to the risk factors, clinical presentation, and diagnostic features of the individual patient.

DIAGNOSTIC APPROACH

The presence of a specific neural autoantibody is a key early differentiating feature between causes of autoimmune meningitis and encephalitis because identifying such an antibody often allows treatment initiation without the need for invasive testing such as brain biopsy. In contrast, many autoimmune causes of meningitis or encephalitis without associated autoantibodies, such as neurosarcoidosis or primary angiitis of the central nervous system (PACNS), do require a tissue specimen for diagnosis and treatment.[3,4] Thus it becomes very useful for clinicians to predict when patients may have a specific autoantibody syndrome, in order to allow time for serologic results to return before pursuing biopsy. Certain autoantibody syndromes are also often associated with specific neoplasms, and identifying these paraneoplastic antibodies prompts a thorough search for associated malignancy. Finally, many antibody syndromes have established treatment practices and therapeutic decisions are frequently streamlined when an autoantibody is discovered.[5] In fact, identifying an autoantibody is so meaningful that within the medical literature, the phrase “autoimmune encephalitis” is often reserved for cases associated with a particular neural autoantibody.[6]

Autoantibody-Associated Encephalitis

All neural antibody-associated diseases of the CNS cause encephalitis or meningoencephalitis; none cause meningitis alone. These autoantibody-associated encephalitides are commonly divided based on whether the affected antigen is intracellular or extracellular (**Table 1**).[1,5] Syndromes related to antibodies against intracellular antigens are frequently associated with cancer and include the classic paraneoplastic disorders such as anti-Hu, anti-Ri, or anti-Yo. Neural injury is thought to occur via cytotoxic T cells, and identified antibodies are likely biomarkers rather than pathogenic because antibodies cannot enter live cells.[1,6] Prognosis for intracellular autoantibody syndromes is often poor, both because neuronal injury is usually irreversible and because the disorder is due to an associated malignancy. In contrast, antibodies targeting extracellular antigens, such as N-methyl-D-aspartic acid (NMDA), voltage-gated potassium channel (VGKC), or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid are thought to be directly pathogenic. These antibodies reversibly impair epitopes of cell surface or associated synaptic proteins and are variably associated with neoplasm. As a result, prognosis is more favorable.[5]

Table 1
General features associated with intracellular and extracellular autoantibody syndromes of the central nervous system

	Intracellular	Extracellular
Antigen targets	Nuclear, cytoplasmic	Cell surface, synaptic
Patient age	Older	Younger
Neoplasm	Common	Variable
Best antibody sensitivity	Serum and CSF	CSF
Prognosis	Unfavorable	Favorable

Abbreviation: CSF, cerebrospinal fluid
Data from Bradshaw MJ, Linnoila JJ. An Overview of Autoimmune and Paraneoplastic Encephalitides. Semin Neurol. 2018;38(3):330-343. https://doi.org/10.1055/s-0038-1660821.

Autoantibody-associated encephalitis may result in a variety of typical neurologic syndromes, including limbic encephalitis, cerebellar degeneration, stiff person syndrome, and encephalomyelitis, among others (**Table 2**). Although there is substantial overlap in the diseases associated with these clinical syndromes, there are still certain presentations that should immediately raise suspicion for a particular antibody. For example, neuromyotonia is strongly associated with Caspr2 antibodies (Isaac syndrome).[5] Faciobrachial dystonic seizures are nearly always associated with anti-LgI1 encephalitis.[6] Extreme delta brush on electroencephalogram is highly specific for NMDA-R encephalitis.[5] Although in many cases clinicians will send a panel of autoantibodies in patients with suspected autoimmune encephalitis, recognizing characteristic presentations and sending targeted testing for single antibodies can be cost- and time-efficient and should be done when possible. Many excellent review articles have been written that organize and characterize neural autoantibody

Table 2
Typical syndromes caused by autoantibody-associated encephalitides

Syndrome	Intracellular Antibodies	Extracellular Antibodies
Limbic encephalitis	Anti-GAD65, Anti-Ma2	Anti-NMDAR, Anti-AMPAR, Anti-LGI1, Anti-GABA(B), Anti-mGluR5
Cerebellar degeneration	Anti-Yo, Anti-Ri, Anti-GAD65, Anti-Ma1	Anti-mGluR1, Anti-Tr, Anti-VGCC
Stiff person syndrome	Anti-GAD65, Anti-amphiphysin	Anti-GlyR, Anti-GABA(A)
Encephalomyelitis	Anti-Hu, Anti-CV2/CRMP5, anti-GFAP	
Opsoclonus-myoclonus	Anti-Ri	
Refractory seizures		Anti-GABA(A), Anti-GABA(B), Anti-LGI1 (faciobrachial dystonic)
Diencephalic	Anti-Ma1, Anti-Ma2	Anti-Aqp4
Brainstem syndrome	Anti-Hu, Anti-Ri, Anti-Ma1, Anti-Ma2	Anti-IgLON5, anti-Aqp4, anti-GQ1b
CNS hyperexcitability	Anti-DPPX	
PNS hyperexcitability (neuromyotonia)		Anti-Caspr2
Sensory neuronopathy	Anti-Hu	

Data from Refs.[6,15,58,59]

syndromes; these may be used to gauge the likelihood of specific antibodies and identify their associated malignancies.[5–7]

Nonautoantibody-Associated Meningitis and Encephalitis

Autoimmune causes of meningitis and encephalitis without an associated antibody are diverse (**Table 3**). These diseases are often diagnosed pathologically and can be categorized as such, including granulomatous/histiocytic, demyelinating, vasculitic, and amyloid-related conditions. Several systemic rheumatologic diseases also can have meningeal and/or parenchymal neurologic manifestations and are more often diagnosed by positive serum studies and exclusion of alternative diseases.

Granulomatous/histiocytic diseases

Neurosarcoidosis is by far the most common granulomatous autoimmune CNS disease and can affect a multitude of structures including cranial nerves, parenchyma, meninges, vasculature, and spinal cord (**Fig. 1**). CSF abnormalities can include elevated opening pressure, pleocytosis, hypoglycorrhachia, and occasionally OCBs or high IgG index.[3] Neurosarcoidosis has a predilection for the hypothalamus and pituitary axis, a characteristic it shares with other histiocytic disorders including Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH). However, where sarcoidosis can indiscriminately affect any segment of the nervous system, ECD and LCH more commonly cause meningitis without encephalitis. Brain parenchymal involvement is instead often limited to circumscribed enhancing masses, although ECD can cause more infiltrative lesions and LCH is associated with degenerative changes of the posterior fossa.[8] Morbidity of brain biopsy may be avoided by use of body PET computed tomography (CT) as a sensitive study to identify systemic targets in suspected cases of neurosarcoidosis, ECD, or LCH.[3,9]

Vogt-Koyanagi-Harada (VKH) disease is a histiocytic disorder common in Asian, Hispanic, and Indigenous populations that primarily causes panuveitis but is accompanied by meningitis in up to 80% of cases.[10] CSF pleocytosis is typically lymphocytic although may be neutrophilic early in presentation.[11] Associated encephalitis is extremely rare and is still accompanied by ophthalmologic involvement.[11,12] Unlike the histiocytic disorders described earlier, VKH does not require a tissue diagnosis and may be made as a diagnosis of exclusion in patients with appropriate ophthalmologic findings and clinical presentation.

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) causes autoimmune encephalitis with a distinctive radiographic signature and pathology demonstrating perivascular lymphohistiocytic infiltration without granuloma or demyelination. Stereotypical brain imaging should demonstrate punctate and curvilinear enhancing lesions of the pons and/or cerebellum involving white and deep gray matter but sparing cortex and CSF may demonstrate mild pleocytosis and/or OCBs.[13] Although diagnosis can be made by observing the signature radiographic pattern without biopsy, caution should be used in those with linear, nodular, ring-shaped, or larger (>3 mm) areas of enhancement, and mimics such as CNS lymphoma or glial fibrillar acidic protein astrocytopathy should be considered and excluded.[14]

Fulminant demyelinating diseases

Acute disseminated encephalomyelitis (ADEM) and acute hemorrhagic leukoencephalitis (AHLE) are 2 fulminant demyelinating diseases that cause autoimmune encephalitis or meningoencephalitis. ADEM typically presents as a monophasic illness in younger patients with acute encephalopathy and multifocal enhancing edematous lesions of the

Table 3
Clinical and radiographic characteristics of autoimmune diseases that cause meningitis or encephalitis without an associated neural autoantibody.
[3,8–10,13–17,19,20,22,23,28,31,32,37,38,40,41,44–47,50,79]

	Syndrome	Described MRI patterns	Helpful systemic workup
Granulomatous/histiocytic			
• Sarcoidosis	M, E, ME	HPA, meningeal, vascular, parenchymal	CT → PET
• Erdheim Chester	M	HPA, infiltrative, mass lesions, meningeal	PET/CT
• Langerhans cell histiocytosis	M	HPA, mass lesions, cerebellar	Skeletal x-ray, skin exam → PET/CT
• Vogt-Koyanagi-Harada	M > E, ME	Often unremarkable; rare brainstem lesions	Ophthalmologic exam with FA
• CLIPPERS	E, ME	Punctate/curvilinear <3mm posterior fossa enhancement	
Fulminant demyelinating			
• ADEM	E, ME	Multifocal enhancing and edematous grey/white	
• AHLE	E, ME	Hemispheric enhancing hemorrhagic edematous lesions	
Vasculitic			
• PACNS	M > E, ME	Discrete or diffuse, ischemia, hemorrhage, enhancement	
• Behçet	M > E, ME	Patchy or confluent brainstem, basal ganglia lesions	Oral/genital skin, ophthalmologic exams, pathergy test
• GPA	M > E, ME	Pachymeningeal > leptomeningeal enhancement	ENT and ophthalmologic exam, ANCA
• EGPA	M	Ischemia, hemorrhage, optic neuropathy	Serum eosinophils, ANCA
• Cogan	M > E, ME	Ischemia, vestibular labyrinth obliteration	TTE, otologic & ophthalmologic exams
• Kawasaki	M	Ischemia, atrophy, subdural effusion, MERS	TTE, ophthalmologic & skin exams
Amyloid related			
• CAARI	E, ME	White matter, leptomeninges, edema, hemorrhage, infarct	Amyloid PET
• ABRA	E, ME	Similar to CAARI	Amyloid PET
Systemic autoimmune disease			
• Sjogrens	M > E, ME	White matter, grey matter, microhemorrhages	SSA/B, Labial or salivary gland biopsy
• RA	M > E, ME	Infarcts, pachymeningitis, dural nodules, rare vasculitis	Anti-RF, CCP

(*continued on next page*)

Table 3
(continued)

	Syndrome	Described MRI patterns	Helpful systemic workup
• Susac syndrome	M, E, ME	Callosal, periventricular, meningeal enhancement	Ophthalmologic exam with FA
• HLH	E, ME	Meningeal, nodular, ring-enhancing, cortical, subcortical	Ferritin, SIL-2R, NK activity, bone marrow
• Localized scleroderma	M, E, ME	Unilateral hyperintensity, atrophy, cysts, calcifications	ANA, Skin biopsy
• Sweet syndrome	M > E, ME	White matter, grey matter, enhancement	Skin biopsy
• Still's disease	M > E, ME	Linear enhancement, infarction, demyelination	Peripheral neutrophilia, ferritin
• IgG 4 related hypertrophic pachymeningitis	M	Thick enhancing leptomeninges and/or pachymeninges	IgG4 level
Other			
• HANDL	M, ME	Often unremarkable; nonspecific T2 hyperintensities	

Abbreviations: ABRA, amyloid beta related angiitis; ADEM, acute disseminated encephalomyelitis; AHLE, acute hemorrhagic leukoencephalitis; CAARI, cerebral amyloid angioopathy with related inflammation; CLIPPERS, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CT, computed tomography; E, encephalitis; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear nose and throat; FA, fluorescein angiography; GPA, granulomatosis with polyangiitis; HaNDL, Headache with neurologic deficits and CSF lymphocytosis; HLH, hemophagocytic lymphohistiocytosis; HPA, hypothalamic pituitary axis; IgG, immunoglobulin G; M, meningitis; ME, meningoencephalitis; MERS, mild encephalopathy with reversible splenial lesion; NK, natural killer cell; PACNS, primary angiitis of the central nervous system; PET, Positron emission tomography; RA, rheumatoid arthritis; SIL-2R, soluble IL-2 receptor; TTE, transthoracic echocardiogram

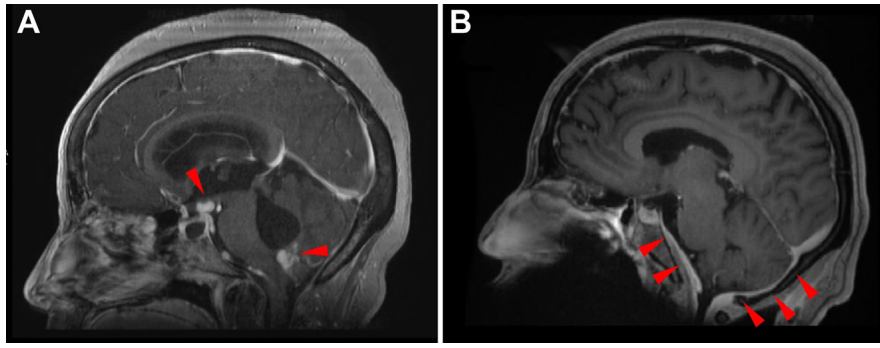

Fig. 1. T1-weighted sagittal postcontrast magnetic resonance images demonstrating (*A*) suprasellar and fourth ventricular enhancing masses and associated hydrocephalus in a patient with probable neurosarcoidosis based on lymph node biopsy and (*B*) pachymeningitis and marked smooth dural thickening at the craniocervical junction in a different patient with biopsy-proven IgG4 disease.

white and deep gray matter without cortical involvement.[15] CSF demonstrates lymphocytic or monocytic pleocytosis, typically without independent OCB or elevated IgG index. In classic presentations, brain biopsy is not typically required after reasonable exclusion of alternative diagnoses. AHLE is a severe variant of ADEM with similar demographic and radiographic features except with the addition of cerebral hemorrhages, progressive edema, and often rapid progression to herniation and death. CSF may also be more polymorphonuclear-predominant, and brain biopsy is frequently performed.[16]

Vasculitic disorders

Although autoimmune vasculitides involving the CNS typically result in ischemia, hemorrhage, or other vascular pathology, patients may also have an accompanying meningitis or less often encephalitis. PACNS is a medium- to small-vessel vasculitis strictly limited to the CNS that can also be associated with meningitis.[17,18] Imaging findings are highly variable and may show discrete or diffuse lesions often involving white matter, potentially with areas of infarct, hemorrhage, enhancement, or mass effect (**Fig. 2**).[19] Although PACNS does not cause a classic encephalitis per se, patients do have focal deficits including weakness, visual impairment, aphasia, and ataxia due to parenchymal disease. Diagnosis of PACNS can be challenging, as CSF demonstrates pleocytosis in only 60% of biopsy-proven cases, and catheter angiography is normal in almost half. Furthermore, brain biopsies performed for suspected PACNS reveal alternative diagnoses in greater than 30% of cases. The diagnosis is therefore best made via brain tissue sampling.[18]

Behçet syndrome is the only systemic autoimmune vasculitis that commonly causes not only meningitis but also encephalitis. Neuro-Behçet syndrome is typically divided into parenchymal (80%) and nonparenchymal (20%) disease, the former of which results in meningoencephalitis and the latter solely in vascular abnormalities. Parenchymal neuro-Behçet syndrome primarily affects the brainstem and less often basal ganglia, centrum semiovale, spinal cord, and cranial nerves, and biopsy is typically required for diagnosis.[19,20] CSF is inflammatory in 60% of parenchymal cases with an early neutrophil predominance that transitions to lymphocytes over days.[21]

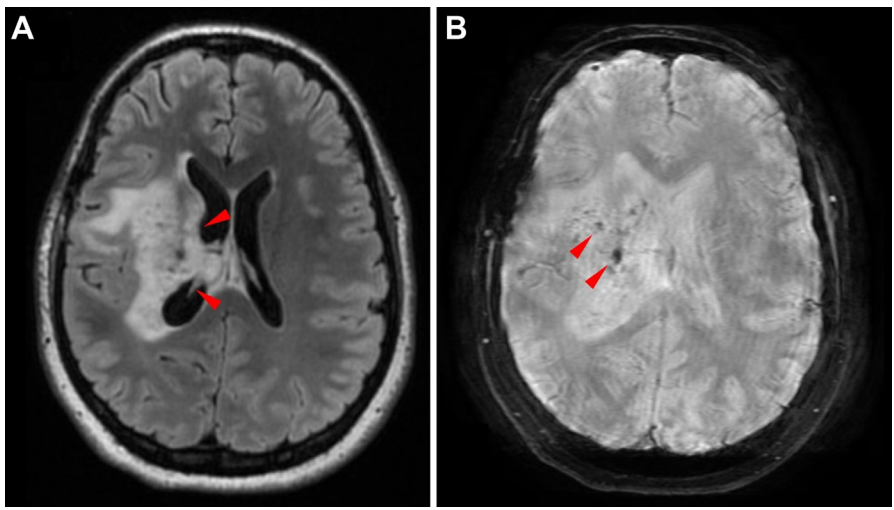

Fig. 2. MRI from a single patient with primary angiitis of the CNS that required 3 brain biopsies to diagnose, demonstrating a masslike T2 hyperintense lesion with interspersed punctate foci of susceptibility artifact on axial (*A*) T2 fluid attenuated inversion recovery (FLAIR) and (*B*) susceptibility weighted imaging (SWI) sequences.

Several systemic vasculitides may occasionally be associated with a meningitis, often in addition to vascular complications of the CNS such as hemorrhage or ischemia. Eosinophilic granulomatosis with polyangiitis is a small-vessel vasculitis nearly always associated with peripheral eosinophilia; approximately 50% of cases are ANCA-positive. CNS manifestations include ischemia, hemorrhage, meningitis, cranial neuropathies, and more uncommonly myelitis or nonspecific T2 lesions.[22] Granulomatosis with polyangiitis involves the nervous system in approximately 33% of patients, most commonly with peripheral or cranial neuropathies, but a small percentage may have a mild neutrophilic meningitis or even more rarely encephalitis.[23–25] Cogan syndrome is a variable-sized vasculitis that causes hearing loss, vertigo, and uveitis and predominantly affects young men; it may be associated with a lymphocytic meningitis.[17,19] Finally, although primarily seen in infants and children, Kawasaki disease can rarely present in adults, and approximately 10% of patients may have a mixed neutrophilic and lymphocytic pleocytosis at presentation.[26–28]

Other autoimmune systemic vasculitides typically do not cause meningitis or encephalitis although case reports have been published describing rare associations. For example, isolated meningitis has been associated with giant cell arteritis, and polyarteritis nodosa has been rarely reported to cause meningoencephalitis.[29,30]

Amyloid-related

Cerebral amyloid angiopathy (CAA) is a vasculopathy characterized by amyloid beta-peptide deposits in small-to medium-sized cortical and meningeal vessels of older adults. Although often noninflammatory, CAA can also be associated with 2 different autoimmune responses, termed (1) CAA-related inflammation (CAARI) when inflammation involves the perivascular space and (2) Amyloid beta–related angiitis (ABRA) when inflammation leads to a destructive, transmural vasculitis.[31–33] Both CAARI and ABRA cause encephalitis with or without associated meningitis; approximately half of the patients demonstrate a cerebrospinal fluid pleocytosis occasionally accompanied by OCBs or elevated IgG index.[31] Imaging findings are heterogeneous with substantial overlap between CAARI and ABRA but often demonstrate white matter abnormalities, leptomeningeal enhancement, vasogenic edema, microhemorrhages, superficial siderosis, and occasional infarction (**Fig. 3**).[32] PET imaging using the amyloid-binding Pittsburgh compound B may be helpful to demonstrate amyloid deposits with the caveat that these may be found in other conditions such as Alzheimer disease.[33] Diagnosis of CAARI and ABRA often requires brain biopsy, but given hemorrhagic potential in these patients, when imaging findings are typical, CSF demonstrates clear inflammation, and amyloid PET is positive, empirical therapy may be considered without tissue diagnosis.[34]

Systemic autoimmune diseases associated with meningitis or encephalitis

Rheumatoid arthritis (RA), Sjögren syndrome, Susac syndrome, and systemic lupus erythematosus (SLE) are 4 systemic autoimmune conditions that have been associated with meningitis and extremely rarely with encephalitis. RA can lead to lymphocyte-predominant meningitis and/or MRI enhancement involving the leptomeninges, pachymeninges, or both.[35,36] Imaging may also reveal infarcts related to an associated vasculitis. Meningoencephalitis associated with RA has very rarely been reported, and diagnosis typically requires brain biopsy.[37] CNS involvement occurs in 2% to 5% of patients with Sjögren syndrome and can include aseptic meningitis, cerebellar syndromes, movement disorders, demyelination, and very rarely encephalitis and/or vasculitis.[38–40] CSF may reveal lymphocytic meningitis, elevated IgG index, or OCBs, and MRI typically shows nonspecific T2 abnormalities.[39,40] Susac syndrome is typically clinically

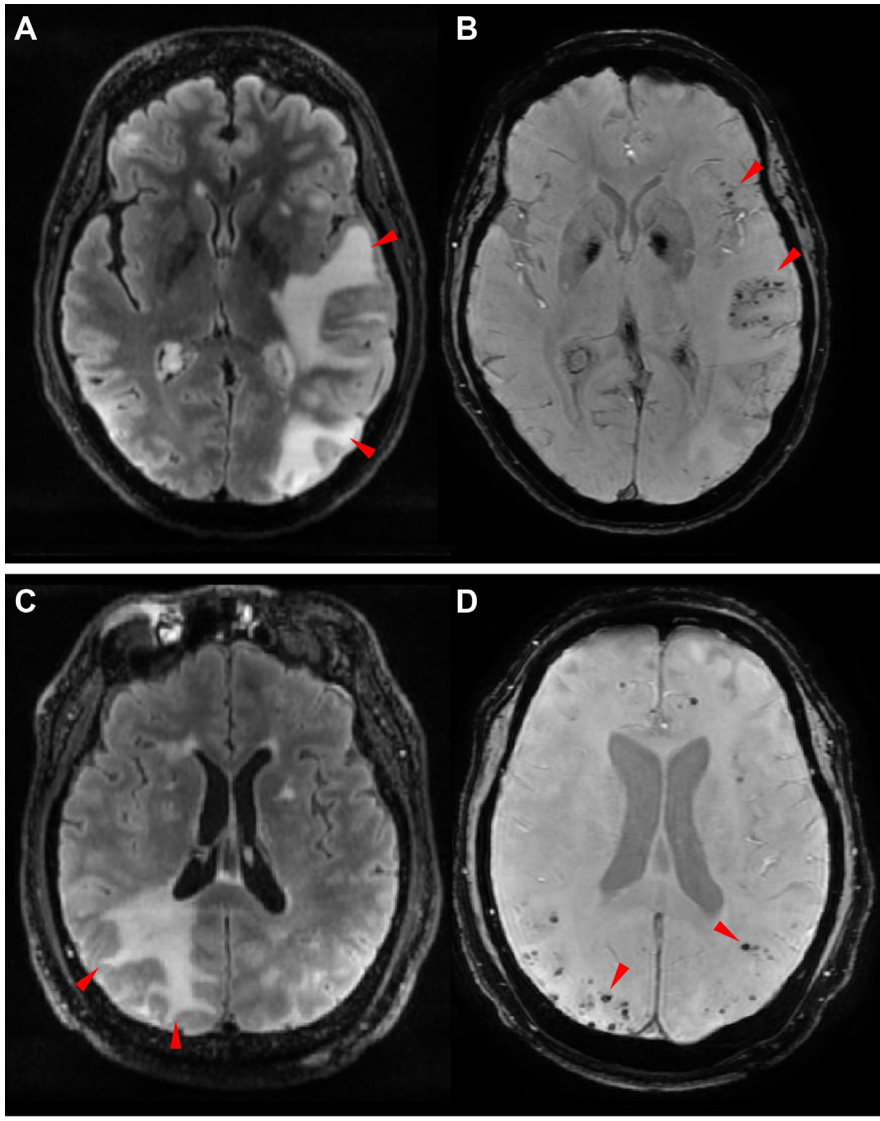

Fig. 3. (*A*) Axial MRI FLAIR and (*B*) SWI sequences in a patient with biopsy-proven cerebral amyloid angiopathy with related inflammation, demonstrating white matter-predominant confluent T2 hyperintensities with associated cortical microhemorrhages. (*C*) Axial FLAIR and (*D*) SWI sequences in a different patient with biopsy-proven amyloid beta–related angiitis demonstrating very similar white matter-predominant T2 hyperintensities and more diffuse cortical microhemorrhages.

diagnosed by its characteristic triad of hearing loss, branch retinal artery occlusions, and CNS dysfunction and may be associated with a modest CSF pleocytosis.[41] MRI nearly always shows callosal and periventricular T2 lesions, sometimes with leptomeningeal enhancement (Fig. 4). Finally, although SLE has been associated with a wide spectrum of neuropsychiatric presentations, meningitis occurs in no more than 3% of patients and in those cases is often better attributed to a drug or infection.[42]

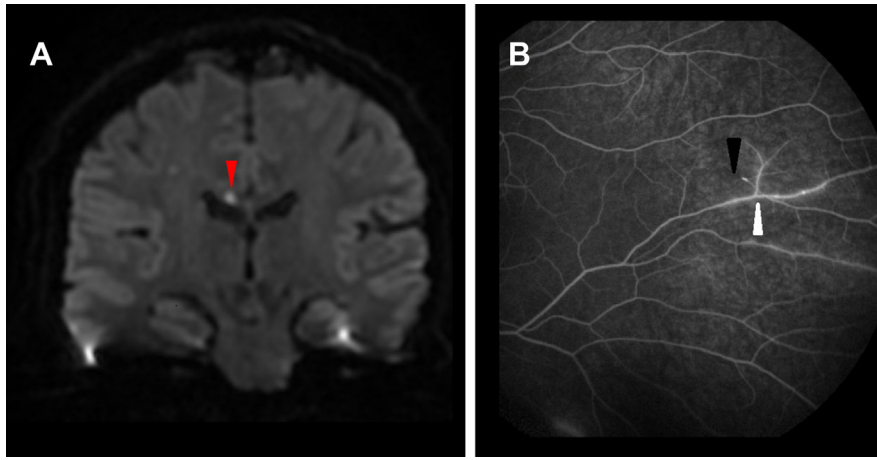

Fig. 4. (*A*) MRI coronal diffusion-weighted image demonstrating a small callosal infarct in a patient with clinically diagnosed Susac syndrome (*red arrow*). (*B*) Ophthalmologic fluorescein angiography demonstrating hyperfluorescent vasculitic changes (*white arrow*) and branch retinal artery occlusion (*black arrow*).

Localized scleroderma affecting the scalp commonly also involves the CNS and is associated with a progressive, relapsing meningitis or encephalitis.[43,44] CNS involvement is classified into 2 overlapping subtypes: linear scleroderma "en coup de sabre" characterized by a linear, thickened patch of skin typically over the scalp, and progressive hemifacial atrophy (Parry-Romberg syndrome) with sparing of overlying skin but involvement of dermis and deeper tissue.[44] Both may lead to epilepsy, and MRI abnormalities are common, including gyral T2 hyperintensities with associated atrophy, calcifications, microhemorrhage, cysts, and parenchymal and/or meningeal enhancement, usually ipsilateral to skin involvement (**Fig. 5**).[44,45] CSF may be normal or shows modest lymphocytic pleocytosis or independent OCBs.[44]

Relative to other systemic rheumatologic disorders, the dermatologic Sweet syndrome is somewhat more commonly associated with meningitis and encephalitis, frequently preceded by fever, peripheral neutrophilia, and erythematous painful nodules, blisters, or plaques. Sweet syndrome may be seen following an infection, during pregnancy, or in the context of hematologic malignancy or a different systemic autoimmune condition.[44] CSF may be normal or show a lymphocytic or neutrophilic predominance with or without OCBs. MRI may demonstrate nonspecific T2 hyperintensities of the cortex, white matter, and basal ganglia, with parenchymal or meningeal enhancement.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening multiorgan inflammatory syndrome involving dysregulation of macrophages, natural killer cells, and cytotoxic lymphocytes as triggered by an infectious, malignant, or iatrogenic event.[46] HLH may involve CNS in approximately 10% of patients, and MRI findings are heterogeneous but may include meningeal enhancement, diffuse white matter changes, or focal cortical or subcortical lesions with variable enhancement patterns; only a minority of patients demonstrate CSF pleocytosis.[47] Patients presenting with CNS HLH should always have systemic involvement, and thus diagnosis usually does not require brain biopsy and can be made using scoring tools supplemented by systemic biopsy such as bone marrow, liver, spleen, or lymph nodes.[46]

Common symptoms of adult-onset Still's disease include fever, arthritis, and evanescent rash; neurologic involvement is present in approximately 7% of patients and can include meningitis and less often encephalitis or infarction. CSF may show

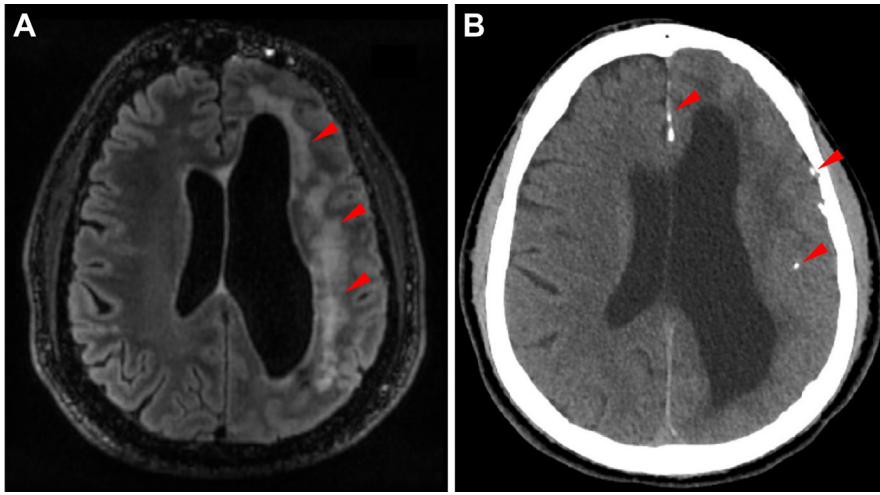

Fig. 5. (*A*) Axial fluid-attenuated inversion recovery MRI of a patient with clinically diagnosed focal scleroderma, demonstrating white-matter predominant T2 hyperintensities with associated hemispheric atrophy and ex-vacuo ventricular dilation. (*B*) Axial computed tomography demonstrates associated calcification.

neutrophilic or lymphocytic pleocytosis and potentially elevated intracranial pressure. Peripheral neutrophilia, hyperferritinemia, transaminitis, and lymphadenopathy may all be helpful systemic disease indicators.[48,49]

Finally, IgG4-related disease may be associated with meningitis, and imaging demonstrates dural thickening with smooth pachymeningeal and/or leptomeningeal enhancement with potential to cause underlying mass effect (see **Fig. 1**).[50] CSF shows lymphocytic meningitis in more than half of patients with CNS involvement, nearly always with elevated IgG index or OCBs. When performed, CSF IgG4 levels may also be markedly increased.[51] Diagnosis of IgG4-related disease often requires biopsy.

Other autoimmune meningitis

Headache with neurologic deficits and CSF lymphocytosis (HaNDL) describes a characteristic clinical syndrome of acute onset headache, lymphocytic meningitis, and temporary neurologic deficits often preceded by a viral-like illness.[52] As biopsy is not performed in these patients due to the very self-limited nature of symptoms, the pathophysiology of HaNDL has been debated but is generally favored to be autoimmune.

Diagnostic Approach

When evaluating patients with meningitis or encephalitis, clinicians must simultaneously consider potential autoimmune, infectious, and neoplastic causes. Important serum testing in most patients will include human immunodeficiency virus serologies, rapid plasma reagin, and rheumatologic screening testing including erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibodies. In cases with higher suspicion for autoimmune diseases, rheumatologic testing should be expanded, especially to include those tests identified in **Table 3**. Workup should also include a brain MRI scan with and without contrast, and lumbar puncture for cell count, differential, protein, glucose, Gram stain and culture, OCBs, and IgG index.[53] Clinicians must use caution interpreting CSF OCBs or IgG index, as both are nonspecific markers for intrathecal antibody production and may be abnormal in both autoimmune and infectious causes of meningitis and encephalitis.[54] Targeted CSF testing for treatable, common organisms such as herpesviruses and cryptococcus should

be done in most patients, as well as CSF cytology and flow cytometry when neoplasm is considered. Finally, given the substantial etiologic overlap between autoimmune and infectious pathologies, broad testing for CNS infections such as metagenomic next-generation sequencing or universal polymerase chain reaction should be strongly considered where available to help broadly evaluate likelihood of infection.[55]

Regardless of whether meningitis or encephalitis is of autoimmune, infectious, or neoplastic origin, systemic workup with imaging and possible biopsy may be helpful and should be aggressively pursued. CT of the chest, abdomen, and pelvis is useful in identifying systemic malignancy and/or sites of extracranial disease involvement, potentially providing opportunity for biopsy. In undifferentiated meningitis or encephalitis, such biopsies should almost always be performed when feasible and low-risk. PET may add sensitivity for finding systemic involvement of malignancy or sarcoidosis and can also identify specific cerebral pathologies such as amyloid.[3,33] Ophthalmologic and dermatologic examinations can reveal suggestive or even diagnostic findings, and vitreal and skin biopsies should be pursued when abnormalities are found. In fact, due to the low associated morbidity, it may even be reasonable to pursue blind skin biopsy when considering certain causes of meningitis or encephalitis.[56] Additional testing for systemic diagnostic clues should be pursued as targeted to the most likely diseases (see **Table 3**), such as transvaginal or scrotal ultrasound in patients with suspected NMDA-R encephalitis.[6]

Narrowing the Autoimmune Differential Diagnosis

It is helpful for clinicians to recognize features that increase the likelihood of an antibody-mediated disorder and thereby defer brain biopsy.[57] Patients presenting with subacute classic syndromes such as cerebellar degeneration or limbic encephalitis should raise suspicion (see **Table 2**).[58] Similarly, MRI scans with abnormalities that demonstrate a particular functional tropism, such as for the temporal lobes, diencephalon, or specific white matter tracts, suggest an antibody-mediated process. In addition, normal MRI scans in patients who nevertheless have a clinical syndrome consistent with a particular functional tropism are also suspicious for an antibody-mediated process.[5,59] CSF for patients with neuroantibodies typically shows either absent or modest CSF lymphocytic pleocytosis (median 4–8 cells/mm^3), normal glucose, and often independent OCBs or elevation in IgG index with some variability.[60–62] Anti-NMDA-R and antiglutamic acid decarboxylase (GAD) encephalitis in particular are associated with oligoclonal bands, which are seen less often in VGKC-complex antibody syndromes.[62,63] In contrast, marked CSF pleocytosis, neutrophilic pleocytosis, and/or hypoglycorrhachia are more typical of several nonautoantibody associated autoimmune causes of meningitis such as sarcoidosis.[3] Finally, patients with a preexisting history or new diagnosis of systemic malignancy, particularly those such as small cell lung cancer, are at particular risk for a paraneoplastic autoantibody.[6]

High likelihood of an antibody-mediated process

When clinical features strongly suggest an autoantibody-mediated process, clinicians should make every effort to maximize the yield of autoantibody testing and await results before pursuing higher risk testing such as brain biopsy.[57] Autoantibody panels should be sent from both serum and CSF, with consideration for simultaneous targeted testing for individual antibodies to hasten diagnosis. Plasmapheresis, intravenous immunoglobulin (IVIG), and steroids may all reduce the yield of antibody assays and thus should be avoided before testing whenever clinically feasible.[58] However, because plasmapheresis and IVIG are unlikely to reduce diagnostic yield of biopsy, either may be used as empirical therapy in patients for whom there is high

suspicion of an antibody-mediated process even before antibody results return. In contrast, initiation of steroids before brain biopsy is strongly associated with a nondiagnostic sample, and so empirical corticosteroids should be avoided until a definitive diagnosis is established whenever possible.[64]

Low likelihood of an antibody-mediated process

In patients with undifferentiated autoimmune meningitis or encephalitis whose disease features do not align well with an antibody-mediated process, either brain or systemic biopsy is commonly required for diagnosis, with primary exceptions including classic presentations of ADEM, Vogt-Koyanagi-Harada disease, Susac syndrome, CLIPPERS, HaNDL, and occasionally amyloid-PET positive ABRA or CAARI. Even in patients seropositive for rheumatologic diseases—for example, a patient with RA and new encephalitis—a biopsy is often critical to exclude other pathologies due to the rarity of meningitis or encephalitis associated with these illnesses. Systemic biopsy sites may be very helpful, such as skin, lymph node, bone marrow, labial, or salivary gland, and should be comprehensively assessed and pursued.[65] However, in the absence of such options, brain biopsy is often the best next step in patients without a diagnosis who are not spontaneously improving.

The choice of whether and when to pursue brain biopsy can be challenging and requires weighing risks and benefits. In patients who are rapidly deteriorating or have severe symptoms (increased intracranial pressure, cerebral edema, hydrocephalus) risks of withholding treatment are greater and brain biopsy should be pursued more aggressively. In patients with easily accessible brain abnormalities characteristic for a disease that requires tissue such as PACNS, pursuing relatively early biopsy may be cost- and time-efficient. Immune suppressed patients have a higher likelihood of diagnostic brain biopsy and of finding a dual diagnosis, and threshold for biopsy should be lower.[65] In contrast, those patients with disease only affecting eloquent brain areas, or who are otherwise at high complication risk, brain biopsy should be avoided when possible. Infratentorial lesions in particular are less likely to yield a diagnosis, perhaps due to hesitancy in obtaining sufficient tissue or due to especially challenging operative approaches.[65] Finally, patients who are already improving on empirical therapy, particularly steroids, will have lower tissue yield and biopsy should be delayed to such a time if and when symptoms recur.

Ultimately, recent evidence demonstrates that more than 70% of brain biopsy samples may provide a specific histologic diagnosis—a percentage much higher than for many solid-organ biopsies.[65] Furthermore, permanent neurologic morbidity and mortality rates are low and compare favorably to complication rates for systemic biopsies.[57,65] It is therefore reasonable for clinicians to consider brain biopsy early in the diagnostic algorithm in patients with a negative less-invasive workup, lack of systemic biopsy options, and an accessible brain lesion, particularly in those tertiary care centers with high levels of expertise and experience.

Maximizing Yield of Brain Biopsy

Once the decision is made to pursue brain biopsy, clinicians should make every effort to maximize tissue yield and minimize morbidity. Steroids should be avoided or minimized for 2 weeks before biopsy to reduce risk of a nondiagnostic sample.[64] Target site should be chosen based on the presence of an imaging abnormality balanced with anatomic eloquence; the presence of enhancement can suggest higher likelihood of yield but the association is not strong.[57,65,66] Autopsy can occasionally yield a specific tissue diagnosis where brain biopsy does not, indicating that sufficient biopsy size is also helpful.[66] It is recommended to sample 1 cubic centimeter containing whichever structures

are of highest clinical interest (dura, leptomeninges, white or gray matter). The decision of where and what structures to biopsy should be a collaborative decision between neurologists, neurosurgeons, and neuroradiologists. Finally, because brain biopsy yield is lower in patients with unspecified encephalitis particularly when additional follow-up pathologic analyses are not performed, providers should discuss which disease entities are of highest suspicion with neuropathology, in order to ensure appropriate specimen handling that enables these follow-up studies.

After the biopsy, platelet count should be maintained greater than 100 G/L for a minimum of 7 days due to the association between thrombocytopenia and brain biopsy complications.[65] In those patients in whom brain biopsy does not yield a specific diagnosis, often pathology results can still be useful in narrowing the differential diagnosis and providing avenues for additional workup.[66]

Special Clinical Situations

Immune checkpoint inhibitor therapy

Immune checkpoint inhibitors (ICIs) target the regulatory steps of T-cell activation and thereby enhance the endogenous immune response against neoplastic disease. Although such therapies have revolutionized cancer therapy, 4% to 14% of patients receiving ICIs develop autoimmune disease of the nervous system.[67] Neuromuscular syndromes are the most common, but CNS manifestations occur almost as often, including hypophysitis, encephalitis, meningoencephalitis, and more rarely isolated meningitis. Brain MRI abnormalities in these patients are variable and include localized T2 hyperintensities, focal atrophy, or parenchymal or meningeal enhancement, whereas CSF will nearly always demonstrate a mild lymphocytic pleocytosis occasionally with independent OCBs. Clinicians should emphasize the evaluation for autoantibody syndromes when assessing patients with suspected ICI-associated encephalitis, as more than half have detectable, known neural-specific autoantibodies, most of which target intracellular or synaptic antigens and present with symptoms typical for the antibody.[67] However, nonantibody-mediated CNS autoimmune disease has also been associated with ICI initiation, including neurosarcoidosis, vasculitis, and Vogt-Koyanagi-Harada syndrome.[67,68] Because neurologic autoimmunity after ICI use typically arises within 3 months of treatment initiation, providers must maintain an especially high suspicion for autoimmune etiologies in patients presenting with meningitis or encephalitis within this period.[67] In fact, in these cases often testing can be abbreviated and invasive diagnostics such as brain biopsy forgone in favor of empirical steroids, IVIG, or plasmapheresis.

Autoimmune disease related to severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has been associated with numerous neurologic complications including encephalitis, meningoencephalitis, and rarely isolated meningitis.[69–72] Some presentations resemble autoantibody syndromes, such as limbic encephalitis, seizures, brainstem dysfunction, involuntary movements, and concurrent acute peripheral nervous system disease, although specific autoantibodies are variably identified.[69,73] Other patients present with fulminant AHLE including typical multifocal white matter lesions with microhemorrhage, enhancement, and edema on MRI and often lymphocytic pleocytosis on CSF.[71] Finally, acute necrotizing encephalopathy has been associated with SARS-CoV2, specifically manifesting as bilateral T2 signal and necrosis in the deep gray matter on MRI and by definition requiring an acellular CSF.[74] It is unclear whether these processes represent direct viral injury, a hyperinflammation syndrome concurrent with acute illness, or a postinfectious autoimmune process, as SARS-CoV2 genetic material is only occasionally detected in

CSF samples.[69,75] However, many patients demonstrate improvement with corticosteroids, IVIG, or plasmapheresis, at least in part supporting an autoimmune cause.[69,74]

Unidentified neural antibodies

Because the spectrum of autoantibody-associated neurologic disease is rapidly evolving and novel antigens are regularly being discovered, it is unsurprising that occasionally a pattern of neural-specific binding may be observed that has not previously been described.[1,76] In these cases the presence of an as-yet unidentified antibody is suspected. Although evidence-based guidance for the management of these cases is lacking, when diagnostic results indicate an unidentified neural autoantibody, it is reasonable for clinicians to complete an abbreviated workup for other diagnoses, aggressively seek systemic neoplastic disease, but forgo brain biopsy and proceed with empirical therapy with corticosteroids, IVIG, or plasmapheresis. Such patients should be referred for research-based testing whenever possible, as technology for novel autoantibody discovery is continuously evolving and such patients are critical to promote ongoing progress in the field.[77]

Management

In cases of autoimmune meningitis or encephalitis, once a specific neural autoantibody is found, a tissue diagnosis made, or a characteristic syndrome identified, diagnostic testing is tapered and clinicians consider therapeutics. However, there are particular situations in which diagnostic errors are especially likely, and this transition should be made carefully to avoid diagnosis momentum.

False-positive test results

Certain autoantibodies, such as GAD-65 and VGKC complex antibodies, may be commonly found in asymptomatic individuals. Clinicians should carefully consider the possibility of a false-positive result when an autoantibody is present in the serum but not the CSF, if the autoantibody does not fit the patient's clinical syndrome, or if the autoantibody is only present at low titers (<1:80).[6] Serologic testing performed after IVIG administration may also lead to false positives.[1] When uncertainty arises, clinicians can discuss results and clinical presentation with the testing laboratory for clarification. Furthermore, although tissue pathology is the gold-standard diagnostic test for many autoimmune disorders of the CNS, results still should be interpreted with caution. For example, noncaseating granulomas suggest sarcoidosis but can also be due to other infectious and noninfectious diseases.[3]

A word of caution is also worth mentioning in the interpretation of elevated antithyroid antibodies, specifically antithyroid peroxidase and antithyroglobulin. These are antibodies that have been classically associated with the diagnosis of steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), originally termed Hashimoto encephalopathy. However, antithyroid antibodies are present in up to 13% of healthy individuals and are likely an indicator of an autoimmune predilection rather than a specific disease.[7] Indeed, recent evidence suggests that greater than 70% of patients with suspected SREAT have a nonimmune-mediated neurologic disorder and more than half do not have evidence of any primary neurologic disorder.[78] The presence of positive antithyroid antibodies should therefore be interpreted with significant caution and should not be used as an independent criterion to determine the presence of CNS inflammation.

Treatment and monitoring

High-dose intravenous corticosteroids are first-line therapy for most of the autoimmune causes of meningitis and encephalitis discussed in this article. In steroid-refractory

fulminant demyelinating conditions and most autoantibody-mediated syndromes, steroids are combined with either IVIG or plasmapheresis as first-line therapy.[5,16] Common second-line treatments for CNS autoantibody syndromes include rituximab or cyclophosphamide.[5] Beyond corticosteroids, the management for autoimmune meningitis or encephalitis without an associated autoantibody is specific to the disease and may include cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, tumor necrosis factor-α inhibitors, and less often rituximab.[3,17,31,38] Patients receiving long-term corticosteroids and other immune suppression should be screened for latent infections and receive up-to-date vaccines before initiation and be prescribed prophylaxis to prevent opportunistic infections, osteoporosis, or gastric ulcers as needed.[58]

Patients with autoimmune meningitis and encephalitis are also at high risk for numerous comorbid complications including seizures, hydrocephalus, and cerebral edema and should be monitored accordingly. Increased intracranial pressure may be seen in AHLE, neurosarcoidosis, HLH, various cerebral vasculitides including ABRA, and SARS-CoV2-associated CNS inflammatory syndromes.[3,16,17,32,47] In addition, although seizures may complicate most CNS disorders, patients with antibody-associated encephalitides are at particular risk for refractory seizures.[1,6]

SUMMARY

Meningitis and encephalitis are inflammatory syndromes of the meninges and brain parenchyma, respectively, and may be identified either by finding definitive evidence of inflammation on tissue pathology or by CSF analysis showing pleocytosis or intrathecal antibody synthesis. Clinicians evaluating undifferentiated meningitis or encephalitis should simultaneously consider autoimmune, infectious, and neoplastic causes, using patient risk factors, clinical syndrome, and diagnostic results including CSF and MRI findings to narrow the differential diagnosis. If an autoimmune cause is favored, an important early diagnostic question is whether a specific neural autoantibody is likely to be identified. If so, clinicians should pursue a thorough evaluation for the autoantibody concurrent with a tailored neoplastic workup and await results of autoantibody testing whenever possible before pursuing brain biopsy. Empiric IVIG or plasmapheresis may be given particularly in deteriorating patients, but if brain biopsy remains a possibility, corticosteroids are often best withheld pending definitive diagnosis. In patients for whom autoantibody-associated disease is not favored, brain or systemic biopsy is often warranted and should be pursued with efforts to maximize its yield. Finally, once the specific cause of autoimmune meningitis or encephalitis is identified and false positives are unlikely, systemic corticosteroids plus additional disease-specific treatment may be initiated.

CLINICS CARE POINTS

- The presence of inflammation in the meninges or brain parenchyma often indicates a treatable disorder, and clinicians should consider infectious, neoplastic, and autoimmune diseases in patients with undifferentiated meningitis or encephalitis. Suspicion for autoimmune disease is heightened in younger patients with subacute disease onset and/or a personal or family history of autoimmunity, but infectious and neoplastic disorders should nevertheless be simultaneously considered and evaluated.
- Early evaluation of suspected autoimmune encephalitis should include assessment for specific neural autoantibodies, as the identification of a positive antibody often precludes the need for brain biopsy and allows therapeutics to commence.
- Numerous autoimmune processes without specific associated neural autoantibodies can cause isolated meningitis, encephalitis, or both concurrently. These diseases may be categorized into histiocytic, fulminant demyelinating, vasculitic, amyloid-related, and

systemic rheumatologic disorders. Although several have characteristic features and may be diagnosed clinically, many require tissue sampling to confirm.

- Although clinicians should aggressively seek alternative systemic biopsy sites when available, brain biopsy is a high-yield and relatively low-morbidity procedure in the appropriate clinical setting.

DISCLOSURE

The author has nothing to disclose.

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