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AUTOIMMUNE ENCEPHALITIS – WHEN TO SUSPECT?

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ABSTRACT Autoimmune encephalitis is a relatively new category of immune-mediated disease involving the central nervous system that demonstrates a widely variable spectrum of clinical presentations, ranging from the relatively mild or insidious onset of cognitive impairment to more complex forms of encephalopathy with refractory seizure. Due to its diverse clinical features, which can mimic a variety of other pathologic processes, autoimmune encephalitis presents a diagnostic challenge to clinicians. 1Autoimmune encephalitis causes subacute deficits of memory and cognition, often followed by suppressed level of consciousness or coma. A careful history and examination may show early clues to particular autoimmune causes, such as neuromyotonia, hyperekplexia, psychosis, dystonia, or the presence of particular tumors.2 In this article we will review autoimmune encephalitis with special emphasis on when to suspect autoimmune encephalitis.

KEYWORDS : Autoimmune, Encephalitis, Neuromyotonia, Hyperekplexia, Psychosis

INTRODUCTION

Autoimmune encephalitis is a difficult clinical diagnosis due to the similarities in the clinical, imaging and laboratory findings of many forms of autoimmune and infectious encephalitis. Ancillary testing with MRI and EEG may be helpful for excluding other causes, managing seizures, and, rarely, for identifying characteristic findings. Appropriate autoantibody testing can confirm specific diagnoses, although this is often done in parallel with exclusion of infectious and other causes. Imaging findings in patients with these disorders can also be quite variable, but recognizing characteristic findings within limbic structures suggestive of autoimmune encephalitis can be a key step in alerting clinicians to the potential diagnosis and ensuring a prompt and appropriate clinical work-up.[2] Patients generally have impaired memory and cognition over a period of days or weeks. There may be clues to specific causes on history of physical examination, but often these specific signs are absent. A broad approach to testing for infectious diseases and various neuronal autoantibodies can lead to the correct diagnosis. If a clear autoimmune cause for the symptoms is established, treatment usually involves escalating immune therapies. The process of caring for these patients requires patience and repeated evaluations to determine the proper degree of immune therapy needed at any given time.

CLINICAL CLUES TO THE DIAGNOSIS OF AUTOIMMUNE ENCEPHALITIS[3]

Subacute onset of memory impairment (short-term memory loss), encephalopathy or psychiatric symptoms

At least 1 of the following:

1. Focal neurological deficits
2. Unexplained seizures
3. CSF pleocytosis (white blood cell count >5 cells per mm3)
4. MRI features suggestive of encephalitis.
5. Exclusion of alternative causes

Important clinical clues to suspect autoimmune encephalitis are subacute onset, fluctuating course, mood and behavior changes, cognitive dysfunction, seizures, dyskinesias and tremors.[4] This may be supplemented by T2 hyperintensity on MRI (most commonly in the mesial temporal region), inflammation in CSF hypometabolism on functional imaging and confirmation comes with detection of specific autoantibody. (Improvement after immunotherapy may be diagnostically informative). However, obtaining autoantibodies urgently in resource poor settings may be challenging and waiting for response to immunotherapy may not be prudent, as some patients may need second line immunosuppressive treatment.

Table 1- Clinical Clues In The Recognition Of Particular Type Of Autoimmune Encephalitis

Clinical findings	Associated Antibody Disorder
Psychosis	NMDAR, AMPAR, GABA-B-R
Dystonia, chorea	NMDAR, Sydenham chorea, D2R
Hyperekplexia	GlyR
Status epilepticus	Most characteristic of GABA-B-R and GABA-A-R but NMDAR is much more common; may occur in other types as well
New onset type 1 diabetes	GAD65
Fasciobrachial dystonic seizures	LGI1
Neuromyotonia, muscle spasms, fasciculations	Caspr2
Stiff-person syndrome and/or exaggerated startle	GAD65, GlyR, Amphiphysin (with GAD65 being most common in stiff person/stiff limb and GlyR in PERM, and Amphiphysin in women with breast cancer)
CNS (myoclonus, startle, delirium) and gastrointestinal hyper-excitability	DPPX
Cranial neuropathies	Ma2, Hu, Miller-Fisher, Bickerstaff (but also infections like Sarcoidosis, Lyme, TB)
Cerebellitis	GAD65, PCA-1 (Yo), ANNA-1 (Hu), DNER (Tr), mGluR1, VGCC

Psychiatric manifestations are common early in the course of autoimmune encephalitis. These may include psychosis, aggression, inappropriate sexual behaviors, panic attacks, compulsive behaviors, euphoria or fear. Symptoms may fluctuate rapidly. Although this presentation is well known for anti-NMDAR encephalitis[5], anti-AMPAR and anti-GABA-B-R both may have prominent early psychiatric manifestations [4].Overall, anti-NMDAR encephalitis is more common and should be suspected first, especially in young adults and children, but they could each cause this presentation across a wide range of ages.

Abnormal movements may be the presenting symptom in several types of autoimmune encephalitis. These include anti-NMDAR encephalitis, where movement symptoms may occur early in the disease course, especially in children, who generally have more motor symptoms and fewer psychiatric symptoms than adults. [6] These may resemble dystonia or chorea, with writhing and fixed abnormal postures of the limbs. In adults with anti-NMDAR encephalitis, writhing movements of the face and limbs may be most prominent in the comatose phases of the illness. GAD65 and GlyR autoimmunity may present with stiff person syndrome (SPS) or progressive encephalomyelitis with rigidity and myoclonus (PERM).[7] A striking feature of PERM with GlyR antibodies is a pathologically exaggerated startle response, resembling hereditary hyperekplexia, a genetic disease caused by GlyR mutations.[8] Although there is some degree of overlap, GAD65 is more associated with classical SPS while GlyR antibodies may be seen more with symptoms of hyperekplexia and myoclonus, which are prominent in PERM. Stiffness or exaggerated startle combined with other symptoms of encephalitis should raise concern for GlyR antibodies. Basal ganglia encephalitis has also been reported with D2R antibodies, although this may be very rare.[9] Sydenham chorea is a well-recognized autoimmune movement disorder thought to be triggered by streptococcal infections and should be considered in children with this presentation.[10]

Seizures are common in autoimmune encephalitis and may be a presenting symptom. In anti-NMDAR encephalitis seizures may occur at any stage of the illness. Autoantibodies to two important inhibitory receptors in the brain, GABA-B and GABA-A receptors (at high titer) convey a high risk of severe seizures and intractable status epilepticus.[11,12] GAD65 antibodies may present with epilepsy, perhaps also with memory impairment, but with few other symptoms to suggest an autoimmune etiology. GAD65 autoimmunity may therefore resemble other forms of treatment resistant epilepsy. Faciobrachial dystonic seizures (FBDS) are brief seizures consisting of rapid jerks of the face and/or ipsilateral arm and shoulder.[13] Seizures may be partial or associated with temporary disruptions in consciousness and may be multifocal and variable on EEG. FBDS are characteristic of LGI1 autoimmunity and may precede other symptoms of the disease by weeks or months. Patients may have hundreds of these seizures per day. These seizures may have only limited response to seizure medications but respond well to immune therapies.

Cerebellitis is a distinct syndrome of ataxia of gait, limb movements, eye movements, voice, and/or swallowing. The precise mixture of symptoms varies from patient to patient. Vertigo and nystagmus are common. Cerebellitis may occur with infectious causes, but the presentation of a subacute cerebellar syndrome portends a good probability a specific autoimmune etiology and also a significant risk of tumors. Paraneoplastic cerebellar degeneration is associated with conventional onconeuronal autoantibodies such as Yo, but also with cell surface autoantibodies targeting mGluR1, DNER, and other antibodies. GAD65 antibodies are perhaps the most common finding in this phenotype in my experience. Autoimmune cerebellitis may result in the irreversible loss of Purkinje neurons, and the prognosis is recovery may be poorer than with other types of autoimmune encephalitis.

Certain types of autoimmune encephalitis may precede or follow neuromuscular manifestations, particularly acquired neuromyotonia (Isaacs syndrome). Isaacs syndrome presents with muscle spasms, cramps and fasciculations due to peripheral nerve hyper-excitability. [14,15] Morvan syndrome (Morvan's fibrilllary chorea) consists of peripheral nerve hyper-excitability with encephalitis and severe insomnia. Some cases of Isaacs syndrome are associated with autoantibodies to Caspr2 or other, often undefined, members of the voltage-gated potassium channel (VGKC) complex.[16,17] Caspr2 antibodies are even more likely in patients with Morvan syndrome, especially patients with thymoma, who may have multiple autoimmune disorders during their disease course. Encephalitis with these neuromuscular manifestations (myasthenia gravis, neuromyotonia) therefore suggests a specific autoimmune etiology.

Detecting particular tumors may therefore also suggest particular autoimmune causes. For instance, the likelihood of anti-NMDAR encephalitis is increased in a young woman with ovarian teratoma, and the likelihood of anti-DNER is higher in patients with cerebellar degeneration and Hodgkin lymphoma.

EXCLUSION OF OTHER AUTOIMMUNE DISORDERS

In addition to the antibody-mediated and paraneoplastic forms of encephalitis, there are other autoimmune diseases that may present with encephalitis.

1. ADEM, encephalitis is a common presentation. The characteristic brain lesions, and sometimes involvement of the optic nerves or spinal cord, are an important clue to diagnosis.
2. Multiple sclerosis (MS) is generally easier to distinguish from autoimmune encephalitis due to more focal symptoms and characteristic brain imaging findings.
3. Lupus may affect diverse areas of the nervous system, causing neuropathy, vasculitis, myelitis, venous sinus thrombosis, stroke, and other manifestations. [18] In one large series, one fourth of deaths from lupus were related to CNS involvement and 16% were due to CNS infection, suggesting vigilance for both autoimmune and infectious encephalitis is warranted for these patients.[19]
4. Vasculitis affecting the CNS may rarely present with symptoms resembling encephalitis. When this is suspected, imaging of the cerebral vessels, search for other evidence of vasculitis (such as serologies for lupus and other rheumatologic diseases) may be useful.
5. Bickerstaff encephalitis and Miller Fisher syndrome enter into the differential diagnosis of autoimmune encephalitis due to the presence of altered mental status and/or cranial neuropathies. These diseases may at first resemble the brain-stem syndrome associated with anti-Ri, but the loss of reflexes is an important clue suggesting Miller Fisher syndrome. Detection of the GQ1b antibody may be helpful in securing these diagnoses.[20]

EXCLUSION OF INFECTIOUS CAUSES

It is typical for patients with autoimmune encephalitis to have testing for various infectious etiologies and they are frequently covered with antibiotic and/or antiviral therapies (such as acyclovir) empirically as infectious causes are excluded. Some of the relevant risk factors for various causes of encephalitis are:

Table 2: Risk Factors For Autoimmune And Infectious Encephalitis

Risk factor	Implications
Travel	Consider infectious causes of encephalitis in visited region
HIV	Opportunistic infections, risk depending on CD4 count
Transplantation	Opportunistic infections (CMV, VZV, HSV1, 6, 7); if recently transplanted, consider infection from donor
Systemic autoimmunity	Consider lupus cerebritis, vasculitis
Cancer	Consider specific paraneoplastic syndromes based on tumor, but also lymphomatous/carcinomatous tumor involvement
Prior encephalitis	Consider relapse of initial encephalitis, secondary autoimmune causes, and (if immunosuppressed) opportunistic infections

EXCLUSION OF OTHER MEDICAL CAUSES

Wernicke encephalitis, due to thiamine deficiency, is most recognized in alcoholics but may also affect patients with gastric bypass or other causes of insufficient nutrition [21,22]. Prompt and thorough repletion with thiamine, often along with other nutrients, may be lifesaving and should not wait on laboratory confirmation of the diagnosis.

Intoxications such a neuroleptic malignant syndrome and serotonin syndrome may often present with similarities to autoimmune encephalitis.[23] Conversely, patients with anti-NMDAR encephalitis may develop psychosis as an initial symptom and be treated with neuroleptics, then later show catatonia, rigidity, autonomic instability and altered level of consciousness; this pattern of findings may be mistaken for neuroleptic malignant syndrome.

Lymphoma or carcinomatous meningitis may present similarly to autoimmune encephalitis[24] Particularly, symptoms may have a subacute onset and involve multiple cranial neuropathies. Both may occur in patients with or without known tumors. Repeating CSF cytology, awareness of known tumors, and screening for malignancy

may all help lead to recognition of these causes.

DIAGNOSTIC APPROACHES

Antibody testing

Autoantibody testing is extremely important for the proper diagnosis of autoimmune encephalitis. However, the tests have complexities that require consideration, and taking certain test results as conclusive evidence of autoimmune encephalitis can be a mistake.

Commercial tests for autoantibodies to NMDAR, LGI1, Caspr2, AMPAR (GluR1, GluR2 subunits), and GABA-B-R are widely available. Newer cell surface antigens like GABAA-R and DPPX are more difficult to test clinically. The synaptic intracellular antigens GAD65 and Amphiphysin, as well as the conventional intracellular "onconeuronal" antibodies are widely available.

NMDAR and other cell surface antibody tests are most sensitive and specific with CSF. Serum may offer a low false positive rate and a higher false negative rate. Pathogenic cell surface or synaptic autoantibodies are IgG responses. NMDAR IgM and IgA responses have been reported in patients with schizophrenia and other psychiatric disease but also in up to 10% of normal controls; these IgM and IgA responses have no established role in diagnosing autoimmune encephalitis.[25]Conversely, the types of IgG responses associated with anti-NMDAR encephalitis are not found in patients with schizophrenia.[26]

However, titers in NMDAR encephalitis have limited clinical utility for several reasons: [27]

1) absolute titers provide little information on disease severity
2) titers in serum do not correlate reliably with disease status
3) CSF titers correlate only roughly to disease status within a given patient using side-by-side comparisons of multiple samples.

Therefore, it is better to focus on the clinical status of the patient and not changes in antibody titer during the early phases of the illness. NMDAR CSF titers may be compared to earlier samples side by-side in assessing whether clinical worsening represents a true relapse, but this is only rarely helpful.

Caspr2 and LGI1 each associate with VGKCs. The VGKC antibody test is based on immunoprecipitation of a complex of protein containing VGKCs, LGI1, Caspr2 and other proteins.

The VGKC test may still detect patients with LGI1 or Caspr2 immunity, but low titer serum positive results have uncertain clinical significance. Paterson et al. reported that only 4 of 32 patients with low titer VGKC results (100-400 pM) actually had an autoimmune disorder. Thus a low titer serum VGKC result without corresponding evidence of LGI1 or Caspr2 antibodies, ideally in the CSF, should not be taken as definitive evidence of autoimmune encephalitis. [28,29,30]

GAD65 antibodies have diverse clinical correlates, including SPS, cerebellar degeneration, epilepsy, and type 1 diabetes.[31] In the context of encephalitis, especially with epilepsy, a CSF GAD65 response is evidence of an autoimmune etiology. In addition, low titer GAD65 serum responses may not be specific for a neurological disorder, and GAD65 serum antibodies provide little additional information in a patient with known type 1 diabetes. Testing CSF of these patients for GAD65 and a panel of other autoantibodies may be informative in these cases.

Hashimoto's encephalopathy is generally defined as encephalopathy associated with thyroid autoantibodies that responds to steroids or other immune therapies[32]. Thyroid antibodies are therefore sometime tested in patients with autoimmune encephalitis. Finding thyroid antibodies should prompt a careful search for responsive other autoantibodies to brain that would provide a more convincing explanation of the symptoms. But if these antibodies are not found immune therapy should be considered.

Imaging

Brain MRI in patients with NMDAR, AMPAR, LGI1, Caspr2, and GABA-B antibodies may be normal or show increased T2 signal, especially in the medial temporal lobes [33,34.] This pattern is similar to the findings seen in HSV encephalitis, where 95% of patients have abnormalities on MRI, [35] or other viral causes of encephalitis. Tuberculosis, Syphilis, or other infections may present similarly. Autoantibodies to DPPX or GABA-A may have less characteristic findings.[36] Brain MRI therefore does not distinguish between infectious and autoimmune causes, and a normal brain MRI does not exclude these causes.

Advanced brain imaging with PET or SPECT has shown diverse areas of regional hyper- or hypo-metabolism in patients with NMDAR, LGI1, Caspr2 or other autoantibodies.[36]

EEG

EEG is useful in patients with autoimmune or infectious encephalitis for excluding subclinical seizures, for prognosis, and sometimes for suggesting particular diagnoses. In patients with HSV encephalitis, EEG may predict prognosis in addition to helping exclude non-convulsive seizures; normal EEG correlates with good outcomes independent of other prognostic factors. [37,38]

Seizures may occur at any point during the disease course of anti-NMDAR encephalitis, including at presentation.[39] The extreme delta brush pattern may be observed in patients with anti-NMDAR encephalitis, most often in patients who are comatose [39].This distinctive EEG pattern should prompt testing for NMDAR antibodies. Patients with anti-NMDAR encephalitis and other forms of autoimmune encephalitis may also have prolonged periods of unresponsiveness and abnormal behaviors that are not due to seizures, so in these cases prolonged EEG monitoring may be very helpful.

Status epilepticus may occur in several forms of autoimmune encephalitis. The highest risk appears to be in patients with autoantibodies to the major brain inhibitory receptors GABA-A and GABA-B. High-titer antibodies to either of these antigens conveys a risk of status, which may be refractory to the unusual treatments. Since these antibodies are both much rarer than autoantibodies to the NMDA receptor, the status epilepticus in the setting of autoimmune encephalitis probably occurs more frequently with NMDAR antibodies overall.

LGI1 antibodies are associated with FBDS, which may present weeks or months prior to other symptoms. The clinical characteristics of these seizures are distinctive, involving rapid jerking of one side of the face and/or upper extremity. Each seizure tends to be unilateral but they may occur on both sides. Some events are simple partial and very rapid, but complex partial seizures may occur as they become more frequent. EEG may show multifocal onset seizures and other abnormalities.

Seizures in autoimmune encephalitis are associated with active disease (e.g., are unlikely to persist after remission of other symptoms of autoimmune encephalitis). These seizures may be very difficult to control with antiepileptic until the autoimmune disease is treated.

Biopsy

Brain biopsy generally is not used in the diagnosis of encephalitis for several reasons. Infections may be detected by PCR, culture or other less invasive methods. The well-defined autoantibody causes typically have antibody tests that are much less invasive and much more definitive. In addition, the results of biopsy are generally not definitive for a particular autoimmune etiology. Overall, the clinical impact of biopsy done for suspected encephalitis is low, with only about 8% of cases having clear benefit.[39]

Cancer screening

Paraneoplastic disorders are, in general, autoimmune disorders that are triggered by tumors. In many cases the target antigen is expressed by tumor tissue, such as HuD proteins in small cell lung cancer and NMDARs in ovarian teratoma.[40] In these patients it is likely that presentation of the antigen in the context of the tumor triggers the autoimmune response. However, other patients without tumors may have an identical clinical syndrome and immunological response (antibody specificity, neuropathology, etc.).

It is important to detect tumors promptly for several reasons.

1) Treating the relevant tumor is thought to be helpful for treating the autoimmune disorder.
2) Tumor therapy and immune therapy may need to be given simultaneously and in a coordinated fashion.
3) Treatment with steroids, rituximab, or cyclophosphamide could

complicate tumor diagnosis in the case of tumors like lymphoma.

In the case of "onconeuronal" antibodies to intracellular antigens such as Hu, the antibodies may occur more commonly in cancer patients than in patients with the autoimmune disease. For instance low titer serum Hu responses are common in small cell lung cancer patients without the anti-Hu neurological syndromes. For this reason, finding such an antibody should prompt a careful evaluation for tumor even if there is not a corresponding autoimmune disease.

Cell surface/synaptic antibodies are generally found in the spinal fluid only in patients with the relevant neurological disorder and are not found incidentally. Each of these antibodies has a cancer risk profile that should inform the search for tumors.

The testing strategy depends on the specific autoantibody and/or clinical syndrome. Where there is risk for lung cancer or other solid tumors, CT scans and PET/CT may be appropriate. In syndromes associated with ovarian teratoma, evaluation with ultrasound or pelvic MRI. In young men where Ma2 is diagnosed or suspected, testicular ultrasound is important. Breast imaging with mammogram or MRI, pap smear, and pelvic imaging may be most helpful in women with anti-Yo. Screening should be broad in patients with high-risk syndromes such as cerebellar degeneration even when a particular antibody is not identified. Tumors may be very small when the neurological symptoms begin, so screening is typically done on initial presentation and repeated at increasing intervals every 6 months. A patient with DNER antibodies (conveying a 90% risk of Hodgkin lymphoma) might have PET-CT at diagnosis then close follow-up with an oncologist and repeat studies starting 3-4 months later.

AUTOIMMUNE ENCEPHALITIS IN CHILDREN

Anti-NMDAR encephalitis is by far the most common type of antibody-mediated encephalitis in children. The age distribution of other types of synaptic autoimmune disorders either skews much older (the median age for LGI1 or Caspr2 antibodies is about 60 years) or the disorders are much less common (GABA-A antibodies) or both. In a study by the California encephalitis project, anti-NMDAR encephalitis was more common than any single viral etiology.[41]

Anti-NMDAR encephalitis in children may present differently than in adults.[42] Children are more likely to have abnormal movements (chorea, incoordination) early in the disease course and also may have atypical motor symptoms such as ataxia or hemiparesis. Children more often have seizures than adults. The classic symptoms of psychosis seen in adults are less common, but behavioral regression is frequently noted. Patients may have prominent speech difficulties.

Treatment strategies are similar in children and adults, but physicians may be more reluctant to use cyclophosphamide, relying more on rituximab as a second line treatment .Responses to treatment are similar in children and adults, with about half failing first line therapies. Ovarian teratoma is less likely in female children before puberty, so tumors are uncommon in young children.

CONCLUSION

The proper diagnosis of autoimmune encephalitis requires an organized approach. Evaluation should begin with a detailed history and physical examination to detect clues to specific causes. A diverse range of infections should be considered, and appropriate testing should be done to exclude relevant pathogens. Ancillary testing with MRI, EEG, and lumbar puncture may further support a diagnosis of encephalitis and potentially suggest particular causes. A broad group of autoantibody tests may be used to diagnose or exclude particular autoimmune causes, but these tests are complex and not every positive result is definite evidence of an autoimmune disorder. The risk of neoplasm should always be considered during initial treatment and follow-up visits, both in terms of diagnosing serious cancers and because specific tumors may suggest particular autoimmune causes. Treatment should depend on the pathophysiology of the disorder (e.g., T-cell-mediated or antibody mediated) and the clinical situation of the patient. Patients may relapse and should receive appropriate follow-up care from a physician familiar with the diseases.

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