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Overview of Diagnosis and Management of Autoimmune Encephalitis

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Abstract: **In this review we discuss the background of diseases, diagnostic and management approaches. Comprehensive search was conducted through; PubMed, Medline, and EBSCO databases, searching literature for relevant studies discussing the management of autoimmune encephalitis, using following Mesh terms: "autoimmune encephalitis" and "management". The appropriate medical diagnosis and management of autoimmune encephalitis needs an organized approach. Evaluation should start with a detailed history and physical examination to detect hints to specific reasons. A diverse variety of infections ought to be taken into consideration, and proper testing should be done to exclude relevant pathogens. Ancillary testing with MRI, EEG, and lumbar puncture might additionally support a medical diagnosis of encephalitis and possibly recommend specific causes. A wide group of autoantibody tests may be utilized to detect or exclude specific autoimmune causes, however these tests are complex and not every positive outcome is certain evidence of an autoimmune condition. The risk of neoplasm need to always be considered throughout initial treatment and follow-up visits, both in terms of diagnosing serious cancers cells and because particular tumors could recommend specific autoimmune causes. Therapy should depend on the pathophysiology of the condition (e.g., T-cell-mediated or antibody mediated) and the clinical situation of the patient. Patients could relapse and needs to receive proper follow-up care from a physician familiar with the illness.**

Keywords: **EBSCO databases, Autoimmune Encephalitis, MRI, EEG, and lumbar puncture.**

1. INTRODUCTION

Autoimmune encephalitis is a difficult clinical diagnosis due to the similarities in the clinical, imaging and research laboratory results of several types of autoimmune and infectious encephalitis. Patients typically have damaged memory and cognition over a duration of days or weeks. There could be hints to particular reasons on background of physical exam, but commonly these particular indications are absent. A broad technique to testing for infectious illness and different neuronal autoantibodies can lead to the proper medical diagnosis. If a clear autoimmune cause for the signs and symptoms is developed, therapy generally involves escalating immune therapies. The procedure of caring for these patients requires patience and duplicated examinations to figure out the appropriate level of immune treatment needed at any given time.

In this review we discuss the background of diseases, diagnostic and management approaches.

2. METHODOLOGY

Comprehensive search was conducted through; PubMed, Medline, and EBSCO databases, searching literature for relevant studies discussing the management of autoimmune encephalitis, using following Mesh terms: "autoimmune encephalitis" and "management". Searching databases was restricted to English published studies up to December, 2017. Furthermore, references from different identified articles were searched for more matches articles that could be useful in this review.

3. DISCUSSION

- **RECOGNIZING THE SYNDROMES OF AUTOIMMUNE ENCEPHALITIS:**

Autoimmune encephalitis can materialize with numerous unique disorders, complicating its recognition. The classical presentation of encephalitis includes a subacute (days to a few weeks) dynamic reduction in the degree of awareness, usually with fluctuations, and altered cognition. Memory, specifically retention of new info, might be impaired early in the clinical program. Patients could progress to coma. While many cases of autoimmune encephalitis are equivalent from each various other or viral encephalitis, there could be clues to certain autoimmune etiologies (Table 1).

Table 1.Clinical clues in the recognition of particular types of autoimmune encephalitis

Clinical finding	Associated autoantibody disorders
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

CNS: central nervous system, TB: tuberculosis.

Psychiatric manifestations are common early during autoimmune encephalitis. These might include psychosis, aggression, inappropriate sexual habits, anxiety attack, compulsive habits, euphoria or anxiety. Symptoms could fluctuate quickly. Although this discussion is popular for anti-NMDAR encephalitis [1], anti-AMPAR and anti-GABA-B-R both might have famous very early psychiatric symptoms [2].(Overall, anti-NMDAR encephalitis is much more usual and need to be suspected initially, particularly in young people and youngsters, but they might each trigger this presentation across a large array of ages).

Abnormal activities may be the presenting sign in numerous types of autoimmune encephalitis. These consist of anti-NMDAR encephalitis, where movement signs might take place early in the condition course, specifically in youngsters, who normally have a lot more motor signs and fewer psychiatric signs compared to grownups [3].These could look like dystonia or chorea, with writhing and taken care of irregular poses of the limbs. In grownups with anti-NMDAR encephalitis, writhing movements of the face and limbs might be most famous in the comatose phases of the health problem. GAD65 and GlyR autoimmunity may offer with rigid person syndrome (SPS) or progressive encephalomyelitis with rigidity and myoclonus (PERM) [4].A striking feature of PERM with GlyR antibodies is a pathologically exaggerated startle reaction, appearing like hereditary hyperekplexia, a genetic illness brought on by GlyR mutations [5].Although there is some degree of overlap, GAD65 is extra linked with classic SPS while GlyR antibodies could be seen more with symptoms of hyperekplexia and myoclonus, which project in PERM. Stiffness or overstated startle integrated with other signs of encephalitis ought to elevate problem for GlyR antibodies. Basal ganglia sleeping sickness has additionally been reported with D2R antibodies, although this could be very rare [6].Sydenham chorea is a well-recognized autoimmune movement disorder believed to be triggered by streptococcal infections and need to be taken into consideration in kids with this discussion [7].

Seizures prevail in autoimmune encephalitis and may be a providing sign. In anti-NMDAR encephalitis seizures may take place at any kind of phase of the health problem. Autoantibodies to 2 vital inhibitory receptors in the brain, GABA-B and

GABA-A receptors (at high titer) convey a high danger of serious seizures and intractable status epilepticus [8], [9].GAD65 antibodies might present with epilepsy, possibly likewise with memory impairment, however with few various other signs to suggest an autoimmune etiology. GAD65 autoimmunity might therefore appear like other kinds of treatmentresistant epilepsy. Fasciobrachial dystonic seizures (FBDS) are quick seizures being composed of quick jerks of the face and/or ipsilateral arm and shoulder [10]. Seizures might be partial or connected with temporary disturbances in consciousness and might be multifocal and variable on EEG. FBDS are characteristic of LGI1 autoimmunity and could precede other symptoms of the illness by weeks or months. Patients might have numerous these seizures daily. These seizures could have only restricted action to seizure medications but react well to immune therapies.

Cerebellitis is an unique disorder of ataxia of gait, limb motions, eye activities, voice, and/or swallowing. The precise mixture of symptoms differs from patient to patient. Vertigo and nystagmus are common. Cerebellitis may take place with infectious reasons, however the presentation of a subacute cerebellar syndrome portends a great possibility a specific autoimmune etiology as well as a considerable risk of tumors. Paraneoplastic cerebellar deterioration is related to conventional onconeuronal autoantibodies such as Yo, but likewise with cell surface area autoantibodies targeting mGluR1, DNER, and various other antibodies. GAD65 antibodies are perhaps one of the most typical finding in this phenotype in my experience. Autoimmune cerebellitis might cause the permanent loss of Purkinje nerve cells, and the diagnosis is healing could be poorer compared to with other sorts of autoimmune encephalitis.

- **DIAGNOSTIC APPROACHES:**

Antibody testing:

Autoantibody screening is incredibly crucial for the proper diagnosis of autoimmune encephalitis. Nevertheless, the examinations have intricacies that call for factor to consider, and taking particular examination results as definitive evidence of autoimmune encephalitis could be a mistake.

Commercial examinations for autoantibodies to NMDAR, LGI1, Caspr2, AMPAR (GluR1, GluR2 subunits), and GABA-B-R are widely available. Newer cell surface area antigens like GABAA-R and DPPX are harder to test medically. The synaptic intracellular antigens GAD65 and Amphiphysin, as well as the conventional intracellular "onconeuronal" antibodies are commonly offered. In the proper clinical context, these antibodies can be diagnostic. However there are complexities to analyzing some of these tests.

NMDAR and various other cell surface antibody tests are most sensitive and particular with CSF. Serum might offer a low false positive rate and a higher false negative rate. Pathogenic cell surface or synaptic autoantibodies are IgG reactions. NMDAR IgM and IgA responses have been reported in patients with schizophrenia and other psychiatric disease but additionally in approximately 10% of typical controls; these IgM and IgA reactions have no well established role in detecting autoimmune encephalitis [11]. Conversely, the sorts of IgG actions connected with anti-NMDAR encephalitis are not located in patients with schizophrenia [12].

The availability of titers for NMDAR antibodies has led some specialists to attempt to make use of these titers to guide therapy. However, titers have restricted clinical utility for a number of factors: 1) outright titers offer little info on condition intensity, 2) titers in serum do not associate reliably with illness standing, and 3) CSF titers associate just roughly to disease condition within a provided patient utilizing side-by-side comparisons of multiple samples [13].Therefore, it is better to concentrate on the clinical status of the patient and not adjustments in antibody titer during the early phases of the disease. NMDAR CSF titers might be compared with earlier samples sideby-side in evaluating whether clinical worsening represents a true regression, but this is just hardly ever helpful

Imaging:

Brain MRI in patients with NMDAR, AMPAR, LGI1, Caspr2, and GABA-B antibodies might be regular or show boosted T2 signal, particularly in the medial temporal lobes [1], [8]. This pattern is similar to the findings seen in HSV encephalitis, where 95% of patients have irregularities on MRI, [14] or other viral sources of encephalitis. Tuberculosis, Syphilis, or other infections could offer likewise. Autoantibodies to DPPX or GABA-A may have less particular searchings for [15].Brain MRI for that reason does not differentiate between infectious and autoimmune causes, and a regular brain MRI does not exclude these causes.

Advanced brain imaging with PET or SPECT has shown diverse areas of local hyper- or hypo-metabolism in patients with NMDAR, LGI1, Caspr2 or various other autoantibodies [16].These studies have not gotten to the point where any type of

certain type of sleeping sickness can be distinguished from one more, so I do not normally rely upon these research studies to regulation in or rule out autoimmune reasons in my method.

EEG:

EEG is beneficial in patients with autoimmune or infectious encephalitis for omitting subclinical seizures, for diagnosis, and often for recommending particular diagnoses. In patients with HSV sleeping sickness, EEG could anticipate diagnosis in addition to aiding leave out non-convulsive seizures; regular EEG correlates with excellent outcomes independent of other prognostic factors [17].

Seizures might happen at any type of factor during the disease training course of anti-NMDAR encephalitis, consisting of at discussion [18].The extreme delta brush pattern may be observed in patients with anti-NMDAR encephalitis, frequently in patients who are comatose [19].This distinct EEG pattern must prompt screening for NMDAR antibodies. Patients with anti-NMDAR encephalitis and other types of autoimmune encephalitis may likewise have lengthened periods of unresponsiveness and unusual actions that are not because of seizures, so in these situations prolonged EEG tracking might be extremely helpful.

Status epilepticus might happen in several forms of autoimmune encephalitis. The highest risk shows up to be in patients with autoantibodies to the major mind inhibitory receptors GABA-A and GABA-B. High-titer antibodies to either of these antigens conveys a danger of standing, which might be refractory to the uncommon treatments. Given that these antibodies are both much rarer than other autoantibodies to the NMDA receptor, the status epilepticus in the setup of autoimmune encephalitis probably happens much more frequently with NMDAR antibodies on the whole.

Biopsy:

Brain biopsy normally is not made use of in the medical diagnosis of encephalitis for numerous reasons. Infections might be detected by PCR, culture or other much less invasive techniques. The well-defined autoantibody causes normally have antibody examinations that are a lot less invasive and a lot more conclusive. On top of that, the results of biopsy are typically not definitive for a specific autoimmune etiology. In general, the clinical influence of biopsy provided for thought encephalitis is reduced, with only concerning 8% of instances having clear benefit [20].

Cancer screening:

Paraneoplastic disorders are, in general, autoimmune disorders that are caused by tumors. In lots of instances the target antigen is expressed by tumor tissue, such as HuD proteins in tiny cell lung cancer and NMDARs in ovarian teratoma [21].In these patients it is likely that presentation of the antigen in the context of the tumor sets off the autoimmune reaction. Nevertheless, other patients without tumors could have a the same medical syndrome and immunological response (antibody specificity, neuropathology, and so on).

It is very important to find tumors without delay for numerous reasons. 1) Treating the relevant tumor is assumed to be useful for treating the autoimmune disorder. 2) Tumor treatment and immune treatment might need to be offered simultaneously and in a collaborated fashion. 3) Treatment with steroids, rituximab, or cyclophosphamide might make complex tumor medical diagnosis in the instance of tumors like lymphoma.

In the situation of "onconeuronal" antibodies to intracellular antigens such as Hu, the antibodies might happen much more typically in cancer patients than in patients with the autoimmune disease. For instance low titer serum Hu feedbacks are typical in tiny cell lung cancer patients without the anti-Hu neurological disorders. Consequently, finding such an antibody ought to trigger a cautious examination for tumor even if there is not an equivalent autoimmune disease. For example, an elderly diabetic smoker could be evaluated (inappropriately) for anti-Hu to assess a light slowly progressive little fiber neuropathy. In this situation, a low titer serum Hu antibody would certainly be far less most likely to clarify the neuropathy than the diabetic issues, yet must however trigger screening for lung cancer. Likewise, a patient with known lung cancer might create neuropathy after chemotherapy; finding Hu antibodies in such a patient ought to not be taken as clear-cut evidence of a paraneoplastic disorder.

- **TREATMENT APPROACHES:**

Treatment for suspected autoimmune encephalitis is often given empirically prior to details antibody test outcomes. This may include steroids and/or IVIG. If a cell-surface/synaptic antibody problem is detected, first treatments may consist of IVIG, plasmapheresis, and/or steroids. Steroids might be useful in a range of autoimmune disorders yet can possibly

develop issues with the medical diagnosis of specific disorders such as CNS lymphoma. IVIG supplies an essential advantage of being not likely to earn infectious encephalitis worse. Plasmapheresis is likewise unlikely to dramatically worsen infectious encephalitis.

If a synaptic/cell-surface antibody is identified and the patient has any type of considerable signs and symptoms, first-line therapy ought to be given if it has not already been attempted. As a whole, prompt therapy, and escalation of treatment in patients that continue to be ill, is related to better results. Although there are not randomized treatment tests, procedures have been suggested for anti-NMDAR encephalitis [1] and these approaches have been applied to various other illness in the cell-surface/synaptic autoantibody classification. Our group commonly makes use of IV solumedrol (1 gram daily for 3-5 days after that a taper over a number of weeks) and IVIg (0.4 g/kg/day for 5 days). Various other groups have promoted plasmapheresis as opposed to IVIg, and so far there is not convincing evidence of superiority for either technique.

If the patient continues to be considerably damaged after first-line treatment, second-line therapies are typically used. Some groups may wait 2 weeks or longer to permit first-line therapies time to function, yet our team frequently proceeds more promptly to 2nd line therapy sooner is patients who are very ill, for example comatose patients with anti-NMDAR encephalitis. Second line therapies include rituximab (usually 375 mg/m2 weekly for 4 weeks) or cyclophosphamide (750 mg/m2 IV monthly till enhancement is noted), or both. Rituximab is a monoclonal antibody targeting CD20, so plasmapheresis usually need to not be done after it is carried out. Rituximab depletes CD19+/ CD20+ B-cells, and circulating degrees of these cells commonly become undetected for several months after therapy. As a result of its relatively desirable security profile, rituximab is more frequently used as monotherapy in kids. Rituximab is assumed to be usually reliable versus neurological conditions where the autoantibodies are of the IgG4 subtype [22].Since IgG4 reactions predominate in LGI1 and Caspr2 encephalitis this gives an added theoretical assistance for making use of rituximab in those conditions. Cyclophosphamide has a number of vital toxicities, consisting of a risk of infertility, specifically in young females that obtained duplicated doses (The risk cumulatively raises, potentially approximately 40% after 12 doses). This threat be can decreased with use of a GnRH agonist in females, [23] or addressed with egg/sperm collection.

4. CONCLUSION

The appropriate medical diagnosis and management of autoimmune encephalitis needs an organized approach. Evaluation should start with a detailed history and physical examination to detect hints to specific reasons. A diverse variety of infections ought to be taken into consideration, and proper testing should be done to exclude relevant pathogens. Ancillary testing with MRI, EEG, and lumbar puncture might additionally support a medical diagnosis of encephalitis and possibly recommend specific causes. A wide group of autoantibody tests may be utilized to detect or exclude specific autoimmune causes, however these tests are complex and not every positive outcome is certain evidence of an autoimmune condition. The risk of neoplasm need to always be considered throughout initial treatment and follow-up visits, both in terms of diagnosing serious cancers cells and because particular tumors could recommend specific autoimmune causes. Therapy should depend on the pathophysiology of the condition (e.g., T-cell-mediated or antibody mediated) and the clinical situation of the patient. Patients could relapse and needs to receive proper follow-up care from a physician familiar with the illness.

REFERENCES

[1] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011; 10:63–74.

[2] Höftberger R, Titulaer MJ, Sabater L, Dome B, Rózsás A, Hegedus B, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013; 81:1500–1506.

[3] Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013; 162:850–856.

[4] McKeon A, Martinez-Hernandez E, Lancaster E, Matsumoto JY, Harvey RJ, McEvoy KM, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013; 70:44–50.

[5] Hutchinson M, Waters P, McHugh J, Gorman G, O'Riordan S, Connolly S, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008; 71:1291–1292.

[6] 6. Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain. 2012; 135(Pt 11):3453–3468.

[7] Walker KG, Wilmshurst JM. An update on the treatment of Sydenham's chorea: the evidence for established and evolving interventions. Ther Adv Neurol Disord. 2010; 3:301–309.

[8] Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA (B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010; 9:67–76.

[9] Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014; 13:276–286.

[10] Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011; 69:892–900.

[11] Lancaster E, Leypoldt F, Titulaer MJ, Honnorat J, Waters PJ, Reindl M, et al. Immunoglobulin G antibodies to the N-Methyl-D-aspartate receptor are distinct from immunoglobulin A and immunoglobulin M responses. Ann Neurol. 2015; 77:183.

[12] Masdeu JC, González-Pinto A, Matute C, Ruiz-de-Azúa S, Palomino A, De Leon J, et al. Serum IgG antibodies against the NR1 subunit of the NMDA receptor not detected in schizophrenia. Am J Psychiatry. 2012; 169:1120–1121.

[13] Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 2014;13:167–177.

[14] Sili U, Kaya A, Mert A HSV Encephalitis Study Group. Herpes simplex virus encephalitis: clinical manifestations, diagnosis and outcome in 106 adult patients. J Clin Virol. 2014;60:112–118.

[15] Tobin WO, Lennon VA, Komorowski L, Probst C, Clardy SL, Aksamit AJ, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014; 83:1797–1803.

[16] Heine J, Prüss H, Bartsch T, Ploner CJ, Paul F, Finke C. Imaging of autoimmune encephalitis - relevance for clinical practice and hippocampal function. Neuroscience. 2015 doi: 10.1016/j.neuroscience.2015.05.037.

[17] Sutter R, Kaplan PW, Cervenka MC, Thakur KT, Asemota AO, Venkatesan A, et al. Electroencephalography for diagnosis and prognosis of acute encephalitis. Clin Neurophysiol. 2015; 126:1524–1531.

[18] Titulaer MJ, Dalmau J. Seizures as first symptom of anti-NMDA receptor encephalitis are more common in men. Neurology. 2014;82:550–551.

[19] Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012; 79:1094–1100.

[20] Bai HX, Zou Y, Lee AM, Lancaster E, Yang L. Diagnostic value and safety of brain biopsy in patients with cryptogenic neurological disease: a systematic review and meta-analysis of 831 cases. Neurosurgery. 2015; 77:283–295. Discussion 295.

[21] Dalmau J, Furneaux HM, Rosenblum MK, Graus F, Posner JB. Detection of the anti-Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuronopathy. Neurology. 1991; 41:1757–1764.

[22] Huijbers MG, Querol LA, Niks EH, Plomp JJ, van der Maarel SM, Graus F, et al. The expanding field of IgG4-mediated neurological autoimmune disorders. Eur J Neurol. 2015; 22:1151–1161.

[23] Clowse ME, Behera MA, Anders CK, Copland S, Coffman CJ, Leppert PC, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. J Womens Health (Larchmt) 2009; 18:311–319.