AUTOIMMUNE ENCEPHALOPATHIES

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Introduction

Autoimmune encephalopathies: Group of complex neurological disorders characterized by rapidly progressive cognitive decline, often associated with antibodies against neural antigens. Includes autoimmune encephalitis (AE or AIE), antibody-associated encephalitis (Ab-AE), and neuronal surface antibody syndromes (NSAS). These disorders encompass a heterogeneous group of neurological syndromes that affect cortical, subcortical, thalamic, cerebellar, and/or brainstem structures. "Autoimmune encephalopathy" is often used to describe disorders that are non-paraneoplastic in nature and implies the role of immune dysregulation in the pathophysiology (or the role of immunotherapy in the treatment) of these disorders. We commonly exclude conditions with chronic or indolent evolution, as these are less likely primarily immune-mediated. The number of non-infectious etiologies for rapidly progressive encephalopathies has expanded in the last decade, and many novel neuronal cell surface proteins and synaptic proteins as targets for autoantibodies have been identified. These targets represent a prominent emerging field in neurology.

- Pittock SJ, Vincent A, editors. Autoimmune Neurology. Amsterdam: Elsevier, 2016.

While recent reports have recognized cognitive impairment associated with antibody-mediated syndromes, this chronic clinical complication is discussed elsewhere (see C122: Neurology Update III – Update on Dementia).

Clinical syndromes

- Limbic encephalitis
- Brainstem encephalitis
- Cerebellar syndrome
- Stiff-person syndrome
- New-onset refractory status epilepticus
- Hypothalamic dysfunction
- Encephalomyelitis
- Myelopathy

Classification

- Paraneoplastic versus non-paraneoplastic/idiopathic/autoimmune
- Antibody associated versus non-antibody associated
- Intracellular/cytoplasmic antigen versus extracellular/surface antigen
- Infectious versus para-infectious

Diagnosis

The cornerstones of the diagnostic approach to autoimmune encephalopathy are the clinical evaluation, neuroimaging, and serum and cerebrospinal fluid (CSF) analyses.

Position paper on "practical, syndrome-based" approach – Graus et al. Lancet Neurol. 2016;15:391-404.

- Outline three levels of clinical evidence for autoimmune encephalitis: possible, probable, and definite.

Criteria for **possible** autoimmune encephalitis – **all 3 criteria must be met:**

1. Subacute onset of:	2. At least one of:	3. Exclusion of other causes
- Working memory deficits - Altered mental status - Psychiatric symptoms	- New focal CNS finding - New seizures - CSF pleocytosis - MRI brain c/w encephalitis	

Criteria for **probable** autoimmune encephalitis – **all 4 criteria must be met:**

1. Subacute onset of:	2. MRI brain:	3. At least one of:	4. Exclusion of other causes
- Working memory deficits - Altered mental status - Psychiatric symptoms	- Bilateral T2 FLAIR abnormalities - Lesions highly restricted to medial temporal lobes	- CSF pleocytosis - EEG w/ temporal lobe epileptic or slow-wave activity	

Criteria for **autoantibody-negative but probable** autoimmune encephalitis – **all 4 criteria must be met:**

1. Subacute onset of:	2. Exclusion of well-defined AIE syndromes:	3. Absence of Ab (CSF & Serum) and at least two of:	4. Exclusion of other causes
- Working memory deficits - Altered mental status - Psychiatric symptoms	- typical LE - Bickerstaff's brainstem encephalitis - ADEM	- MRI brain c/w encephalitis - CSF pleocytosis, CSF OCB or elevated IgG index, or both - Brain biopsy showing inflammatory infiltrates	

Serum and CSF biomarkers are available through commercial and non-commercial research-based testing. Importantly, a negative biomarker study does not exclude an autoimmune encephalopathy.

Therapeutic approaches and considerations

Treatment for autoimmune encephalopathies involves immunosuppressive therapies.
- There are no guidelines for treatment - approaches are based on expert opinion and retrospective case series.
- There are no randomized controlled trials to guide treatment in autoimmune encephalopathy.
- Immunosuppressive therapy for autoimmune encephalopathy is off-label in all instances.
- First-line therapy often includes high-dose intravenous steroids, intravenous immunoglobulin (IVIG), plasma exchange (PE), or immunoadsorption (IA).
- Second-line therapy often includes cyclophosphamide, mycophenolate, or rituximab.
- The timelines for response to therapy are not well-defined.

There are case reports reporting other agents for the treatment of refractory disease:
Bortezomib (26S proteasome inhibitor)
- Behrendt et al. JAMA Neurol. 2016;73(10):1251-1253.
- Schiebe et al. Neurology. 2017;88(4):366-370.

Tocilizumab (monoclonal antibody against IL-6 receptor)
- Lee et al. Neurotherapeutics. 2016;13:824-832.

IA versus PE in NSA encephalitis – Heine et al. J Neurol. 2016 Dec;263(12):2395-2402.
Study design: prospective, observational case control
Population: encephalitis with intracellular and extracellular autoantibodies
Outcome measure: Modified Rankin Scale (mRS)
Adverse events: 3 with PE, none with IA
Result: favorable and comparable effects of IA and PE

Seizure outcome following immunotherapy – Byun et al. PLoS One. 2016 Jan 15;11(1):e0146455.
Study design: retrospective case series
Population: encephalitis with new-onset seizure with intracellular and extracellular autoantibodies
Outcome measure: seizure frequency
Result: favorable efficacy of immunotherapy

Clinical trials

IgNiTE trial: protocol for IVIG in pediatric encephalitis – Iro et al. BMJ Open. 2016;6:e012356.
Study design: multicenter randomized control trial
Sites: 30 hospitals in United Kingdom
Population: children (age 6 mo to 16 yr) with all-cause encephalitis
Outcome measure: Glasgow Outcome Score Extended-pediatric version at 12 months

Clinical observations

Investigations in anti-NMDAR encephalitis
Cerebellar atrophy
- Iizuka et al. JAMA Neurol. 2016:73(6):706-713.
Identification of anti-NMDAR encephalitis in HIV-1 infected patients.

- Patarata et al. Case Rep Neurol. 2016 Dec 13;8(3):251-257.
- Cunill et al. J Neuroimmunol. 2016 Dec 15;301:49-52. doi: 10.1016/j.jneuroim.2016.10.008.

Investigations in the association of autoantibodies with seizures/epilepsy:
Antibodies to $GABA_A$ receptors
- Spartola et al. Neurology. 2017. doi: http://dx.doi.org/10.1212/WNL.0000000000003713.
Seizures with autonomic peri-ictal findings may be associated with autoantibodies.
- Baysal-Kirac et al. J Neurol. 2016 Mar;263(3):455-466.
Autoantibodies are not associated with focal epilepsy in pediatric patients.
- Borusiak et al. Eur J Paediatr Neurol. 2016 Jul;20(4):573-579.
Association of autoantibodies in adults with epilepsy of unknown origin.
- Dubey et al. JAMA Neurol. 2017 Feb 6. doi: 10.1001/jamaneurol.2016.5429.

Expanded associations and characterizations of autoantibodies with neurological syndromes:
Association with Herpes Simplex Virus (HSV) encephalitis
- Armangue et al. Neurology. 2015 Nov 17;85(20):1736-1743.
- Bradshaw et al. Neurology. 2015 Dec 15;85♾24):2176-2177.
SREAT: of 251 published cases <20% searched for anti-neuronal autoantibodies.
- Laurent et al. Autoimmunity Reviews. 2016;15(12):1129-1133.
Antibodies to metabotropic glutamate receptor type 1 (mGluR1).
- Lopez-Chiriboga et al. Neurology. 2016;86(11):1009-1013.

There were multiple studies published in 2016 addressing VGKC associated syndromes:
LE associated with anti-LGI1 and thyroid antibodies.
- Wang et al. Neurology. 2016 Jan 12;86(2):e16-8.
Motor cortex and hippocampus as principal cortical targets of anti-LGI1 encephalitis.
- Navarro et al. Brain. 2016. Apr;139(Pt 4):1079-93.
VGKC autoantibody testing.
- van Sonderen et al. Neurology. 2016;86(18):1683-1691.
Antibodies to CASPR2.
- van Sonderen et al. Neurology. 2016;87(5):521-528.
Antibodies to LGI1.
- van Sonderen et al. Neurology. 2016;87(14):1449-1456.
Association of LGI1 with unique HLA subtypes.
- Kim et al. Ann Neurol. 2016 Dec 27. doi: 10.1002/ana.24860.
Hippocampal damage and cognitive deficits in anti-LGI1
- Finke et al. JAMA Neurol. 2017:74(1):50-59.

Autoimmune encephalitis is distinct patient populations:
Autoimmune encephalitis in the ICU.
- Mittal et al. Neurocrit Care. 2016 Apr;24(2):240-250.
Autoimmune encephalitis following immune checkpoint inhibitor use.
- Williams et al. JAMA Neurol. 2016;73(8):928-933.

<u>Novel autoantigens</u>
Adenylate kinase 5 – Do et al. Neurology. 2017 Feb 7;88(6):514-524.
Clinical syndrome: limbic encephalitis
Cancer association: none
Immunotherapy response: poor

Microtubule associated protein 1B – Gadoth et al. Ann Neurol. 2017 Jan 11. doi: 10.1002/ana.24872.
Antigen of Purkinje Cell Antibodies (PCA-2)
Clinical syndrome: neuropathy, cerebellar ataxia, dysmetria/dysarthria, encephalopathy
Cancer association: small cell lung carcinoma
Immunotherapy response: not reported

Neurochondrin – Miske et al. Neurol Neuroimmunol Neuroinflamm. 2016 Dec 5;4(1):e307.

Clinical syndrome: cerebellar degeneration
Cancer association: not reported
Immunotherapy response: favorable

Neurexin-3a – Gresa-Arribas et al. Neurology. 2016 Jun 14;86(24):2235-2242.
Clinical syndrome: limbic encephalitis
Cancer association: not reported
Immunotherapy response: favorable

Patient resources: listed through National Organization of Rare Disorders at https://rarediseases.org/
Autoimmune Encephalitis Alliance - https://aealliance.org/
The Encephalitis Society - https://www.encephalitis.info/
Encephalitis Global - http://www.encephalitisglobal.org/
The Anti-NMDA Receptor Encephalitis Foundation - http://www.antinmdafoundation.org/