



Neuropsychiatry of Inflammatory Disorders

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Neither I nor my spouse has a relevant financial relationship with a commercial interest to disclose

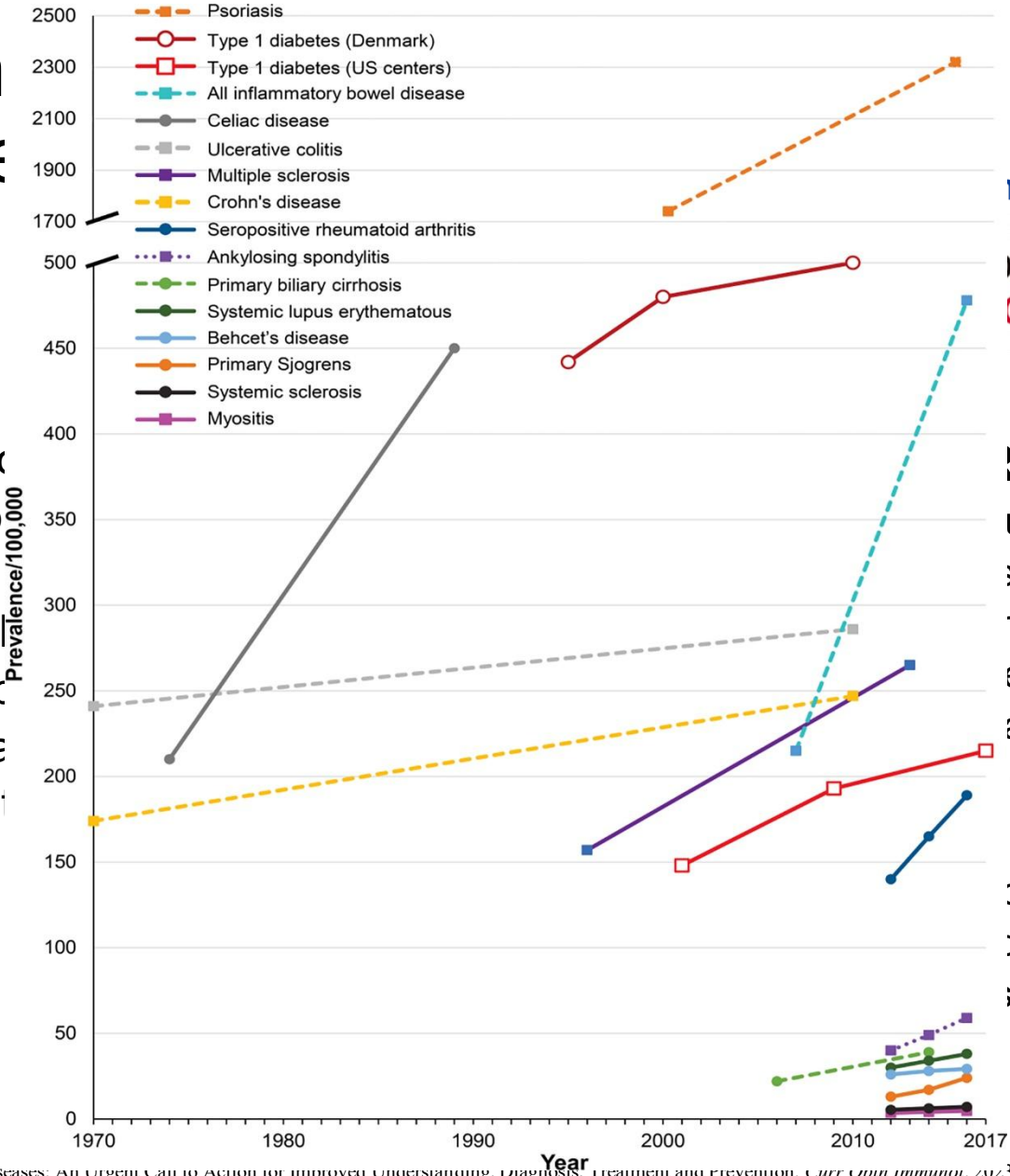
For this talk, I will consider Inflammatory Diseases = Autoimmune Diseases.

- Despite being rare epidemiologically, autoimmune diseases are commonly encountered in clinical practice.
- These often lead to various psychiatric symptoms and share a bidirectional relationship with psychiatric disorders.
- Autoimmune diseases are extremely relevant to neuropsychiatry/behavioral neurology because they can also present with rapidly progressive cognitive decline and dementia which can be reversible if detected and managed in a timely manner.

Some Autoimmun encountered in Ne

Neurological

- a. Multiple Sclerosis, Neur Oligodendrocyte Glycop (MOGAD)
- b. Autoimmune Encephal
- c. Cerebral Amyloid Angiop
- d. Hashimoto Encephalopa
- e. Encephalopathy with au
- e. CNS Vasculitis



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d Pediatric Autoimmune Neuropsychiatric

sociated with Streptococcal infection

Miller FW. The Increasing Prevalence of Autoimmunity and Autoimmune Diseases: An Urgent Call to Action for Improved Understanding, Diagnosis, Treatment and Prevention. *Curr Opin Immunol.* 2023;80:102266.

Neuropsychiatric syndromes associated with Autoimmune Disorders



- Adjustment Disorder
- Grief
- **Major Depressive Disorder**
- **Anxiety disorders**
- PTSD
- Psychosis
- Catatonia
- Mania
- OCD
- ADHD
- Autism-spectrum Disorder
- Eating Disorders
- Substance Use Disorders
- Pathological laughter and crying
- Delirium/Encephalopathy
- **Fatigue**
- **Cognitive impairment/Dementia**
- Headache
- Personality changes/behavioral symptoms – apathy, irritability, disinhibition, impulsivity, etc.
- Movement disorders
- Chronic Pain

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Cognitive Profiles of patients with Autoimmune Diseases



- A meta-regression analysis of patients with SARDs found **moderate impairment** across all domains tested:
 - Overall cognition (SMD -0.57).
 - Complex attention/executive function (SMD -0.57).
 - Memory (SMD -0.55).
 - Language/verbal fluency (SMD -0.51).
- In treatment-naïve patients with Limbic AE, deficits predominantly involved long-term memory, autobiographical-episodic memory, emotion recognition, praxis, visuoconstruction, and flexibility.
- A Danish study found multidomain impairment in ~45% of those anti-NMDA receptor encephalitis and ~43% of those with Limbic AE.
 - Notably, **15%** of patients **with AE** had **postencephalitic dementia**
- Cognitive impairment is one of the most prevalent and persistent sequelae of AE.

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Factors explaining the occurrence of psychiatric disorders in those with Autoimmune Diseases



1. **Psychosocial burden** of Autoimmune Diseases
2. **Direct CNS involvement**, for example, Neurolupus, Neurosarcoidosis, NeuroBehcet syndrome, CNS Vasculitis, Autoimmune Encephalitides, etc.
3. **Iatrogenic**.
4. **Complications/Organ dysfunction** due to autoimmune diseases, which in turn increase the risk of psychiatric disorders (for example, SLE -> renal failure -> increased risk of depression).
5. **CNS/systemic infections** secondary to the treatment of autoimmune diseases.
6. **Genetic overlap**.
7. **Common psychosocial risk factors**.

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Voskarides K, Giannopoulou N, Eid R, Parperis K, Chatzittofis A. Genome-wide association studies reveal shared genetic haplotypes of autoimmune rheumatic and endocrine diseases with psychiatric disorders. *Brain Behav*. 2023;13(4):e2955.

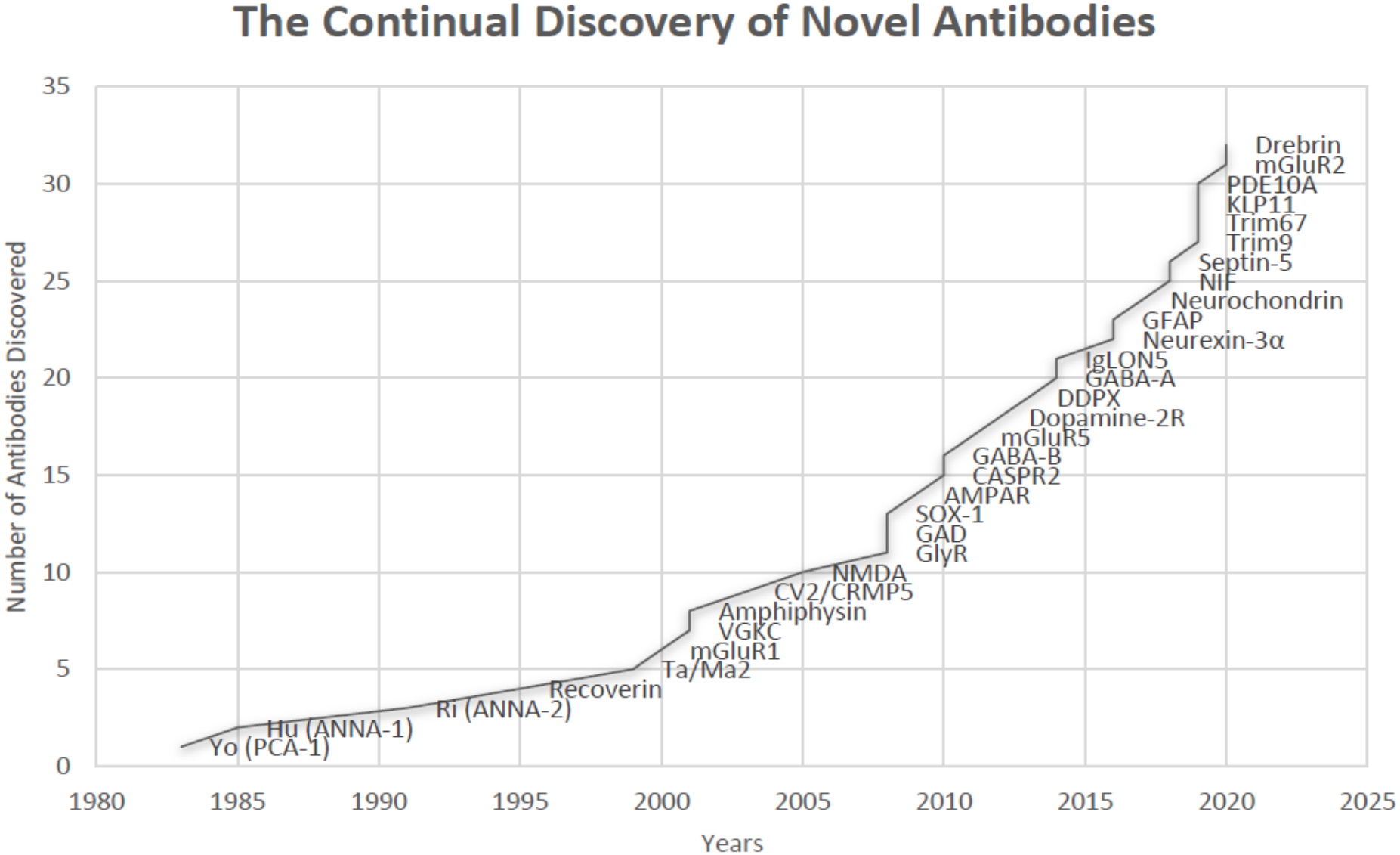
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Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative Childhood Stress and Autoimmune Diseases in Adults. *Psychosom Med*. 2009;71(2):243-250.

McKay MT, Cannon M, Chambers D, et al. Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatr Scand*. 2021;143(3):189-205.

Overview

- Autoimm
- The infec



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Patel A, Meng Y, Najjar A, Lado F, Najjar S. Autoimmune Encephalitis: A Physician’s Guide to the Clinical Spectrum Diagnosis and Management. *Brain Sciences*. 2022;12(9):1130

Overview of AE



- Types of AE:
 - Idiopathic
 - Paraneoplastic
 - Post-infectious (Post Herpes Simplex Encephalitis anti-NMDA receptor antibody encephalitis)
 - Iatrogenic (Post Immune Checkpoint Inhibitor treatment; drugs against CTLA-4, PD-1, and PD-L1)
- They may be further classified based on the site of involvement:
 - Limbic – Anti-LGI1 antibody encephalitis, mGluR5 receptor antibody encephalitis
 - Brainstem – anti-Kelch-like protein-11 (KLHL11)-IgG associated encephalitis
 - Basal ganglia – anti-Dopamine (D2) receptor encephalitis
 - Panencephalitis – anti-GABA-A receptor encephalitis

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Types of AE based on pathophysiology



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Two main categories based on the antibody location:

Those in which the antibody targets an **intracellular antigen**

- Occur in older patients
- More often paraneoplastic
- Respond poorly to immunotherapy.
- Pathogenic activity mediated by CD8+ cytotoxic T-cell immunity

Those in which the antibody targets a **cell surface/synaptic antigen**

- More common in younger patients
- Less often paraneoplastic
- Typically respond favorably to immunotherapy
- Cell-surface antibodies are often directly pathogenic, leading to reversible neurotransmitter receptor internalization and/or blockade.

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AE associated with antibodies against cell surface antigens

Target Antigen	Primary Symptoms	Other Manifestations	Associated Tumor(s)	Demographic Data	Outcomes With Proper Therapy
NMDA receptor	Psychosis, seizures, autonomic instability, dyskinesias	Viral prodrome, changes in speech, catatonic features, hypoventilation	Ovarian teratoma*	75% women; 35% children and adolescents	75%–80% substantial improvement or full recovery
AMPA receptor	Memory loss, confusion, agitation, seizures	Psychotic symptoms, affective changes	Breast or lung cancer, thymoma	Predominates in women, ages 50–70	Most improve; frequent relapse
GABA _B receptor	Seizures, memory loss, confusion	Hallucinations, paranoia, odd behaviors	Small-cell lung cancer	Either gender, middle-aged	~50% improve
LGI1	Amnesia, seizures, confusion, disorientation	Autonomic dysfunction, apathy/irritability, hyponatremia	Rare, thymoma	~2:1 male: female, middle-aged	~80% full recovery or mild deficits
Caspr2	Neuromyotonia, dysautonomia, confusion, insomnia	Amnesia, seizures, neuropathic pain, weight loss	Rare, thymoma	~4:1 male: female, middle-aged	~80% substantial improvement

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AE associated with antibodies against intraneuronal antigens



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Antibody ^a	Associated Tumor(s)	CSF Changes ^b	MRI Findings of Limbic Encephalitis ^c	Predominant CNS Symptoms	Other Behavioral Symptoms	Patients' Response to Treatment
Hu	Small cell lung cancer	Common	Common	Short-term memory deficits, confusion	Depression	Poor; 20% survive to 3 years
Ma2	Testicular germ cell tumor	Common	Common	Short-term memory deficits, diencephalic/brainstem encephalitis	REM sleep disorder, obsessive-compulsive disorder (OCD), anxiety	50%–70% stabilize or improve
CV2/CRMP5	Small cell lung cancer, thymoma	Common	Common	Subacute dementia, chorea	Memory dysfunction, OCD, disorientation	Poor

Kayser MS, Dalmau J. The Emerging Link Between Autoimmune Disorders and Neuropsychiatric Disease. J Neuropsychiatry Clin Neurosci. 2011;23(1):90-97

AE-associated autoantibodies with associated malignancies

Antibody	Oncological Association	Frequency of tumor
VGKC complex, LGI1+, Caspr2+, LGI1-, Caspr2-	Small-cell Lung Carcinoma (SCLC), Thymoma or Adenocarcinoma of breast or prostate	<20%
NMDAR	Ovarian Teratoma, Testicular Germioma, Neuroblastoma	Varies with age, gender, and ethnicity
AMPA	Thymic tumors, Lung Carcinoma, Breast adenocarcinoma	70%
GABA-B receptor	SCLC, other neuroendocrine neoplasia	70%
mGluR5 receptor	Hodgkin Lymphoma	>90%
DPPX	B-cell neoplasm	
P/Q- and N-type VGCC	SCLC, Breast cancer	~50%
ANNA-1 (Anti-Hu)	SCLC	>90%
Ma1, Ma2	Testicular (Ma2), Breast, Colon, Testicular (Ma1)	>90%
CRMP-5	SCLC, Thymoma	>90%
Amphiphysin	SCLC, Breast adenocarcinoma	>90%
GAD65	Thymoma, Renal Cell Carcinoma, Breast, Colon adenocarcinoma	<5%

Toledano M, Pittock SJ. Autoimmune Epilepsy. *Semin Neurol*. 2015;35(3):245-258

Hara M, Ariño H, Petit-Pedrol M, et al. DPPX antibody-associated encephalitis. *Neurology*. 2017;88(14):1340-1348

Antibody Prevalence in Epilepsy and Encephalopathy (APE2 Score)



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1A: Antibody prevalence in epilepsy and encephalopathy (APE ² score)	Value
New onset, rapidly progressive mental status changes that developed over 1–6 weeks or new onset seizure activity (within one year of evaluation)	(+ 1)
Neuropsychiatric changes; agitation, aggressiveness, emotional lability	(+ 1)
Autonomic dysfunction [sustained atrial tachycardia or bradycardia, orthostatic hypotension (≥ 20 mmHg fall in systolic pressure or ≥ 10 mmHg fall in diastolic pressure within three minutes of quiet standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility] ^a	(+ 1)
Viral prodrome (rhinorrhea, sore throat, low grade fever) to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset	(+ 2)
Faciobrachial dystonic seizures ^c	(+ 3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+ 2)
Seizure refractory to at least to two anti-seizure medications	(+ 2)
CSF findings consistent with inflammation ^b (elevated CSF protein > 50 mg/dL and/or lymphocytic pleocytosis > 5 cells/mcL, if the total number of CSF RBC is < 1000 cells/mcL)	(+ 2)
Brain MRI suggesting encephalitis ^b (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation) ^c	(+ 2)
Systemic cancer diagnosed within 5 years of neurological symptom onset ^c (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+ 2)
Total	(max: 18)

Proposed autoimmune encephalopathy and dementia diagnostic criteria	
Possible autoimmune encephalopathy ^a :	APE ² score ≥ 4
Neural specific antibody positive autoimmune encephalopathy:	APE ² score ≥ 4 and positive neural specific antibody ^b
Probable autoimmune encephalopathy ^a :	APE ² score ≥ 4 and successful immunotherapy trial or APE ² score ≥ 7 (neural antibody evaluation negative ^b or not available)

High sensitivity and variable/low specificity

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Work-up for suspected AE



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Subacute onset (<3 months) of **new neuropsychiatric symptoms**:
Encephalopathy – cognitive decline, altered sensorium
Psychiatric symptoms – variable

Accompanying features:
Viral prodrome preceding the symptom onset
New seizures
Abnormal movements (except tics)
Focal neurological deficits (e.g., aphasia, dysarthria, ataxia)
Autonomic dysfunction
Recent viral encephalitis
Recent (in 5 years) or concurrent systemic malignancy

Is history and exam suggestive of AE?

Yes

No

Initiate AIE work-up:

Perform a **detailed neurologic exam**, including MoCA

Obtain Serology for SARDs (ANA, TPO, Thyroglobulin antibody, ESR, CRP, IgG/M/A levels, **Serum Autoimmune encephalitis panel**)

CSF studies – Opening Pressure, Cell Count, Total Protein, Glucose, Gram stain/culture, Oligoclonal Bands, IgG index, Beta-2 Microglobulin, Flow Cytometry, Cytology

CSF Autoimmune encephalitis panel

Consider relevant infectious disease studies (e.g., HSV PCR)

EEG – Long-term monitoring preferred when seizures suspected

Imaging – **MRI Brain with and without contrast**
Consider FDG PET Brain

Evaluate for systemic malignancy – CT
Chest/Abdomen/Pelvis vs Whole body PET
Testicular Ultrasound in Males
Pelvic Ultrasound in Females

Evaluate for alternate causes

Obtain CBC, CMP, TSH with reflex, Vit B12, Folate, serum Copper, serology for HIV, Syphilis, Urine toxicology

Consider Porphyrins, Ceruloplasmin

Consider Primary Psychiatric etiology

Is work-up suggestive of AE?

Yes

No

Initiate
first-line
treatment

Consider alternative etiologies
If suspicion for AE persists, then consult Neuroimmunology for further guidance

Clinical significance of autoantibody related to AE

- Like SARDs, having autoantibodies does not automatically prove the occurrence of AE.
- The clinical specificity of neural antibody testing using commercial immunoblot kits alone is relatively high (~95%)
 - But the **positive predictive value** is **only 30-50%**.
- The presence of autoantibodies is significant only in the context of a typical clinical presentation.
- Autoantibodies only play a **supportive** role in diagnosing AE.

Diagnosing individuals indiscriminately with AE can be harmful!

- A retrospective, international, multi-center study across several AE subspecialty outpatient clinics **evaluated adults who presented with a diagnosis of AE (n=393)** and were **eventually given an alternative diagnosis**.
- Around **1/4th** of the patients had a misdiagnosis of AE.
- Around **3/4th** of the patients didn't meet diagnostic criteria for AE.
- **Onset was insidious (>3 months) in 48%.**
- The median age was 48 years; **~60% were women.**
- Correct diagnoses included **functional neurologic disorder (25%), neurodegenerative disease (~20%), primary psychiatric disease (18%),** cognitive deficits from comorbidities (10%), cerebral neoplasm (~10%), etc.
- **Adverse reactions from immunotherapies occurred in 20% of the patients;** mostly due to steroids and IVIg.
- Potential contributors to misdiagnosis included:
 - **overinterpretation of positive serum antibodies (50%)**
 - nonspecific cognitive dysfunction interpreted as encephalopathy (38%).
 - misinterpretation of functional/psychiatric symptoms

Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, et al. Autoimmune Encephalitis Misdiagnosis in Adults. JAMA Neurol. 2023;80(1):30-39

Prognosis of patients with AE



- In the case of AE with autoantibodies against cell surface antigens, the prognosis is good when the treatment is **initiated within a month** of the symptom onset.
- Early removal of the tumor, wherever applicable, may improve prognosis.
- Avoid treatment delay awaiting diagnostic confirmation with autoantibodies when there is a strong suspicion of AE.
- **Mortality** ranges between 0%-40%.
 - It is **lowest** in **anti-CASPR2 encephalitis**, intermediate in anti-NMDA-R encephalitis, and **highest** in **anti-GABA-B receptor encephalitis** and **paraneoplastic encephalitides**.

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Factors associated with AIE misdiagnosis



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- Clinical
 - Insidious onset
 - Multiple comorbidities that can cause cognitive deficits
 - Exam consistent with Functional Neurologic Disorder
 - Features of Mitochondrial disease
 - Normal cognitive testing
- MRI Brain
 - Normal
 - Progressive atrophy without any signal changes or enhancement
 - Lesions expanding despite immunotherapy
- CSF
 - Bland
- Serology
 - Low titer GAD65 antibodies
 - VGKC antibodies negative for LGI1 or CASPR2
 - Anti-NMDA receptor antibodies positive in serum but negative in CSF

When to suspect autoimmunity in neuropsychiatric symptoms presentation?



Illness trajectory

- Viral-like prodrome
- Acute/subacute onset
- Atypical age of onset
- Rapid progression

Salient history

- Presence/history of malignancy
- No family history of psychiatric illness
- Personal/Family history of autoimmune disease

Clinical features

- New-onset severe **headache** or clinically significant change in the headache pattern
- Decreased consciousness
- Insufficient response to antipsychotics
- **Neuroleptic sensitivity**
- Catatonic symptoms
- **Prominent cognitive symptoms**
- **Abnormal movements – dyskinesia**
- **Seizures/suspicion of seizures**
- **Focal neurologic signs**
- **Autonomic symptoms**
- Unexplained hyponatremia
- Presence of other systemic symptoms and signs

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Pollak TA, Lennox BR, Müller S, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. Lancet Psychiatry. 2020;7(1):93-108.

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General management of neuropsychiatric disorders associated with autoimmune diseases



- Work-up includes screening for systemic and CNS inflammation using blood-based biomarkers, neuroimaging, EEG, serum and CSF autoimmune panels, consult with Neurology, Rheumatology, etc.
- Proving causation is difficult; avoid biological reductionism and utilize the biopsychosocial approach.
 - Due to the high prevalence of psychiatric disorders (n/100) compared to autoimmune diseases (n/100,000), individuals with autoimmune disorders are more likely to have primary psychiatric disorders.
- It is challenging to diagnose an autoimmune disease when a patient presents to a psychiatrist first.
 - Often, an autoimmune disorder is already diagnosed before a Psychiatrist is consulted to “troubleshoot.”
- The key to diagnosing autoimmune disorders is pattern recognition, aided by the detection of antibodies in the serum and/or CSF associated with specific autoimmune diseases.
- Sometimes, psychiatric symptoms may improve just by suppressing the autoimmune activity.
 - Otherwise, the treatment of psychiatric disorders is empirical.

Treatments used for autoimmune diseases and their neuropsychiatric adverse effects



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- **Steroids** – Depression, panic symptoms, suicidality, agitation, insomnia, mania, psychosis, delirium, and cognitive impairment.
- **IVIg** – Aseptic meningitis, Posterior reversible encephalopathy syndrome (PRES), seizures
- **Small molecule immunosuppressants** (Cyclophosphamide, Methotrexate, Cyclosporine, Mycophenolate, Azathioprine, etc.) – Depression, cognitive symptoms
- **Interferons** – Depression
- **TNF-alpha inhibitors** – Depression, mania, and psychosis
- **CAR (Chimeric Antigen Receptor) T-cell therapy** – Encephalopathy

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THANK YOU SO MUCH FOR YOUR ACTIVE LISTENING

Now time for Q&A



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MGB Neuroimmunology Division

MGB Psychiatry Leadership

My clinic patients

For further questions, please feel free to contact me via  rgupta29@bwh.harvard.edu or  [@RishabGupta_84](https://twitter.com/RishabGupta_84)