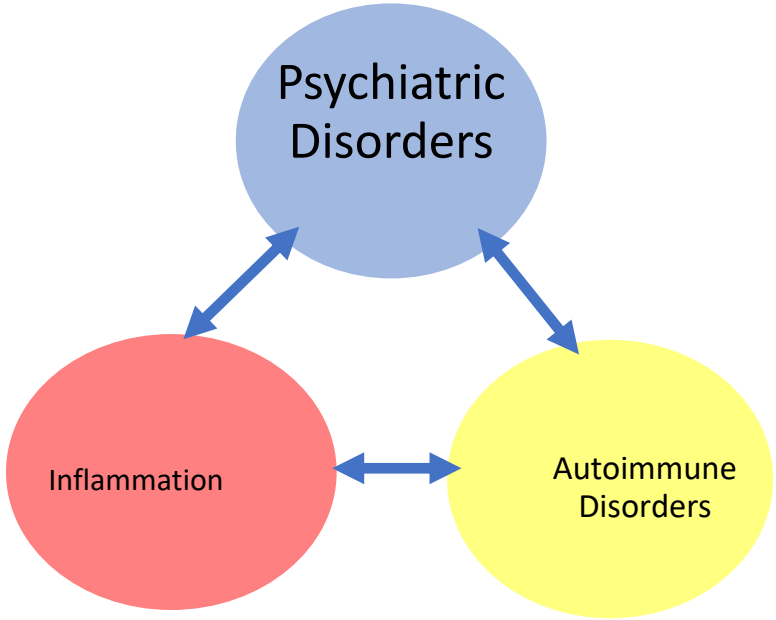
Mass General Brigham
Brigham and Women's Faulkner Hospital

HARVARD MEDICAL SCHOOL

Inflammation, Autoimmune Disorders, and Psychiatric Illness



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Gruchot J, Herrero F, Weber-Stadlbauer U, Meyer U, Küry P. *Brain Behav Immun*. 2023;107:242-252

Rishab Gupta, MD
Associate Psychiatrist, Brigham & Women's Faulkner Hospital
Instructor in Psychiatry, Harvard Medical School
09/21/2025

Introduction

- Psychiatric disorders can occur in the context of infectious diseases, autoimmune diseases, and malignancies.
- **Interferon therapy can lead to depression**.
- **TNF-alpha inhibitors reduce depressive symptoms** in individuals with inflammatory arthritides.
- Overexpression of the classical complement cascade protein, C4, is implicated in the pathogenesis of Schizophrenia.

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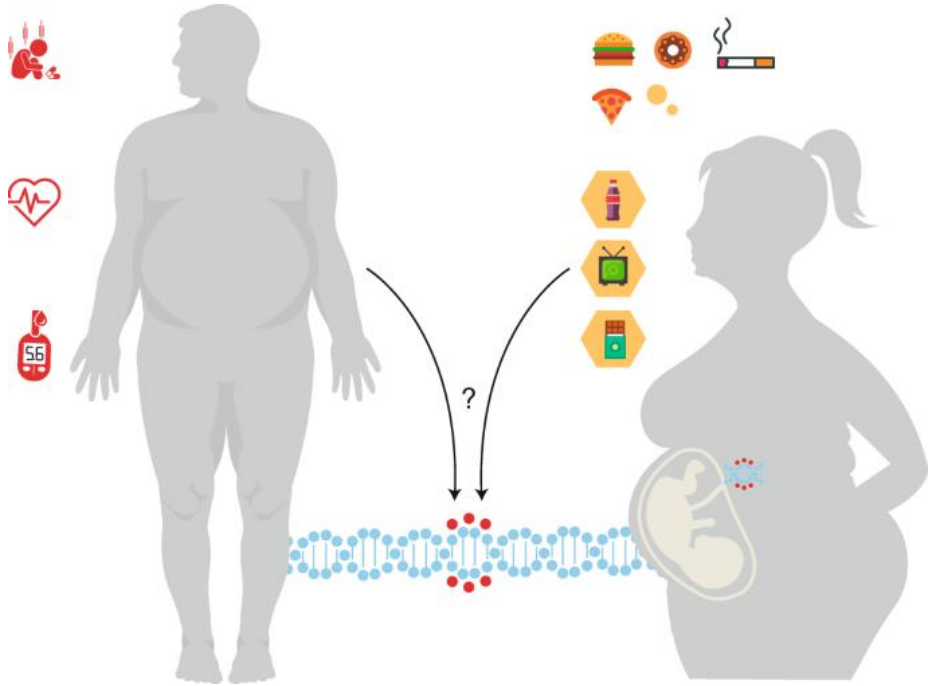
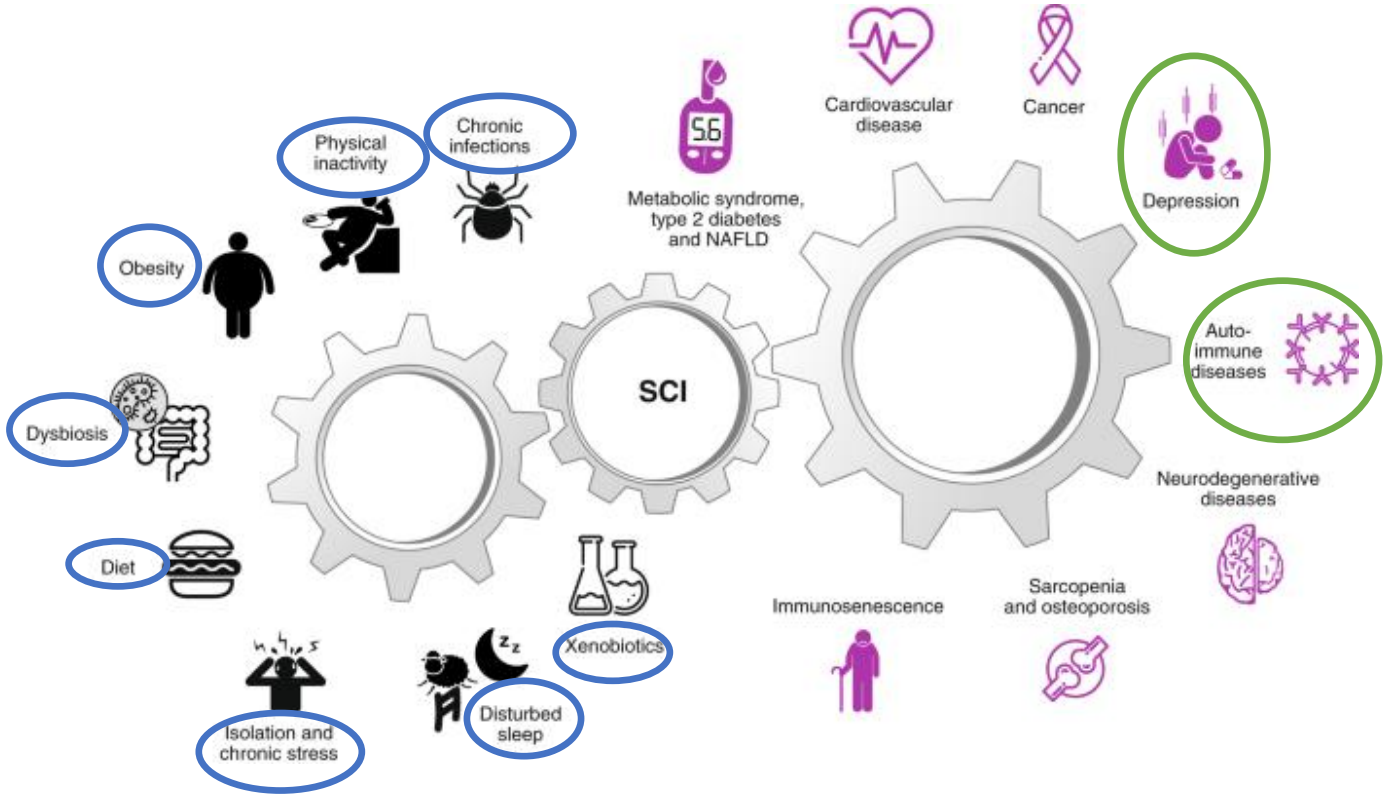
Pape K, Tamouza R, Leboyer M, Zipp F. Immunoneuropsychiatry - novel perspectives on brain disorders. Nat Rev Neurol. 2019;15(6):317-328
Lai JY, Ho JX, Kow ASF, et al. Interferon therapy and its association with depressive disorders – A review. Front Immunol. 2023;14:1048592
Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry. 2018;23(2):335-343
Abbott R, Whear R, Nikolaou V, et al. Tumour necrosis factor-α inhibitor therapy in chronic physical illness: A systematic review and meta-analysis of the effect on depression and anxiety. J Psychosom Res. 2015;79(3):175-184.

Introduction

The **maternal exposome** and Low-grade Systemic Chronic Inflammation (SCI)



Causes and consequences of
Low-grade Systemic Chronic Inflammation



Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25(12):1822-1832
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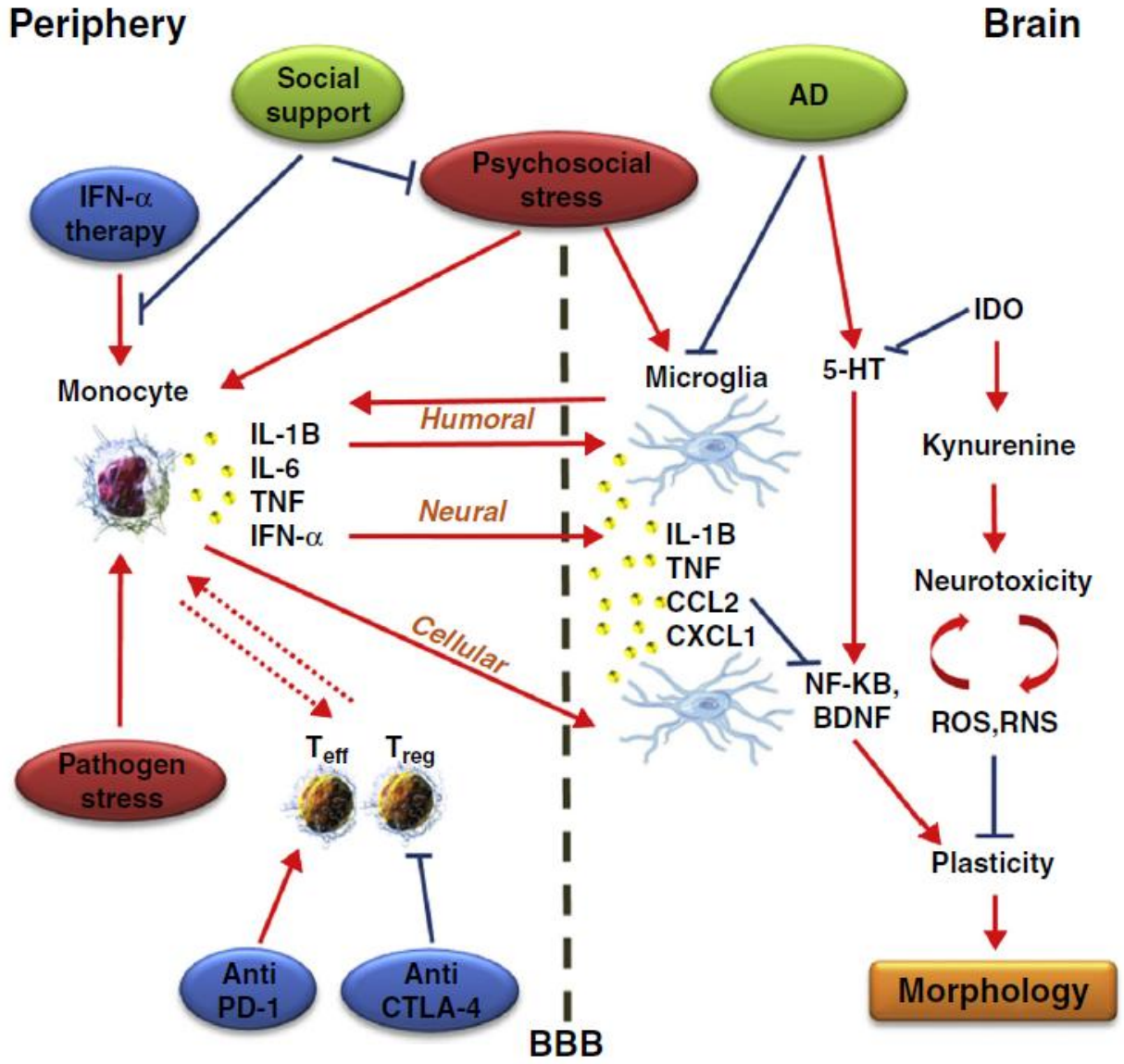
Introduction



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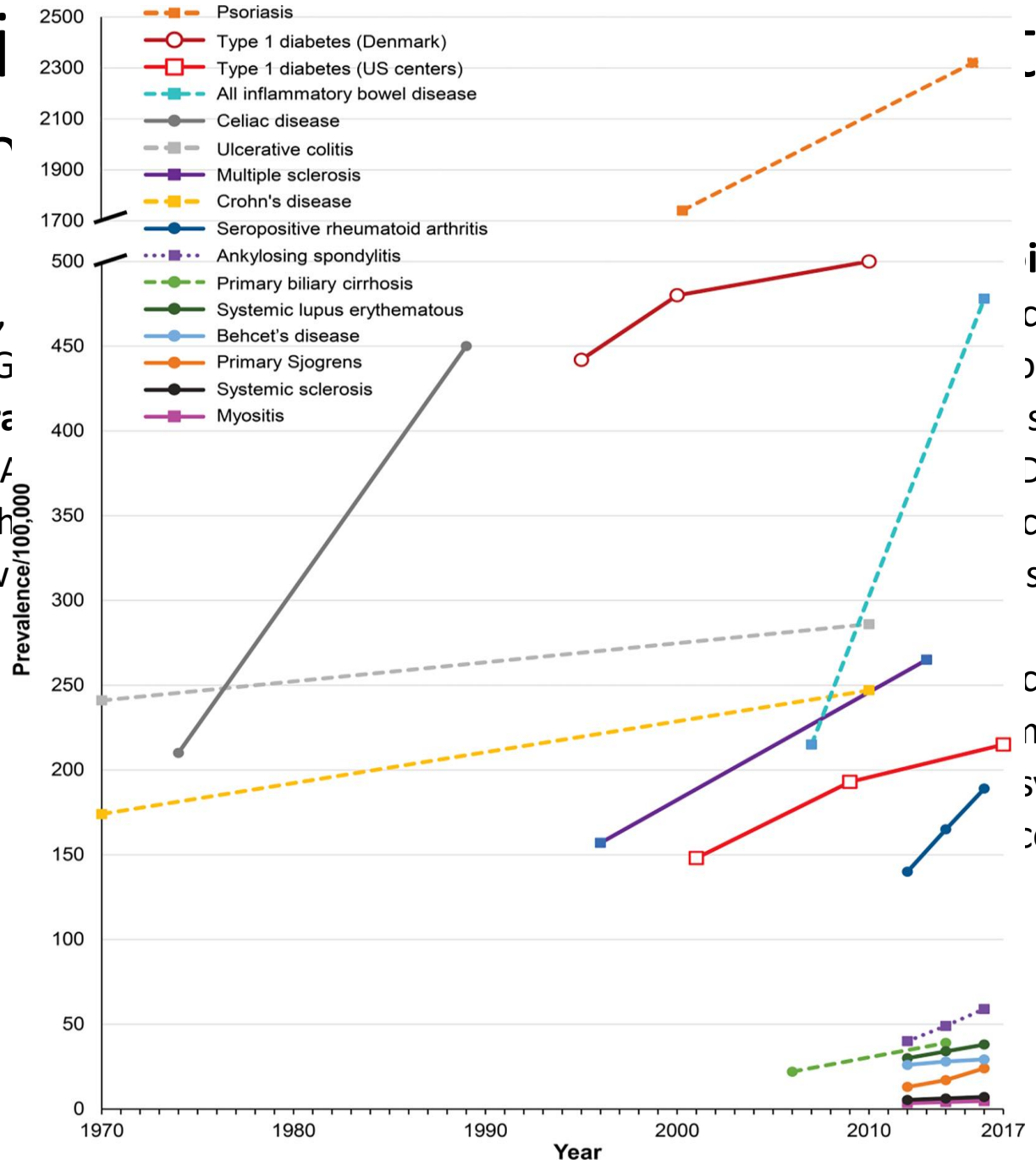
Kovacs D, Kovacs P, Eszlari N, Gonda X, Juhasz G. Psychological side effects of immune therapies: symptoms and pathomechanism. Curr Opin Pharmacol. 2016;29:97-103

Some Autoi … tered in Neuropsych …

Neurological

a. Multiple Sclerosis, Oligodendrocyte G…
b. Autoimmune/Para…
c. Cerebral Amyloid A…
d. Hashimoto Enceph… Encephalopathy w…
e. CNS Vasculitis



…immune Rheumatologic Diseases

…c Lupus Erythematosus (SLE)
…osis
… syndrome
…Disease
…c vasculitides
… spholipid Antibody Syndrome

…c Acute-onset Neuropsychiatric …ne (PANS) and Pediatric Autoimmune …sychiatric Disorder associated with …coccal infection (PANDAS)

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 symptoms/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
- Movement disorders
- Chronic Pain

Pape K, Tamouza R, Leboyer M, Zipp F. Immunoneuropsychiatry - novel perspectives on brain disorders. Nat Rev Neurol. 2019;15(6):317-328
Sloan M, Wincup C, Harwood R, et al. Prevalence and identification of neuropsychiatric symptoms in systemic autoimmune rheumatic diseases: an international mixed methods study. *Rheumatology*. 2024;63(5):1259-1272

Clinical Features of some Autoimmune Diseases

Disorder	Distinguishing clinical features
SLE	Dermatologic manifestations (e.g., malar rash, oral ulcers, alopecia), synovitis, serositis, renal injury (e.g., proteinuria), low blood cell counts (anemia, leukopenia, and/or thrombocytopenia), seizures, neuropathy (cranial or peripheral), myelitis, fatigue, vision loss (e.g., due to optic neuritis, retinopathy, vitreous hemorrhage), arterial strokes
Sjögren syndrome	Peripheral neuropathy, stroke or MS-like symptoms, sicca syndrome (dry mouth, dry eyes), enlarged parotid glands
Behçet disease	Oral/GI and genital ulcers, erythema nodosum, arthritis, uveitis, venous and arterial thrombi, ophthalmoparesis, cranial neuropathy, cerebellar dysfunction, extrapyramidal dysfunction, myelopathy, hemiparesis, hemisensory loss, seizures

Kayser MS, Dalmau J. The Emerging Link Between Autoimmune Disorders and Neuropsychiatric Disease. J Neuropsychiatry Clin Neurosci. 2011;23(1):90-97
Harder J, Katz T, Skylar-Scott IA. Neuropsychiatry of Inflammatory, Autoimmune, and Infectious Disorders. In: *Neuropsychiatry and Behavioral Neurology: Principles and Practice*. First Edition. McGraw Hill / Medical; 2021

Clinical Features of some Autoimmune Diseases

Disorder	Distinguishing clinical features
Susac syndrome	Branch retinal arterial occlusion (BRAO), hearing loss
CNS vasculitis	Prodromal period lasting months, headache, focal neurologic signs (e.g., hemiparesis or vision loss, including due to strokes or transient ischemic attacks), ataxia, seizures, papilledema, diplopia
Sarcoidosis	**Neurologic:** seizures, hyperreflexia, cerebellar syndrome, cranial neuropathies, peripheral neuropathies **Extraneurologic:** malaise, fever; erythema nodosum, hepatosplenomegaly, uveitis, exophthalmos, diabetes insipidus, amenorrhea

Kayser MS, Dalmau J. The Emerging Link Between Autoimmune Disorders and Neuropsychiatric Disease. J Neuropsychiatry Clin Neurosci. 2011;23(1):90-97
Harder J, Katz T, Skylar-Scott IA. Neuropsychiatry of Inflammatory, Autoimmune, and Infectious Disorders. In: *Neuropsychiatry and Behavioral Neurology: Principles and Practice*. First Edition. McGraw Hill / Medical; 2021

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

1. **Psychosocial Burden**
2. **Complications/Organ dysfunction**
3. **Direct CNS involvement**
4. **Iatrogenic**
5. **CNS/systemic infections**
6. **Genetic overlap**
7. **Common psychosocial risk factors**

Grygiel-Górniak B, Limphaibool N, Puszczewicz M. Cytokine secretion and the risk of depression development in patients with connective tissue diseases. *Psychiatry and Clinical Neurosciences*. 2019;73(6):302-316.

Judd LL, Schettler PJ, Brown ES, et al. Adverse consequences of glucocorticoid medication: psychological, cognitive, and behavioral effects. *Am J Psychiatry*. 2014;171(10):1045-1051.

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.

Tylee DS, Sun J, Hess JL, et al. Genetic correlations among psychiatric and immune-related phenotypes based on genome-wide association data. Am J Med Genet B Neuropsychiatr Genet. 2018;177(7):641-657.

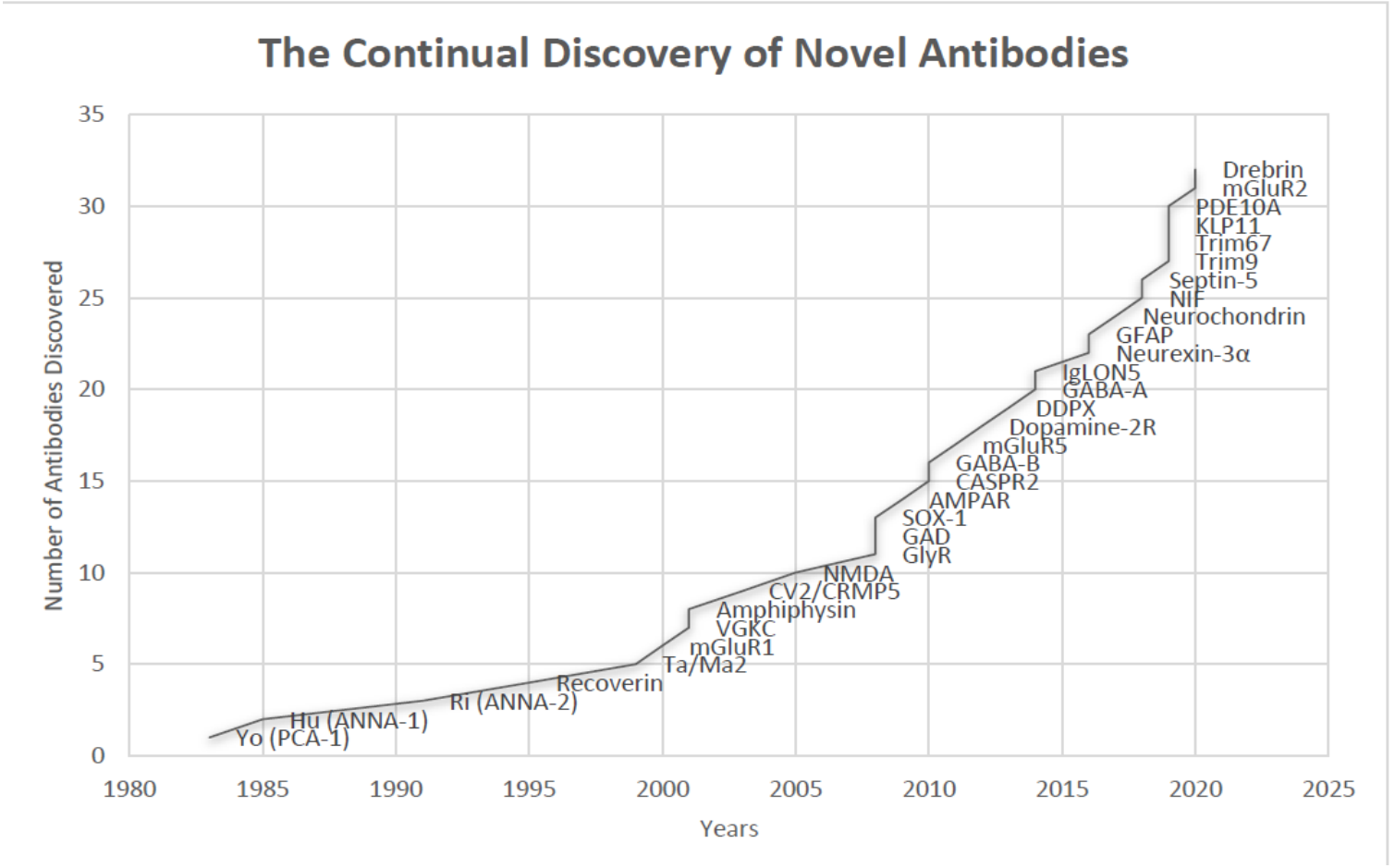
Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative Childhood Stress and Autoimmune Diseases in Adults. Psychosom Med. 2009;71(2):243-250.

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.

Autoimmune/Paraneoplastic Encephalitides

Overview of autoantibody-associated encephalitis

- Autoimmune Encephalitides (AIE) have gained significant interest and importance in recent times.
  - The incidence and prevalence (0.8/100,000; 13.7/100,000) of autoimmune encephalitides are **comparable** to that of **infectious encephalitides** (1/100,000; 11.6/100,000)



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.

Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol*. 2018;83(1):166-177.

AIE-associated antibodies with potential for associated malignancy

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 Germinoma, Neuroblastoma	Varies with age, gender, and ethnicity
AMPAR	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

Overview of autoantibody-associated encephalitis

- Types of Autoantibody-associated Encephalitides:
  - Autoimmune
  - Paraneoplastic
  - Post-infectious (Post Herpes Simplex Encephalitis)
  - Iatrogenic (Post Immune Checkpoint Inhibitor treatment; drugs against CTLA-4, PD-1, and PD-L1)
- Armangue et al. found ~27% of the patients developed AIE after Herpes Simplex Encephalitis; ~18% had anti-NMDA receptor antibodies.
- They may be further classified **based on the site of involvement**:
  - Limbic – Anti-LGI1 encephalitis, mGluR5 receptor antibody encephalitis
  - Brainstem – Kelch-like protein-11 (KLHL11)-IgG associated encephalitis
  - Basal ganglia – anti-NMDA receptor encephalitis
  - Panencephalitis – anti-NMDA receptor encephalitis

Velasco R, Villagrán M, Jové M, et al. Encephalitis Induced by Immune Checkpoint Inhibitors: A Systematic Review. *JAMA Neurology*. 2021;78(7):864-873.
Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol*. 2018;83(1):166-177.
Brierley JB, Corsellis JA, Hierons R, Nevin S. Subacute Encephalitis of Later Adult Life. Mainly affecting the limbic areas. Brain. 1960;83(3):357-368.
Corsellis JA, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma. Brain. 1968;91(3):481-496.
Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol. 2018;17(9):760-772.
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

Different types of AIE based on pathophysiology

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 often directly pathogenic, leading to reversible neurotransmitter receptor internalization and/or blockade.

Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391-404
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

AIE 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

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

AIE associated with antibodies against intracellular antigens

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, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. Am J Psychiatry. 2010;167(9):1039-1050

Anti-NMDA receptor AIE

- It is **one of the commonest** autoantibody encephalitis and is associated with **CSF IgG antibodies against the GluN1 subunit of the NMDA receptor**.
- It mainly affects **young** individuals (**95% <45 years**, 37% <18 years) with a **female sex predominance** of 4:1.
  - Female predominance is less evident in children <12 years and adults >45 years.
  - Around 58% of women >18 years have associated ovarian teratoma, older adults may have carcinoma.
- **Around 5% of the patients present with purely psychiatric symptoms.**
- **Teenagers and adults usually present with psychiatric symptoms** (delusions, hallucinations, agitation, aggression, catatonia, irritability, insomnia), followed by speech dysfunction, dyskinesias, memory deficits, autonomic instability, and a decrease in consciousness.
  - Seizures may occur at any time during the disease; earlier in males.
  - Over time, central hypoventilation may occur.
- Some patients also develop cerebellar ataxia or hemiparesis.
- About 4% of patients develop a demyelinating disease (MOG-related or aquaporin 4 (AQP4)-related) that can occur separately or simultaneously.

Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391-404
Saraya AW, Worachotsueptrakun K, Vutipongsatorn K, Sonpee C, Hemachudha T. Differences and diversity of autoimmune encephalitis in 77 cases from a single tertiary care center. BMC Neurology. 2019;19(1):273

Anti-NMDA receptor AIE

Probable anti-NMDA receptor encephalitis is diagnosed when **all three** of the following criteria have been met:

- 1. **Rapid onset** (<3 months) of **at least four of the six** following major groups of symptoms:
  a) Abnormal behavior or cognitive dysfunction
  b) Speech dysfunction (pressured speech, verbal reduction, mutism)
  c) Seizures
  d) Movement disorder, dyskinesias, or rigidity/abnormal postures
  e) Decreased level of consciousness
  f) Autonomic dysfunction or central hypoventilation
- 2. **At least one of the following**:
  - **Abnormal EEG** (focal or diffuse slow or disorganized activity, epileptic activity, or **extreme delta brush**) OR
  - **CSF** with pleocytosis or oligoclonal bands
- 3. Reasonable exclusion of other disorders

Diagnosis can also be made in the presence of **three** of the above groups of symptoms, accompanied by a **systemic teratoma.**

Definite anti-NMDA receptor encephalitis

- Diagnosis can be made in the **presence of ≥1 of the six major groups of symptoms** and **IgG anti-GluN1 antibodies**.

Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391-404

Diagnosis of autoantibody-associated encephalitis

- Graus et al. proposed diagnostic criteria for autoimmune limbic encephalitis with a hierarchical degree of confidence, viz., possible, probable, and definite.
- Diagnostic criteria for **Definite Autoimmune Limbic Encephalitis**
  - Diagnosis can be made when **all four** of the following criteria have been met.
  1. **Subacute onset** (rapid progression of less than 3 months) of **working memory deficits**, **seizures**, OR **psychiatric symptoms** suggesting involvement of the limbic system.
  2. **Bilateral MRI brain abnormalities on T2 FLAIR** **OR** **FDG-PET brain highly restricted to the medial temporal lobes.**
  3. **At least** one of the following:
     1. **CSF** pleocytosis (WBC count of >5 cells per mm^3) OR
     2. **EEG** with epileptic or slow-wave activity involving the temporal lobes
  4. Reasonable exclusion of alternative causes
- If one of the first three criteria is not met, a diagnosis of **definite limbic encephalitis** can be made only with the **detection of antibodies** against cell-surface, synaptic, or onconeural proteins.

Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391-404

Clinical significance of finding an autoantibody related to AIE

- Like SARDs, having autoantibodies does not automatically mean that an individual has AIE.
- The clinical specificity of neural antibody testing using commercial immunoblot kits alone is relatively high (~95%), but the **positive predictive value** of this approach in studies is **only 30% to 50%.**
- The presence of autoantibodies is significant only in the context of a typical clinical presentation.
  - Autoantibodies only play a **supportive** role in diagnosing AIE.

Budhram A, Yang L, Bhayana V, Mills JR, Dubey D. Clinical Sensitivity, Specificity, and Predictive Value of Neural Antibody Testing for Autoimmune Encephalitis. J Appl Lab Med. 2022;7(1):350-356

DIAGNOSTIC EVALUATION OF SUSPECTED AUTOIMMUNE ENCEPHALITIS IN ADULTS

When to suspect autoimmune encephalitis?

Presentation: **subacute onset (<3 months)** of new neuropsychiatric symptoms

- *Encephalopathy* may include: cognitive decline, altered level of consciousness, confusion, memory deficits
- *Psychiatric symptoms* variable

Accompanying features:

- Viral-like prodrome preceding onset
- New epileptic seizures
- Abnormal movements (except tics)
- Focal neurologic deficits (i.e. aphasia, dysarthria, ataxia)
- Autonomic dysfunction
- History of recent viral encephalitis
- History of (within 5 years) or concurrent systemic malignancy

Is history & exam suggestive of autoimmune encephalitis?

NO → Evaluate for alternative causes*

*Serology evaluation of alternative causes of neuropsychiatric symptoms: CBC, CMP, TFTs, B12, folate, Copper, HIV, syphilis (FTA-Abs), serum & urine toxicology, consider porphyrins ceruloplasmin, consider primary psychiatric etiology

YES ↓

Initiate work-up for autoimmune encephalitis

Perform complete neurologic examination, including MoCA

Serology	Evaluate for alternative causes* Assess for autoimmune tendency: - ANA, TPO, thyroglobulin Abs, ESR, CRP, IgA/M/G - Serum autoimmune encephalopathy panel *(includes paraneoplastic panel, NMDA, LGI1)* - Serum anti-Ma/Ta antibody - Serum Glycine-R antibody
Lumbar puncture	CSF studies: - Opening pressure - Cell count, total protein, glucose, gram stain/culture, oligoclonal bands, IgG index, beta-2 microglobulin, flow cytometry, cytology - CSF autoimmune encephalopathy panel - CSF anti-Ma/Ta antibody - CSF Glycine-R antibody - Consider infectious studies as appropriate *(i.e., HSV PCR)* - Save extra
EEG	LTM preferred when suspect epileptic events
Imaging	Brain MRI w/ and w/o contrast Consider brain PET (especially if brain MRI normal) Evaluate for systemic malignancy - CT chest/abdomen/pelvis vs whole body PET - Testicular ultrasound in males - Pelvic ultrasound in females

Is work-up suggestive of autoimmune encephalitis?

YES → Initiate first-line treatment

NO

- Consider alternative etiologies
- If suspicion for autoimmune encephalitis despite unrevealing work-up, consult neuroimmunology for further guidance

Antibody Prevalence in Epilepsy and Encephalopathy (APE2 Score)

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)

APE2 score ≥ 4 was 99% sensitive and 93% specific for neural-specific-antibodies

Dubey D, Kothapalli N, McKeon A, et al. Predictors of neural-specific autoantibodies and immunotherapy response in patients with cognitive dysfunction. J Neuroimmunol. 2018;323:62-72
Dubey D, Pittock SJ, McKeon A. Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability. Epilepsia. 2019;60(2):367-369

Case Vignette

A case of a woman with subacute-onset psychotic symptoms, cognitive symptoms, and seizures in her 30s

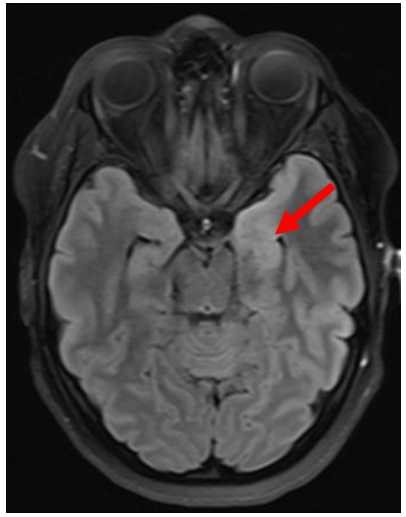
- She presented with acute-onset intermittent, brief-duration **auditory hallucinations, visual hallucinations, and olfactory amplification**, along with episodic dizziness, nausea, and **cognitive symptoms** that started 8 months ago.
  - **MRI brain** showed regions of patchy enhancement of the left hippocampus.
  - **EEG** showed left temporal slowing.
  - Detailed CSF studies were negative.
  - She was treated empirically for HSV encephalitis with Acyclovir.
- At 3 weeks after illness onset, **seizures began**; antiseizure medication initiated.
- At 6 weeks, she developed functional hand tremors and icepick headaches.
- **At 4 months**, she saw neuroimmunology, her MoCA score was 22/30, **empirically trialed on IV Methylprednisone**, and shortly thereafter, IVIg as well
  - **Serum testing** showed **autoantibodies against the LGI-1 protein.**
- Iatrogenic complications included Cushingoid features, 20 lbs weight gain, Diabetes, and DVT leading to Pulmonary thromboembolism.
- Neurological symptoms improved, but psychiatric symptoms continued
  - Initiated on Aripiprazole with mild improvement.

APE2 score = 4

A case of a woman with subacute-onset psychotic symptoms, cognitive symptoms, and seizures in her 30s

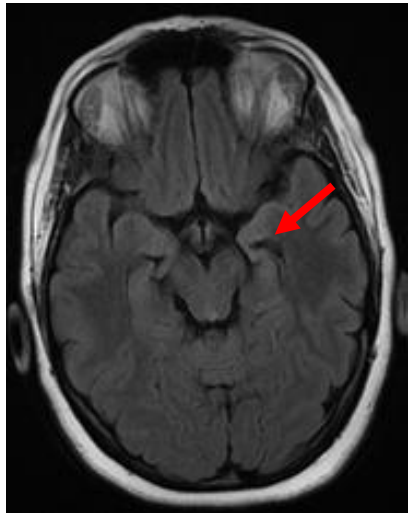
- **Past Psychiatric History:** Major Depressive Disorder, recurrent, anxiety disorder, unspecified, 1 suicide attempt 15 years ago.
- **Past Neurologic History:** Two concussions 3 years ago, led to **post-concussion symptoms** that lasted for several weeks.
- **Past Medical History:** Migraine, Mast-cell activation syndrome, Excessive Body Weight (BMI ~35 Kg/m2), Polycystic Ovarian Disease, and Prothrombin/Factor II gene variant G20210A carrier.
- **Family History:** Mother has Migraine, Excessive body weight, PCOD, and MCAS; sister has Autism-spectrum Disorder, and Maternal aunt has Myasthenia Gravis.
- **Mental Status Exam:** bilateral, **distractible, coarse, postural hand tremor**, soft, slowed, and lilting speech with frequent pauses, sad and anxious affect, tearful.

A case of a woman with subacute-onset psychotic symptoms, cognitive symptoms, and seizures in her 30s

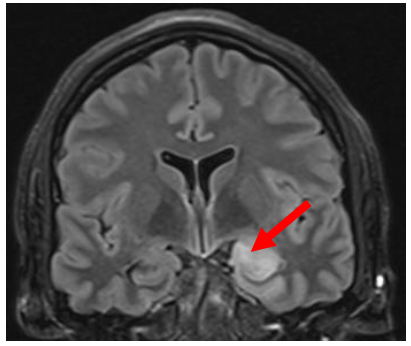


Axial T2 FLAIR

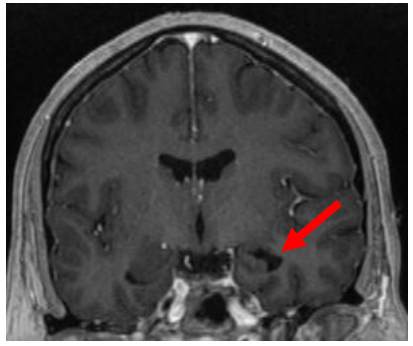
5 months after illness onset



Axial T2 FLAIR



Coronal T2 FLAIR



Coronal T2 Post-contrast

Seronegative Autoimmune Encephalitis (SNAE)

- Not every patient with autoimmune/paraneoplastic encephalitis will have a detectable autoantibody.
  - In a **substantial proportion** of cases, **autoantibodies are not found**.
  - Diagnosis requires strong clinical suspicion.
- SNAE may have unidentified pathogenic autoantibodies or T cell-mediated neuronal cytotoxicity.
- The absence of autoantibodies impedes prognostication and treatment decisions.
- A large retrospective chart review from Seoul reported 147 patients with SNAE; with 60% being SNAE among all cases of AIE diagnosed at that single center.
  - Around 47% were women, and the median age was 40 years.
  - **Psychiatric symptoms were present in ~76% of the patients**
  - Around 80% had seizures; ~80% had impaired consciousness; >90% had memory dysfunction; ~80% had gait impairment/ataxia; ~25% had dyskinesia/dystonia.
  - Around 57% had persistent disease at 6 months.
  - **Underlying malignancy was identified in only three of 147 patients.**
  - Cerebellar atrophy on MRI brain at 6, 12, and 24 months was associated with poor 2-year outcomes.

Lee WJ, Lee HS, Kim DY, et al. Seronegative autoimmune encephalitis: clinical characteristics and factors associated with outcomes. Brain. 2022;145(10):3509-3521
van Steenhoven RW, Titulaer MJ. Seronegative autoimmune encephalitis: exploring the unknown. Brain. 2022;145(10):3339-3340

Diagnosing individuals indiscriminately with AIE can be harmful!

- A retrospective, international, multi-center study across several AIE subspecialty outpatient clinics **evaluated adults who presented with a diagnosis of AIE (n=393)** and were **eventually given an alternative diagnosis**.
- Around **27% of patients had a misdiagnosis** of AIE, and 72% of them did not even fulfill diagnostic criteria.
- 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%), and other (7%).
- **Onset was insidious (>3 months) in 48%.**
- **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%)**, misinterpretation of functional/psychiatric symptoms, or nonspecific cognitive dysfunction as encephalopathy (38%).

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

Factors associated with AIE misdiagnosis

- 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
  - NMDA antibodies positive in serum but negative in CSF

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

Autoimmune/Paraneoplastic Encephalitides – Prognosis

- Paraneoplastic encephalitides have a poorer prognosis compared to autoimmune encephalitides.
- In the case of AIE 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 AIE.
- Mortality ranges between 10% and 40%.
  - It is lowest in anti-LGI1 encephalitis, intermediate in anti-NMDA receptor encephalitis, and highest in anti-GABA-B receptor encephalitis and paraneoplastic encephalitides.

Blum RA, Tomlinson AR, Jetté N, Kwon CS, Easton A, Yeshokumar AK. Assessment of long-term psychosocial outcomes in anti-NMDA receptor encephalitis. Epilepsy Behav. 2020;108:107088. doi:10.1016/j.yebeh.2020.107088

Schubert J, Brämer D, Huttner HB, et al. Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment. Neurology - Neuroimmunology Neuroinflammation. 2019;6(1)

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

When to suspect autoimmunity as an underlying cause in those presenting with neuropsychiatric illness/symptoms?

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 or sensitivity to antipsychotics
- 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

Hauptman AJ, Ferrafiat V. Neuroinflammatory syndromes in children. Curr Opin Psychiatry. 2023;36(2):87-95
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.
Oldham M. Autoimmune Encephalopathy for Psychiatrists: When to Suspect Autoimmunity and What to Do Next. Psychosomatics. 2017;58(3):228-244

General management of neuropsychiatric disorders associated with autoimmune diseases

- Work-up includes screening for systemic and CNS inflammation using blood-based biomarkers, neuroimaging (MRI brain, PET brain), EEG, serum and CSF autoimmune panels, hormone assays, consult with Neurology, Rheumatology, etc.
- Causation is difficult to ascertain; avoid biological reductionism and utilize the biopsychosocial approach.
- Due to the high incidence and prevalence of psychiatric disorders compared to autoimmune diseases, statistically, 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."

General management of neuropsychiatric disorders associated with autoimmune diseases

- 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.
- Psychiatric symptoms may improve just by suppressing the autoimmune activity with steroids or disease-modifying drugs (immunomodulators).
  - Otherwise, the treatment of psychiatric disorders is empirical.
- It is crucial to rule out infections that may worsen before initiating immunosuppressive treatments.
- Immunosuppressants may lead to neuropsychiatric complications as well.

Treatment of specific neuropsychiatric symptoms/disorders

- MDD, Anxiety disorders, OCD – antidepressants, psychotherapy
- Psychosis – atypical antipsychotics, Benzodiazepines, ECT
- Catatonia – Supportive, Benzodiazepines, ECT
- Mania – mood stabilizers, atypical antipsychotics
- Headache – NSAIDs
- Fatigue – Lifestyle modification, Exercise, Amantadine (in case of MS), Modafinil, SSRIs (in case of MS), certain supplements like CoQ10, L-Carnitine, etc.
- Cognitive symptoms – Stimulants, Cognitive rehabilitation
- Delirium – Supportive care
- Personality change – depending upon the specific change (stimulants for apathy, antidepressants/mood stabilizers for disinhibition, impulsivity, irritability)
- Movement disorders – depending upon the type of movement disorder

Oldham M. Autoimmune Encephalopathy for Psychiatrists: When to Suspect Autoimmunity and What to Do Next. Psychosomatics. 2017;58(3):228-244

Neuropsychiatric adverse effects of treatments used for autoimmune diseases

- **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, and Mycophenolate, Azathioprine) – Depression, cognitive symptoms
- **Hydroxychloroquine** – some evidence of depression, anxiety, psychosis but a recent large multinational study didn't find any evidence for that.
- **Interferons** – Depression
- **TNF-alpha inhibitors** – Depression, mania, and psychosis
- **CAR (Chimeric Antigen Receptor) T-cell therapy** – Encephalopathy

Thillard EM, Gautier S, Babykina E, et al. Psychiatric Adverse Events Associated With Infliximab: A Cohort Study From the French Nationwide Discharge Abstract Database. Frontiers in Pharmacology. 2020;11. Accessed September 17, 2023.
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THANK YOU SO MUCH FOR YOUR ACTIVE LISTENING

Now time for Q&A

Acknowledgments:
MGB CL Psychiatry colleagues
MGB CBMM colleagues
MGB Psychiatry Leadership
My clinic patients

For further questions, please feel free to contact me via **rgupta29@bwh.harvard.edu** or **@RishabGupta_84**

Assessment and Differential Diagnosis