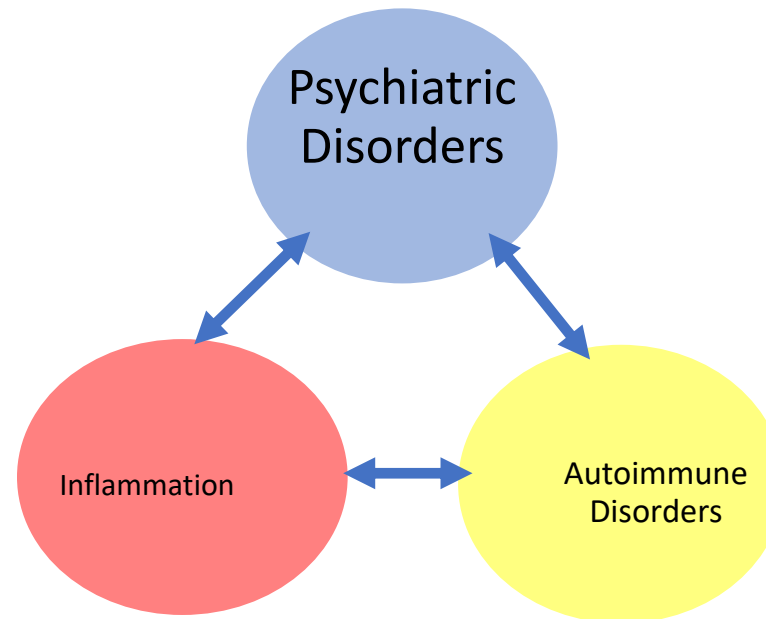




Inflammation, Autoimmune Disorders, and Psychiatric Illness



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09/20/2026

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

Introduction

- Psychiatric disorders can occur in the context of infectious diseases, autoimmune diseases, and malignancies.
- **Interferon therapy can lead to depression.**
- **TNF- α 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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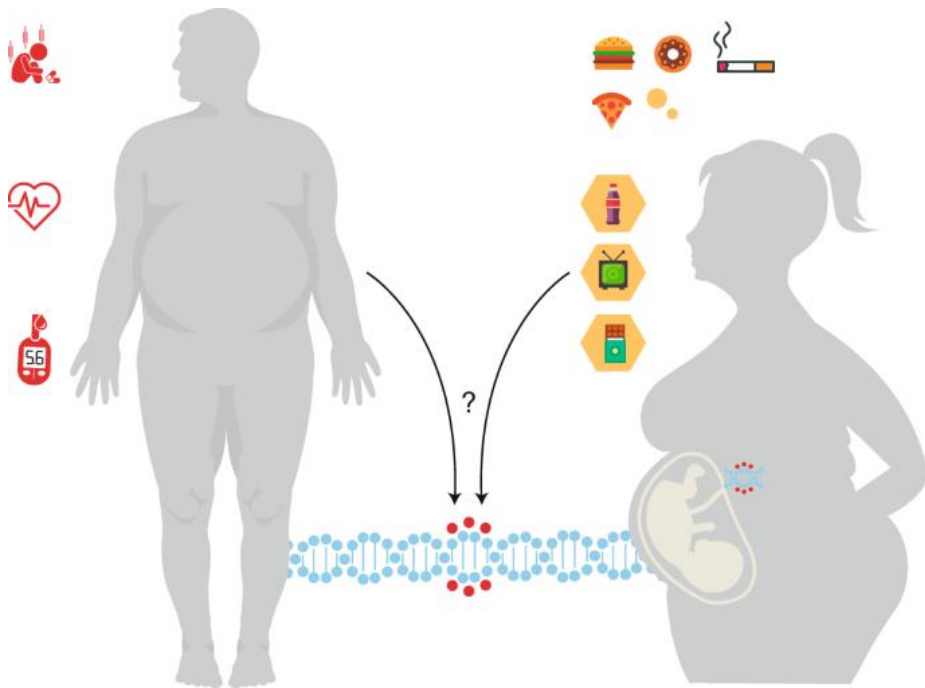
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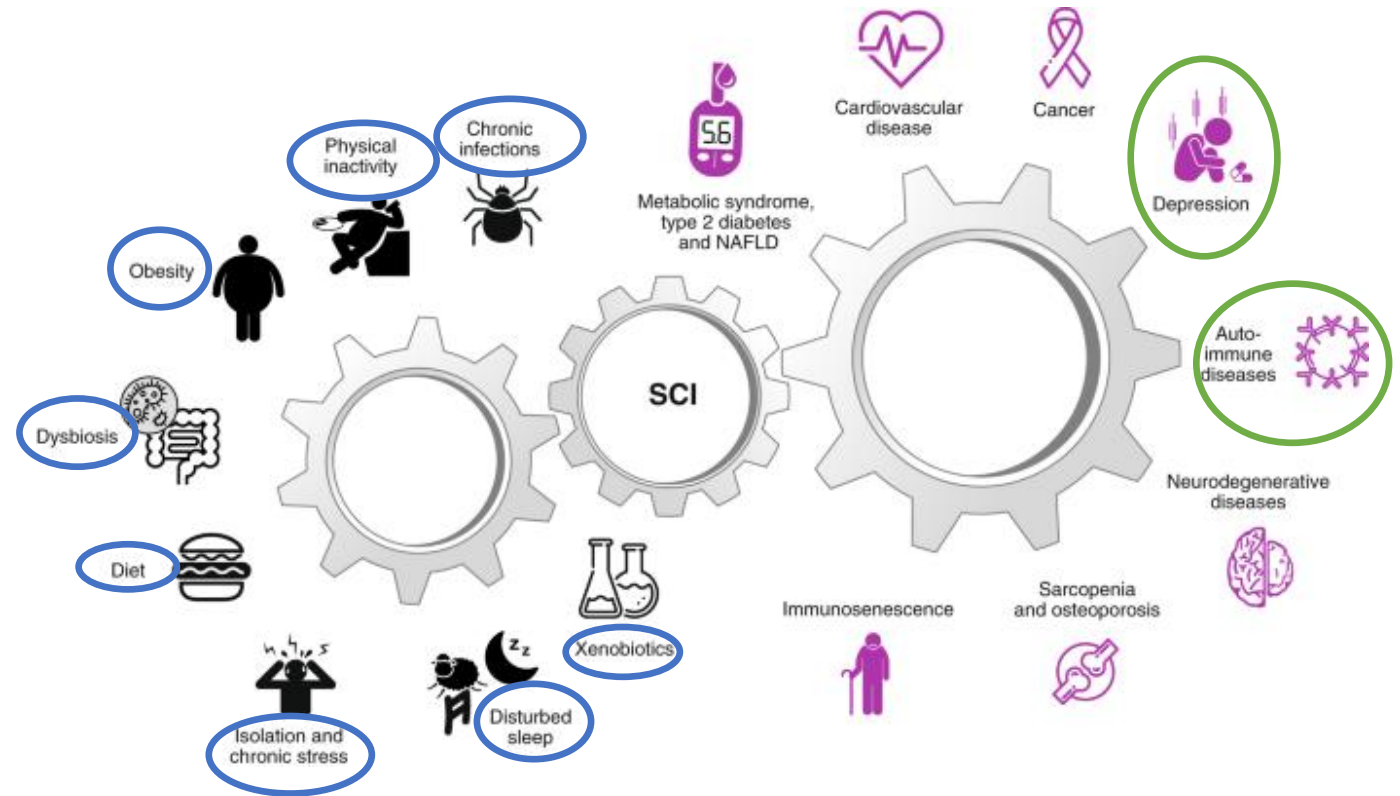
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Introduction

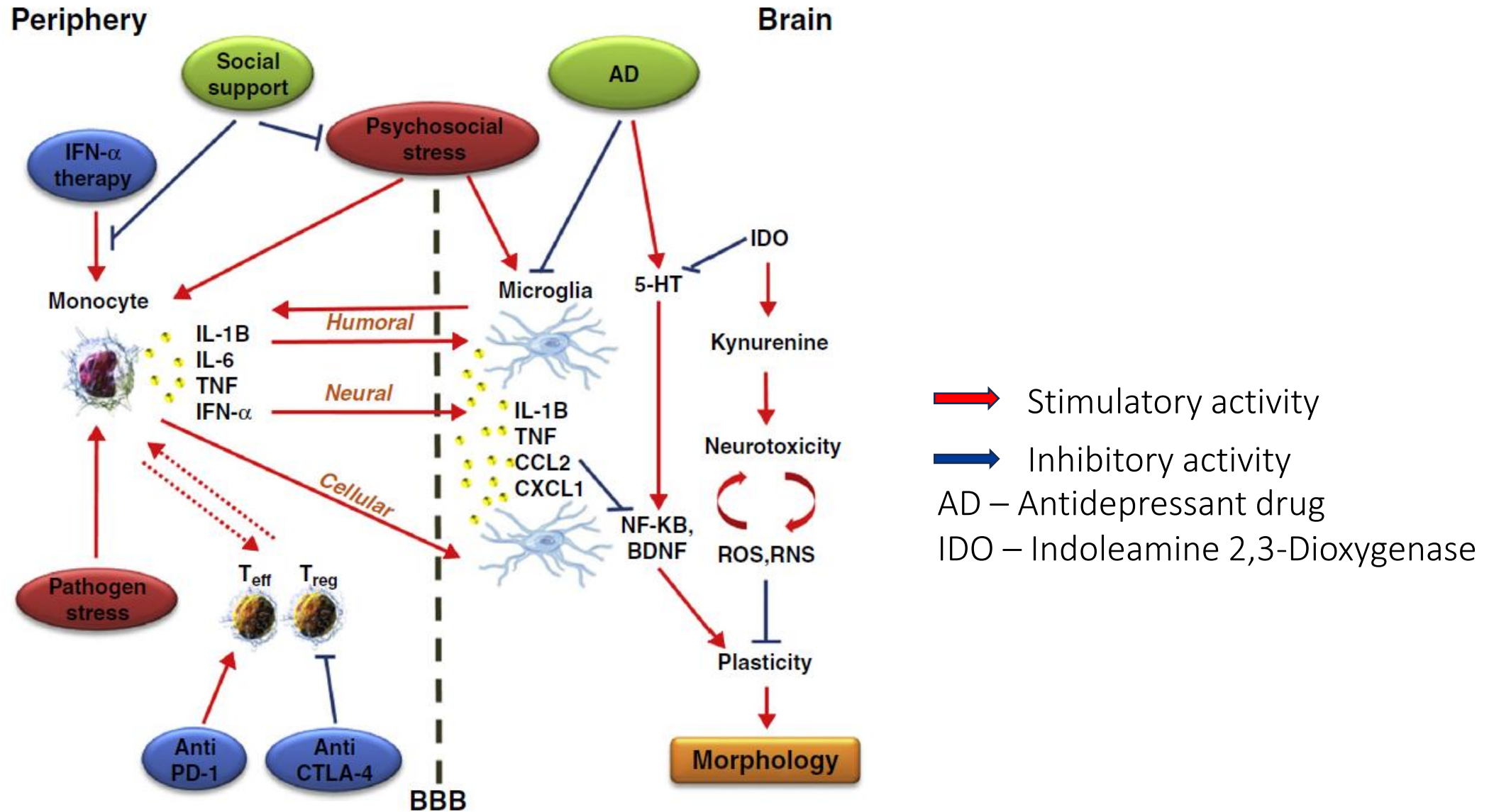
The **maternal exposome** and
Low-grade Systemic Chronic
Inflammation (SCI)



Causes and consequences of
Low-grade Systemic Chronic Inflammation



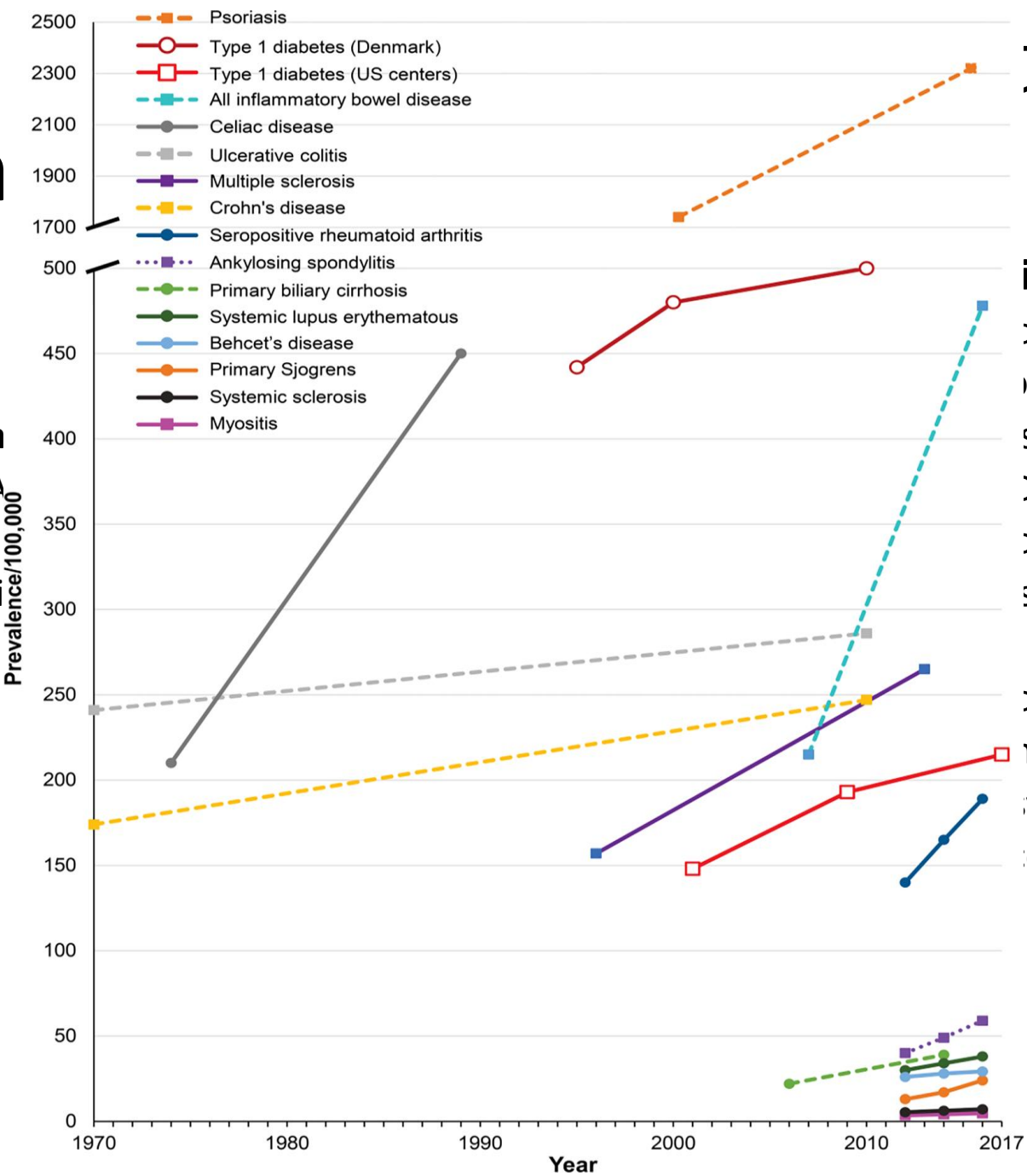
Introduction



Some Autoimmune Neuropsych

Neurological

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



erred in

immune Rheumatologic Diseases

- : Lupus Erythematosus (SLE)
- osis
- syndrome
- Disease
- : vasculitides
- spholipid Antibody Syndrome
- : Acute-onset Neuropsychiatric
- ne (PANS) and Pediatric Autoimmune
- ychiatric Disorder associated with
- occal infection (PANDAS)

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

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**

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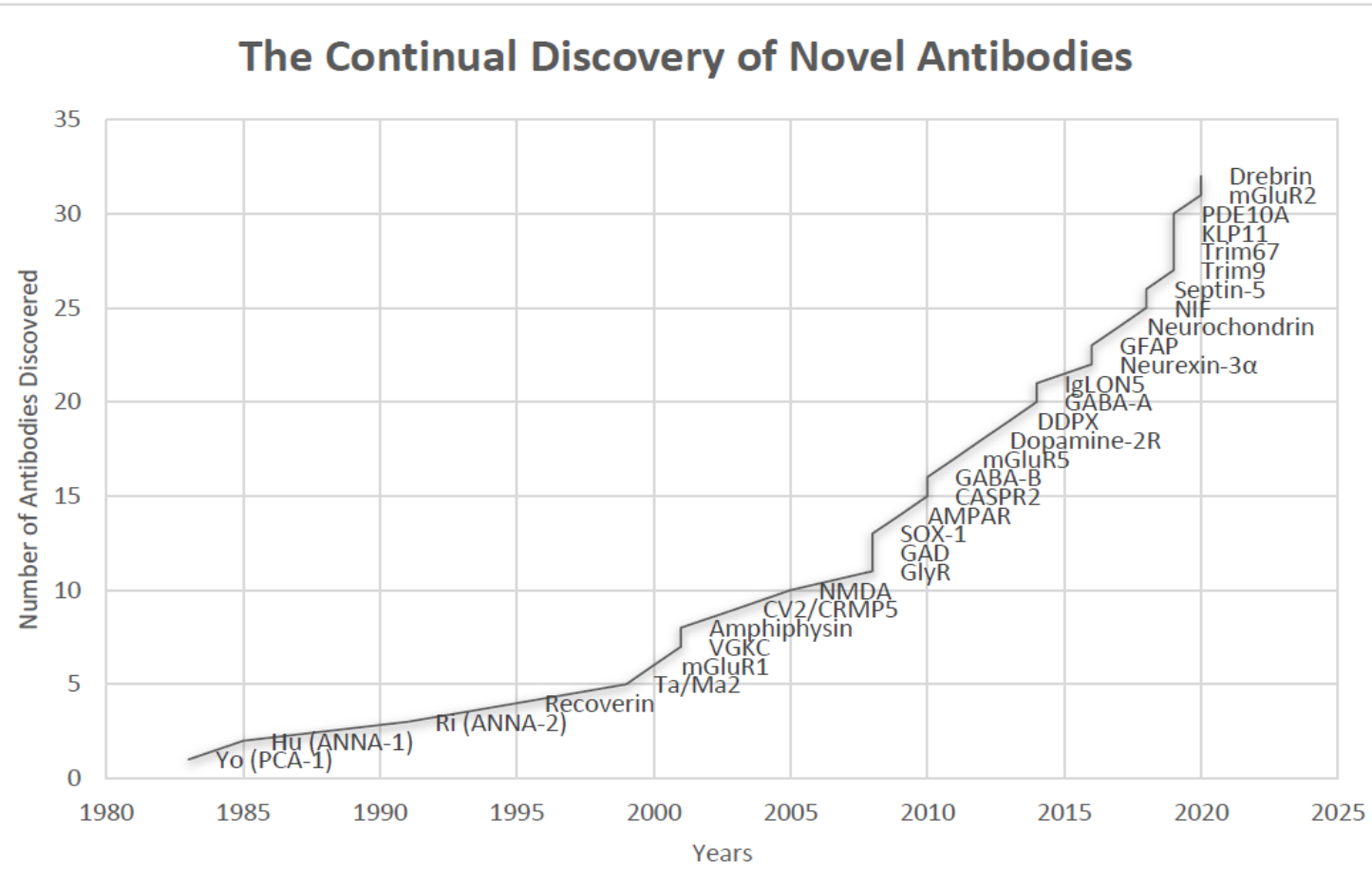
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Autoimmune Encephalitides (AIE)

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)



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
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%

Overview of AIE

- Types of AIE:
 - Idiopathic
 - 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

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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.

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

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

Anti-NMDA receptor AIE

- It is **one of the commonest** AIE 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 MOGAD or NMO that can occur separately or simultaneously.

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.

Diagnostic approach for suspected AIE

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 AIE?

No

Yes

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

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

Is work-up suggestive of AIE?

Yes

No

Initiate first-line treatment

Consider alternative etiologies
If suspicion for AIE persists, then 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

Case Vignettes

Case 1: A woman with subacute-onset psychotic symptoms, cognitive symptoms, and seizures in her 30s

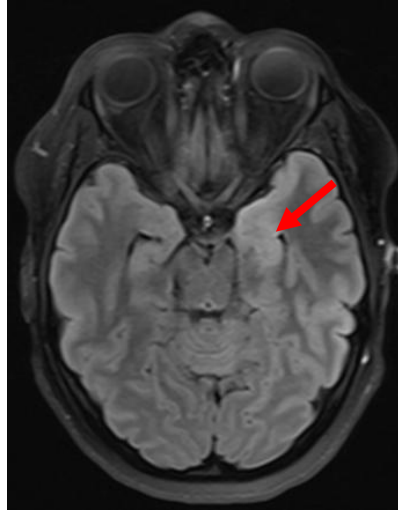
- She presented with acute-onset intermittent, brief-duration **auditory hallucinations, visual hallucinations, and olfactory amplification**, along with episodic dizziness, nausea, and **cognitive symptoms** that started 8 months ago.
 - **MRI brain** showed regions of patchy enhancement of the left 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 20 lbs weight gain, Cushingoid features, worsening of Diabetes, and DVT leading to Pulmonary thromboembolism.
- Neurological symptoms improved, but psychiatric symptoms continued
 - Initiated on Aripiprazole with mild improvement.

APE2 score = 4

Case 1: A woman with subacute-onset psychotic symptoms, cognitive symptoms, and seizures in her 30s

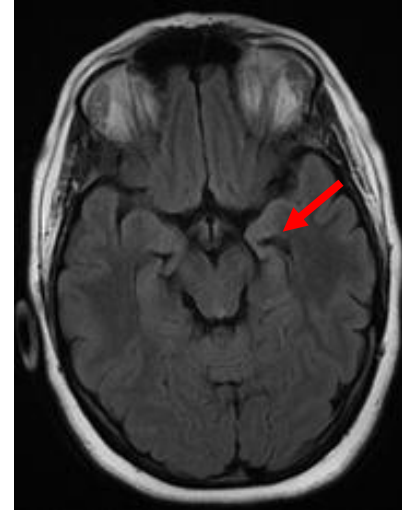
- **Past Psychiatric History:** Major Depressive Disorder, recurrent, anxiety disorder, unspecified, 1 suicide attempt 15 years ago.
- **Past Neurologic History:** Two concussions 3 years ago, led to **post-concussion symptoms** that lasted for several weeks.
- **Past Medical History:** Migraine, Mast-cell activation syndrome, Excessive Body Weight (BMI ~35 Kg/m²), Diabetes mellitus type 2, 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.

Case 1: A woman with subacute-onset psychotic symptoms, cognitive symptoms, and seizures in her 30s

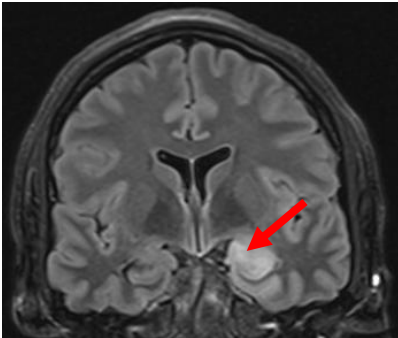


Axial T2 FLAIR

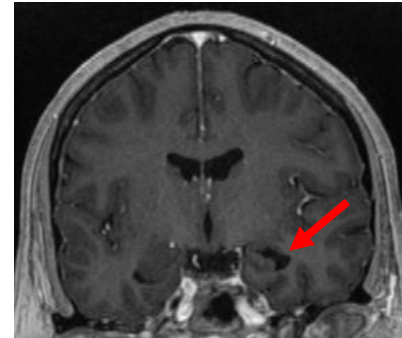
5 months after illness onset



Axial T2 FLAIR



Coronal T2 FLAIR



Coronal T2 Post-contrast

Case 2: A man with subacute-onset cognitive symptoms, anxiety symptoms, and psychotic symptoms in his 30s

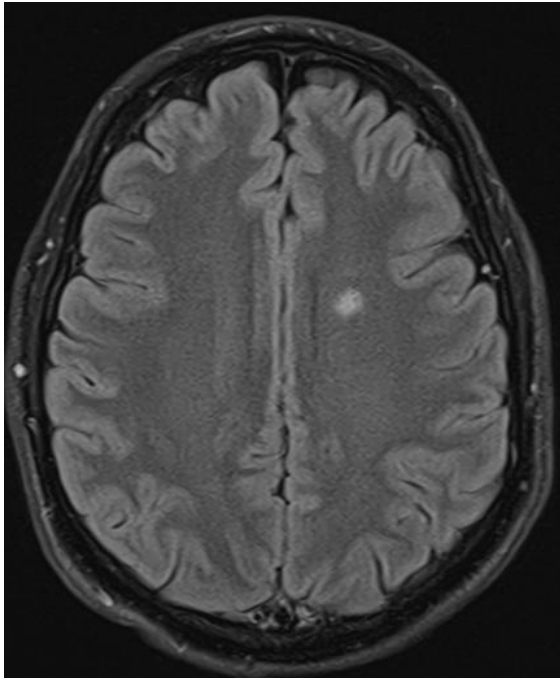
- He presented to my clinic after 4 months of illness-onset characterized by subacute-onset irritability and progressive cognitive impairment for 3 months followed by rapidly worsening anxiety (and panic attacks), insomnia, night sweats, chills, jaw pain, suicidal ideation and plan, auditory hallucinations, persecutory delusions, and referential ideas.
- At 4 months, he developed worsening motor coordination, muscle stiffness, slurred speech, left eyelid drooping, double vision, right arm and shoulder twitching intermittently.
 - **MRI brain** showed one 9x7 mm enhancing and T2/FLAIR hyperintense lesion in the left frontal centrum semiovale.
 - **EEG** showed occasional irregular left temporal theta slowing with rare broader sharply contoured theta over the left side.
 - **CSF studies showed lymphocytic pleocytosis and anti-NMDA-R antibodies.**
- Following Prednisone initiation, he developed manic symptoms requiring hospitalization.
- His manic symptoms have remitted since then.
- He continues to experience mild degree of executive dysfunction, anxiety symptoms, and insomnia.
- He was on Aripiprazole 5mg/day, Buspirone 10mg TID, Escitalopram 20mg QAM, Lorazepam 2mg BID PRN, and Trazodone 100mg QHS at the time of presentation to my clinic.
 - His symptoms relapsed in the context of steroid taper, and slow discontinuation of Escitalopram and Buspirone.

APE2 score = 5

Case 2: A man with subacute-onset cognitive symptoms, anxiety symptoms, and psychotic symptoms in his 30s

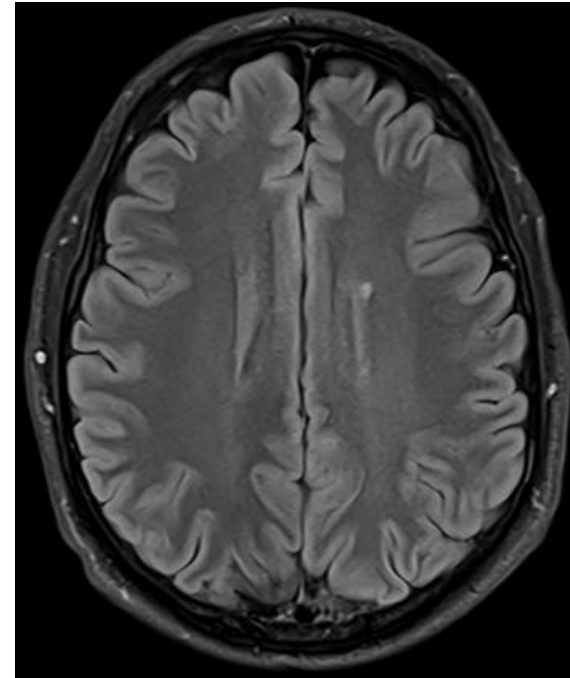
- **Past Psychiatric History:** None.
- **Past Neurologic History:** None.
- **Past Medical History:** Hypercholesterolemia, Excess body weight
- **Family History:** Father has PTSD and anxiety, mother has depression, one sister has OCD and excoriation disorder, one sister has anxiety, paternal grandfather has PTSD, and paternal uncle and aunt have alcohol misuse.
- **Mental Status Exam:** mild left eyelid ptosis

Case 2: A man with subacute-onset cognitive symptoms, anxiety symptoms, and psychotic symptoms in his 30s



Axial T2 FLAIR

4 months post immunotherapy



Axial T2 FLAIR

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.
 - Around 57% had persistent disease at 6 months.
 - **Underlying malignancy was identified in only three of 147 patients.**

Clinical features	Frequency
Psychiatric symptoms	~76%
Seizures	~80%
Impaired consciousness	~80%
Memory impairment	>90%
Gait impairment/ataxia	~80%
Dyskinesia/Dystonia	~25%

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%).

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

Autoimmune/Paraneoplastic Encephalitides – Prognosis

- Prognosis: Idiopathic AIE > SNAE > Paraneoplastic AIE.
- 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.
- A substantial minority of patients with AIE will suffer a relapse.
- Mortality ranges between 0%-40% based on the type of AIE and other factors.
 - It is lowest in anti-CASPR2 encephalitis, intermediate in anti-NMDA receptor encephalitis, and highest in anti-GABA-B receptor encephalitis and paraneoplastic encephalitides.

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

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 by suppressing the autoimmune activity with steroids or disease-modifying drugs (immunomodulators) alone.
 - 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.

THANK YOU SO MUCH FOR YOUR ACTIVE LISTENING

Now time for Q&A



Acknowledgments:

BWH CL Psychiatry colleagues

BWH 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](#)