Evaluation and Management of Autoimmune Brain Disorders: A Psychiatry Perspective

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OBJECTIVES

- To outline neuropsychiatric presentations of autoimmune encephalopathies
- To understand the differential diagnoses and overlap with psychiatric conditions
- Understand emerging patterns with phenotype recognition
- Learn how to evaluate and diagnose AE in both inpatient/outpatient settings

A LOOK BACK…

A Historical Perspective

- Biological psychiatry
  - Emphasizes the union between neurology and psychiatry
- Contemporaries with Freud
  - (1859-1939)

Organic Psychosis

- Historical Concept explored in biological psychiatry for centuries
  - Infectious causes
  - Post infectious causes
  - Immune system mediation

Psychiatry Nobel Prizes

- **1927** Julius Wagner-Jauregg

  Discovery of malaria treatment for neurosyphilis or "general paresis of the insane" (GPI)
- **1949** Egas Moniz

  Development of lobotomy procedure
- **2002** Eric Kandel

  neuropsychiatrist who discovered signal transduction in nervous system within memory formation

Organic Psychosis

- Example: Neurosyphyllis

  1927

  - Known as the "disease of the century"
  - Middle age/middle class
  - Delusions, psychosis, paralysis, dementia, fatal
  - Approximately 5-10% of psychiatric admissions before 1942 were attributed to neurosyphillis

The timeline

1926

- Dr. Karl Menninger (Psychiatrist, Boston)
- described unique post infectious psychosis in 175 patients who had experienced influenza symptoms immediately preceding onset of psychosis
- 60 were reported to resemble dementia praecox and 35 of 50 patients followed over time reportedly had complete resolution

Menninger KA. Influenza and schizophrenia: An analysis of post-influenza "dementia precox," as of 1918, and five years later. 1926 [classical article]. Am J Psychiatry. 1994;151(6):182-187.

The timeline

1937

- Dr. Lehman Facius (Neuropathology, Germany)
- Theory: schizophrenia is caused by an organic destructive process
- Goal: to describe autoantibodies against brain structures in schizophrenia by taking CSF from individuals with schizophrenia and observing whether CSF will react to normal brain tissue

Khandaker GM, Cousins L, Deakin J, et al. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry. 2015 Mar;2(3):258–270

The timeline

1992

- Chemist Ronald Smith proposes a T-lymphocyte mechanism of schizophrenia
- Clinical observation: IL-2 given to psychiatrically typical individuals produces severe positive & negative schizophrenia symptoms in majority of individuals

Smith "A comprehensive macrophage-T-lymphocyte theory of schizophrenia" Med Hypothesis, 1992.

A new era of organic psychosis:

2005 - 2007

- Dr. Josep Dalmau MD, PhD (Neurologist/Neuroimmunologist from Barcelona, Spain)
  - description internationally of NMDA autoantibody
  - clinical phenotype often presenting as acute psychiatric symptoms (psychosis, mania, delirium, etc)
  - Responsive to IV immunoglobulin and IV steroids

- Defining Autoimmune Encephalitis…

Autoimmune Encephalitis

- An immune mediated inflammatory disorder of the central nervous system
  - may be post-infectious → **self limited**
  - may be paraneoplastic
  - or may be a primary autoimmune process → **self propagating**

Autoimmune Encephalitis

- Acute to subacute neuropsychiatric deficits crossing multiple domains
  - Cognitive decline/ memory impairment
  - Psychosis
  - Mood disorders
  - Sleep disorders
  - Movement disorder
  - Seizures
- Diagnosis made based upon a consistent clinical course **with supportive paraclinical testing**

THE LANCET
Neurology

Position Paper

A clinical approach to diagnosis of autoimmune encephalitis

Prof Francesc Graus, MD, Maarten J Titulaer, MD, Ramani Balu, MD, Susanne Benseler, MD, Prof Christian G Bien, MD, Tania Cellucci, MD, Irene Cortese, MD, Prof Russell C Dale, MD, Jeffrey M Gelfand, MD, Michael Geschwind, MD, Carol A Glaser, MD, Prof Jerome Honnorat, MD, Romana Höftberger, MD, Takahiro Iizuka, MD, Sarosh R Irani, MD, Eric Lancaster, MD, Frank Leypoldt, MD, Harald Prüss, MD, Alexander Rae-Grant, MD, Prof Markus Reindl, PhD, Prof Myrna R Rosenfeld, MD, Kevin Rostásy, MD, Albert Saiz, MD, Arun Venkatesan, MD, Prof Angela Vincent, FRS, Prof Klaus-Peter Wandinger, MD, Patrick Waters, PhD, Prof Josep Dalmau, MD

Published: 19 February 2016

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Clinical Features of Patients with anti-NMDAR encephalitis

- Seen in all age ranges
  - Most commonly young adults (8 months-85 yrs)
  - 1/3 of cases occur in children (< 18 yrs)
- Occurs more commonly in women (81%)
  - Although more commonly in males if < 12 or > 45 years
- Prodromal symptoms may occur
  - Fever, fatigue, headache, URI, vomiting, or diarrhea

Titulaer MJ et al. Lancet Neurol 2013;12:157-65

Original Slide Adapted from Dr. William Gallentine

Diagnostic criteria for possible autoimmune encephalitis

- Diagnosis can be made when all 3 of criteria met:
  - Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
  - At least one of the following:
    - New focal CNS findings
    - Seizures not explained by a previously known seizure disorder
    - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
    - MRI features suggestive of encephalitis: T2 lesions in one or both temporal lobes, or in multifocal areas involving grey matter, white matter or both compatible with demyelination or inflammation
  - Reasonable exclusion of alternative causes

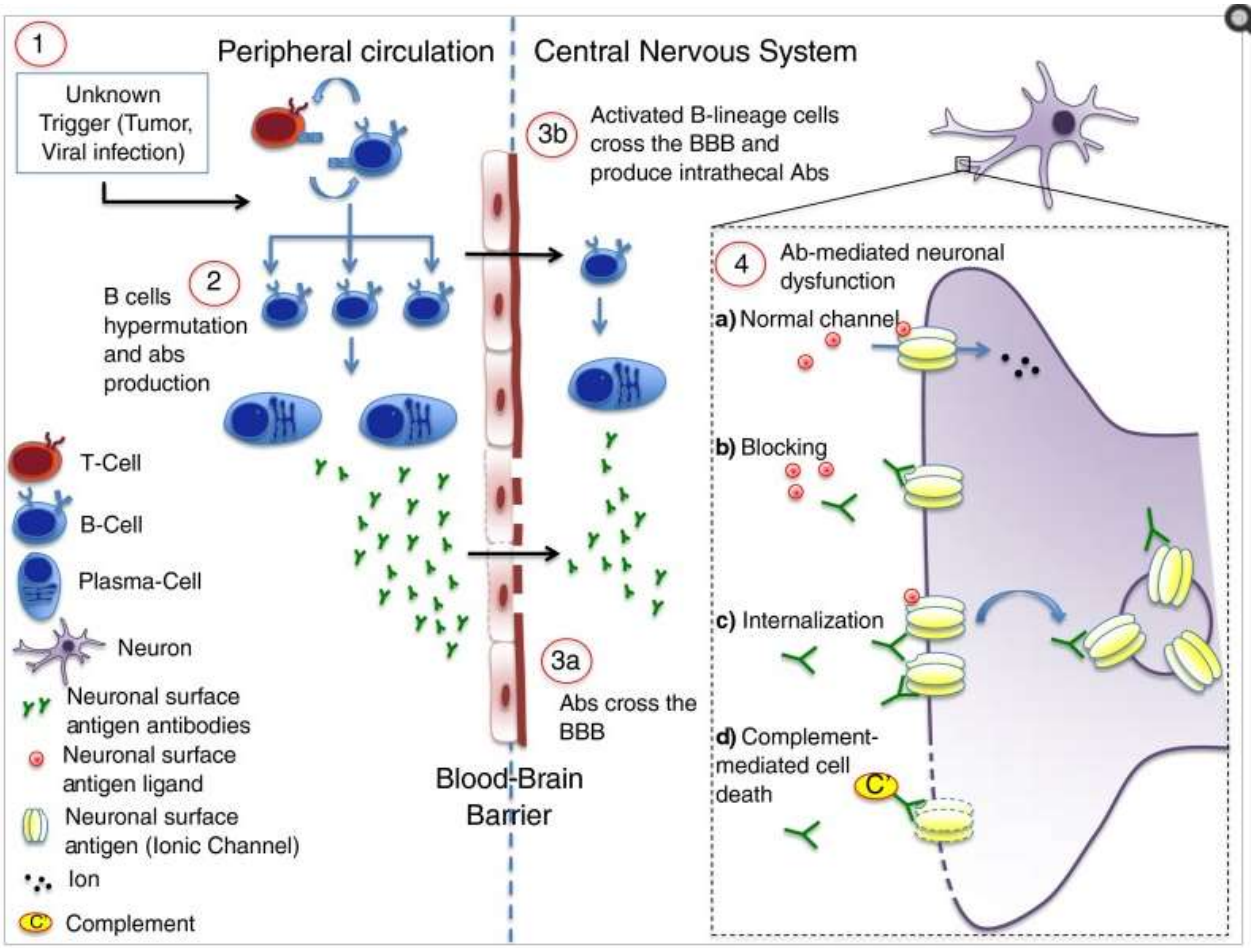
Graus F, et al. *Lancet Neurology* , 2016;15:391-404.

Diagnostic criteria for auto-antibody negative but probable autoimmune encephalitis

- Diagnosis can be made when all four of the following criteria have been met:
  - Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
  - Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
  - Absence of well characterized autoantibodies in serum and CSF, and at least two of the following criteria:
    - MRI abnormalities suggestive of autoimmune encephalitis
    - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both*
    - Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)
  - Reasonable exclusion of alternative causes

Graus F, et al. *Lancet Neurology* , 2016;15:391-404

Potential pathogenic mechanisms in antibody mediated autoimmune Encephalitis



Gastaldi et al, Neurotherapeutics, 2016. 13:147-162

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Neuropsychiatric Presentations

- AE can become one of the “great mimickers”

Neuropsychiatric Presentations

- Impulsivity
- Disinhibition
- Mood lability
- Acute onset personality changes
- Loss of executive function

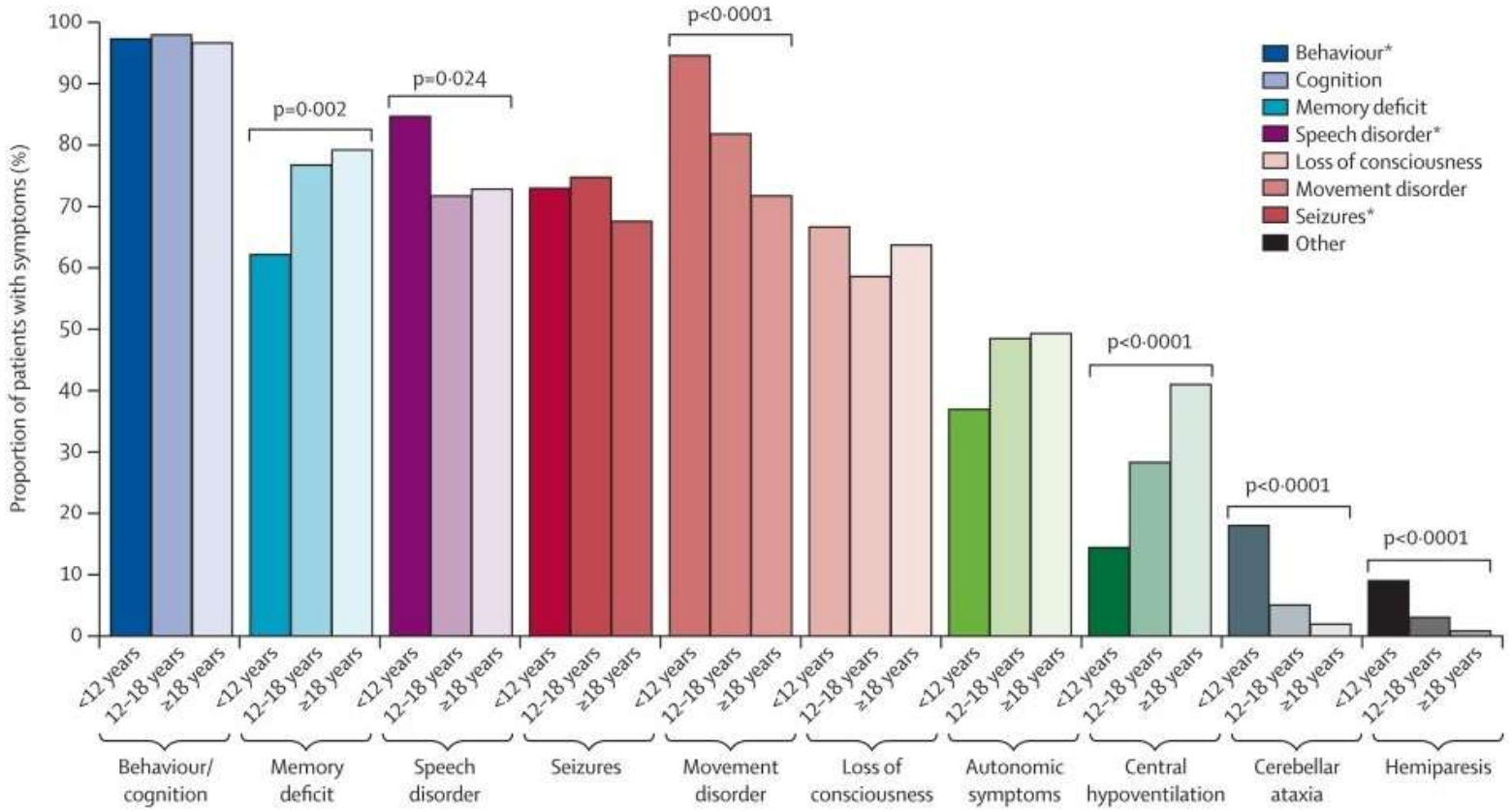
Neuropsychiatric Presentations

- Seizures
- Movement disorders
- Insomnia/sleep disruption
- Gait changes
- Enuresis/encopresis

Neuropsychiatric Presentations

- Sensory perceptual disturbances
- Delusions
- Paranoia
- Obsessions
- Compulsions

Clinical Features of Patients with anti-NMDAR encephalitis at 1 month (n=577)



Original slide courtesy of Dr. William Gallentine

Differential Diagnosis

- First episode Psychosis → but with abrupt onset without premorbid history – often a specific day that symptoms began

Differential Diagnosis

- Bipolar affective illness→but without response to neuroleptics or mood stabilizers

Differential Diagnosis

- Autism spectrum disorder→ but atypical timeline without premorbid history

Differential Diagnosis

- OCD → but with multiple cognitive domains concurrently effected

Capgras delusions

- NMDA autoimmune encephalitis
- Seronegative autoimmune encephalitis

Short term memory impairments

- May be protective → patients often amnestic for portions of hospital course
- May be source of agitation →more difficult to de-escalate

Delirium and catatonia exist on a spectrum in patients with AE

- Master class in Ativan may be required
  - high doses, frequent intervals
- PICU level of care often due to autonomic instability and refractory seizures

Delirium

- Judicious use of atypicals/typicals
- Monitor closely due to higher risk for NMS
- Cornell Assessment of Pediatric Delirium (CAPD)
- Pediatric Confusion Assessment Method (PCAM- ICU)

Catatonia

- Bush Francis Catatonia Rating Scale
- Ativan
- ECT

Clues…

- Worsening response to atypicals? typicals?
- Clinical course not in keeping with usual pattern for primary psychiatric illness?

Clinical features suggestive of an autoimmune encephalitis diagnosis	Clinical features that argue against an autoimmune encephalitis diagnosis
Abrupt onset	Chronic symptoms/indolent course
Rapid decline	Plateau in symptoms
Multifocal drug resistant epilepsy	
Autonomic instability	
Gait/balance disturbances/Ataxia	Lack of fine/gross motor impairments
Enuresis/encopresis	No impairment in activities of daily living
Delirium ←→ Catatonia	
Cognitive decline	Maintaining cognitive capabilities
Symptoms present in all environments	Environmental specific symptoms only
Multiple domains involved in symptoms	Solely psychiatric symptoms

Mooneyham, Child Adolesc Psychiatric Clin N Am (2017)

- WORKUP…

Approach to diagnosis

- Not all patients with new onset neurologic or psychiatric symptoms need an AE workup
- Diagnostic work up should both evaluate for AE and exclude mimics
  - Large differential including
    - Infections
    - Metabolic disease
    - Toxins
    - Other primary neurologic or psychiatric disease
    - Other inflammatory brain diseases
- Not all patients need the same work up

Who needs a workup?

- History is KEY - Clinical course is the anchor for diagnosis
  - Acute to subacute onset of neuropsychiatric symptoms (rapid progression over ≤3months)…
    - Seizures plus
    - Psychosis plus
    - Cognitive decline
- Requires a careful history
  - behavior/psychiatric symptoms
  - cognition, memory loss
  - Regression of language, ADLs

Herken et al.

- Initial chart review found:
  - 1/3 patients initially hospitalized in psychiatric unit
  - Psychiatric abnormalities presenting sign in 60% of patients
  - Sx onset between 2013 and 2016, mean delay in diagnosis 74 days
  - Sx onset between 2007 and 2012, mean delay in diagnosis 483 days
- Results:
  - Identification of “red flags” and “yellow flags”
  - Reanalysis of charts applying flag criteria reduced delay from symptom onset to diagnosis from 10 to 4 weeks

TABLE 4 | Warning signs pointing to an autoimmune etiology in new-onset psychosis.

Yellow flags 	• Decreased levels of consciousness • Abnormal postures or movements (orofacial, limb dyskinesia) • Autonomic instability • Focal neurological deficits • Aphasia or dysarthria • Rapid progression of psychosis (despite therapy) • Hyponatremia • Catatonia • Headache • Other autoimmune diseases (e.g., thyroiditis)
Red flags 	• Cerebrospinal fluid (CSF) lymphocytic pleocytosis or CSF-specific oligoclonal bands without evidence for infection • Epileptic seizures • Faciobrachial dystonic seizures • Suspected malignant neuroleptic syndrome • MRI abnormalities (mesiotemporal hyperintensities, atrophy pattern) • EEG abnormalities (slowing, epileptic activity or extreme delta brush)

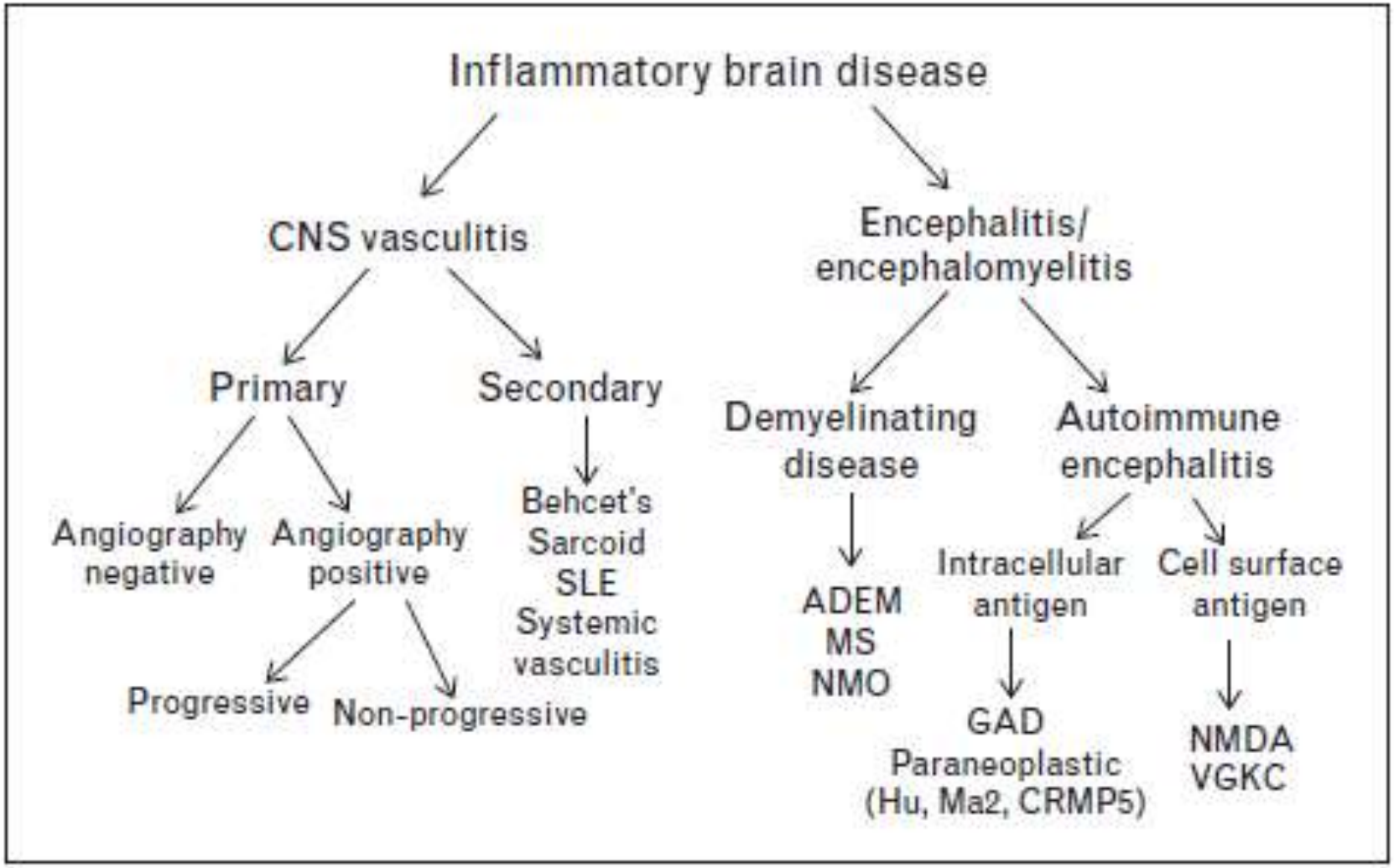
"Red flag" criteria should always prompt determination of anti-neuronal autoantibodies in psychiatric patients. "Yellow flag" criteria should raise suspicion of an autoimmune etiology and include autoimmune encephalitis in the differential diagnoses, in either case if several findings are present.

Julia Herken and Harald Prüss. Front. Psychiatry 2017. 8:25.

Differential Diagnosis

Neurologic	Migraines with vasospasm, Multiple Sclerosis, ADEM
Rheumatologic	Systemic lupus erythematosis, Behcet's, Sarcoidosis, Primary Central nervous system angiitis (CNS vasculitis), ANCA associated vasculitis
Infectious	HSV, Mycoplasma, Lyme, Bartonella, Arboviruses, EBV, CMV, HHV6, HIV, Post-varicella
Neoplastic	Leptomeningeal Carcinaomatosis (Leukemia, Lymphoma), Paraneoplastic disease (teratoma)
Metabolic	Amino acidopathies, Organic academia, Urea cycle defects, Mitochondrial disorders, Disorders of fatty acid oxidation, Lysosomal storage disorders
Endocrine	Thyroid disease (Hashimoto's encephalitis)
Vascular	Stroke, Reversible Cerebral Vasoconstriction Syndrome, Moyamoya, Fibromuscular dysplasia
Hematologic	Thromboembolic events, Sickle cell disease
Toxic	Recreational drugs (Cocaine), Heavy metals, Inhalants/solvents
Psychiatric	Schizophrenia, Bipolar, Major Depression

Differential



Van Mater H. Curr Opin Rheumatol 2014 Sep;26(5):553-61.

AE vs PANS/PANDAS

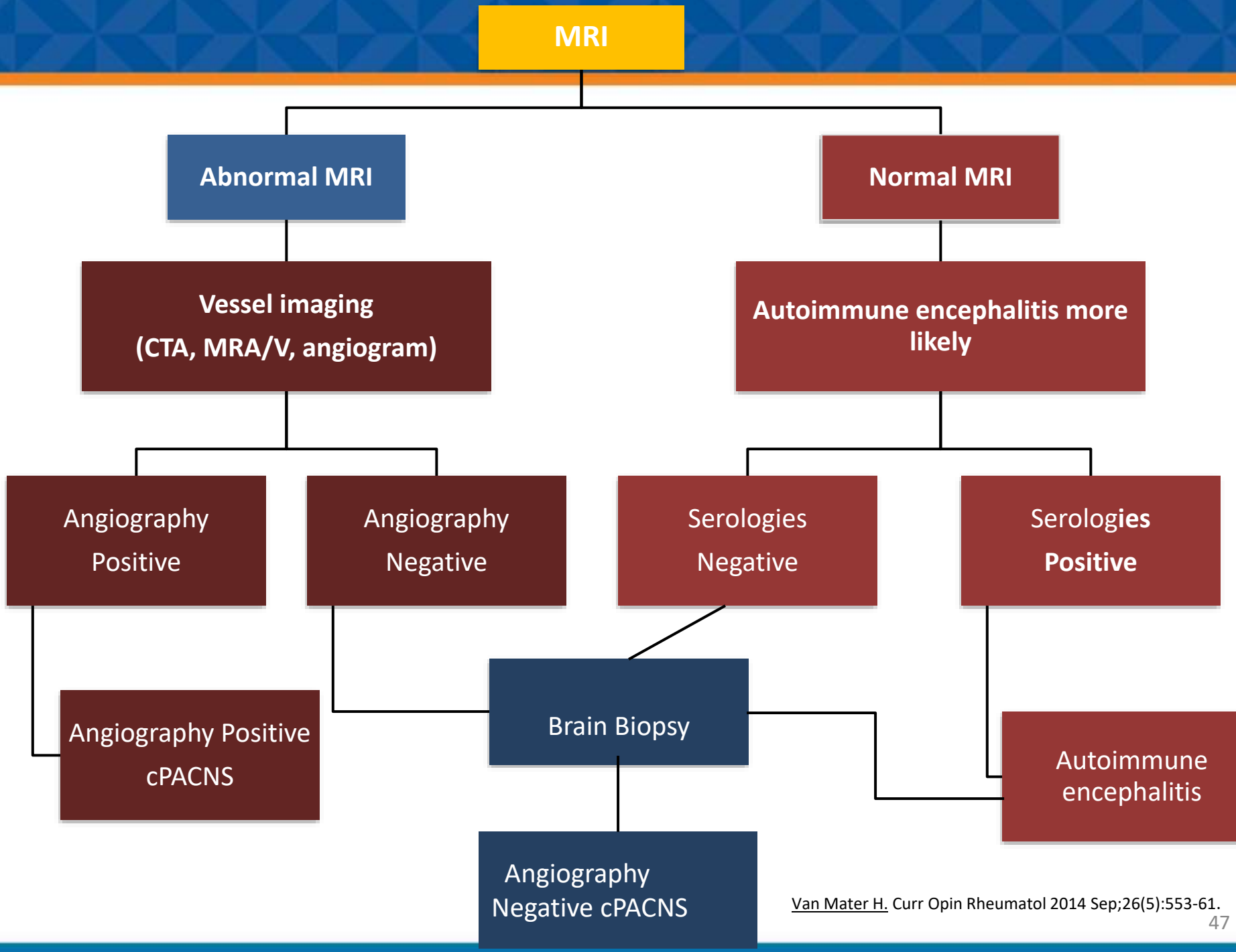
- Different diseases based on history, duration of symptoms, progression and treatment response
- If concern for AE, should have evaluation of MRI, LP and EEG with appropriate labs
- Current recommendations for evaluation for PANS/PANDAS focuses more on infectious disease triggers

Why the work up matters?

- The diagnosis matters to know what to target in the treatment
- Infectious trigger
  - Role of antibiotics?
  - Self-limited disease?
- Autoimmune disease
  - Treatment target?
    - Antibody mediated vs other components of immune system
  - Chronic/persistent disease
    - Duration of therapy?
  - Expected course/recovery period

Workup

- Imaging:
  - MRI with and without contrast
    - CT insensitive (only abnormal in ~30%)
    - Consider MRA if severe HA, "stroke-like features"
    - Consider CT Angiogram or conventional angiogram if concern for vasculitis/stroke
- Procedures:
  - LP (opening pressure, cell counts, protein, Oligoclonal bands/IgG index, autoimmune encephalopathy panel, extra tube)
  - EEG- epileptiform activity, diffuse slowing, multifocal seizures



Van Mater H. Curr Opin Rheumatol 2014 Sep;26(5):553-61.

Workup: Labs

Standard labs:

CBC,
Comprehensive metabolic panel

Inflammatory markers:
ESR, CRP

Metabolic/Mitochondrial evaluation: Will vary based on clinical Scenario
Lactic Acid
varies based on clinical scenario

Genetic Evaluation:
Will vary based on clinical Scenario
Monogenetic diseases
-POLG, RANBP2
-With inflammatory component: CIAS1, ADA2, PRF1, MUNC 13-4

Drug/Tox screen

Autoimmune labs:
Will vary based on clinical Scenario

Autoimmune encephalopathy panel
"Lupus evaluation":
- ANA
- ENAB (Smith, Ro, La, RNP)
- Anti-double stranded DNA
- Anti-phospholipids
  - (Lupus anticoagulant, anti cardiolipin and anti B2 glycoprotein)
- Complement (C3, C4)

"Vasculitis":
- ANCA
- vonWillebrand Factor,
- ACE

Other:
- Thyroid Profile and antibodies
- Celiac panel

Summary of Workup

SERUM TESTS	CSF TESTS	IMAGING	ANCILLARY STUDIES
CBC with differential **CMP** **ANA** **Anti-thyroid ab panel** **Thyroid profile** ***Serum AE ab panel** **Anticardiolipin ab** **Anti- beta 2 glycoprotein** **Lupus anticoagulant** **ESR, CRP** **VonWillebrand factor Ag** **Anti Sm, Ro, La ab** **ACE level** **Anti-DNAse B** **ASO titer** **Mycoplasma IgG/IgM** **C3, C4** **Serum immunoglobulins** **Serum copper** **Creatine kinase**	Opening Pressure Cell count Glucose Protein Gram stain culture ACE level *CSF AE ab panel Oligoclonal bands/IgG index Infectious workup (VZV, HSV, HHV-6)	**MRI brain** **EEG routine** **Video EEG** **PET Scan** **MRAngiography**	Strep swab Throat culture Respiratory viral panel Mycoplasma swab 24 hr urine copper Neuropsych testing Testicular/ovarian US

Mooneyham GC, Gallentine, WB, Van Mater H. Evaluation and management of autoimmune encephalitis: A clinical overview for the practicing child psychiatrist.
Child and Adolescent Psychiatric Clinics of North America. Oct 20, 2017 childpsych.theclinics.com. DOI: http://dx.doi.org/10.1016/j.chc.2017.08.011

Boundaries of Autoimmune Encephalitis

- Can AE exist outside of current diagnostic criteria
- -itis vs opathy
- Are there key features that can help distinguish AE from primary psychiatric disease
- Is there ever a time when one would do a diagnostic trial of therapy

Clinical Phenotypes

- BRIEF SNAPSHOTS
- A retrospective chart review was performed, recording demographic information, time to diagnosis from symptom onset, and psychiatric, neurologic, rheumatologic symptoms present at the onset of illness.

Clinical Phenotypes

- 10 patients with NMDA + Ab
- 5 patients with GAD + Ab
- 5 patients with VGKC + Ab

Clinical Phenotypes

- 10 patients with NMDA + Ab
  - 90% had aphasia
- 5 patients with GAD + Ab
  - 40% had aphasia
- 5 patients with VGKC + Ab
  - 40% had aphasia

Clinical Phenotypes

- 10 patients with NMDA + Ab
  - 90% had aphasia
- 5 patients with GAD + Ab
  - 40% had aphasia
  - Anxiety more commonly seen
- 5 patients with VGKC + Ab
  - 40% had aphasia
  - ADHD more commonly seen

Clinical Phenotype

- The three groups did not differ significantly in the frequency of other psychiatric symptoms, including cognitive impairment, features of psychosis, depression, developmental regression, or OCD.

Clinical Phenotypes

- statistically significant difference in average time to diagnosis (p= <.001)
  - patients with NMDA: 0.86 months
  - patients with GAD65: 20.3 months
  - Patients with VGKC AE: 12.4 months

Clinical Phenotypes

- statistically significant difference in average time to diagnosis (p= <.001)
  - patients with NMDA: 0.86 months
  - patients with GAD65: 20.3 months
  - Patients with VGKC AE: 12.4 months

Full Panel Testing

- NMDA was the first antibody discovered
- There are many additional antibodies
- Importance of sending FULL panel
  - heterogeneity in clinical presentations
  - Not able to predict specific antibody reliably

Full Panel Testing

- ENC1 (Mayo AE panel) spinal fluid
- ENS1 (Mayo AE panel) serum

- ANN1C, ANN2C, ANN3C, AGN1C, PCA2C, PCTRC, AMPHC, CRMC, CRMP5, NMO/AQP4, AMPA-R, GABA-B-R, NMDA, LGI1, CASPR2, GAD-65, VGKC ect