

Treatment of Autoimmune Brain Disorders: A Medical Perspective

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DISCLOSURES

- Research funding from Duke University and the Autoimmune Encephalitis Alliance
- I do not intend to discuss any unapproved or investigative use of commercial products or devices. However, there may be discussion of off label medication usage.

OBJECTIVES

- To learn about treatments used to reduce underlying inflammation in AE
- To review treatments used to manage psychiatric symptoms, seizures and sleep disturbances
- To discuss how to provide collaborative and supportive care for patients with AE
- To provide an overview of the specialized clinic at Duke

Rational for Treatment Decisions: Goals of Treatment

- Decrease inflammation
- Control symptoms
- Maximize functionality
- Achieve remission
- Maintain remission



What are we treating?

- AE vs vasculitis vs other -
Importance of completing workup prior to starting immunotherapy
- Targets include both the underlying inflammatory/autoimmune process and symptomatic management
- Reversible vs Non-reversible
 - Active inflammatory process vs injury/sequelae

Once you treat with immunotherapy you can alter the results of workup

- Steroids:
 - MRI inflammatory changes can be altered within hours
 - Alter antibody levels and WBC (Increase neutrophils but reduces lymphocytes), inflammatory parameters
 - Seizures
- IVIG
 - Are antibodies present from the patient or IVIG (issue especially when low to medium titer antibody) Aseptic meningitis (CSF pleocytosis from IVIG reaction or inflammation pre-treatment)
- Pheresis
 - Removes antibodies

Key Questions

- When to start treatment?
- What treatment to start?
- When to escalate treatment?
- How long to treat?



When to start?

Once patient meets

Possible Autoimmune Encephalitis criteria

AND

the work up is complete!

When to start?

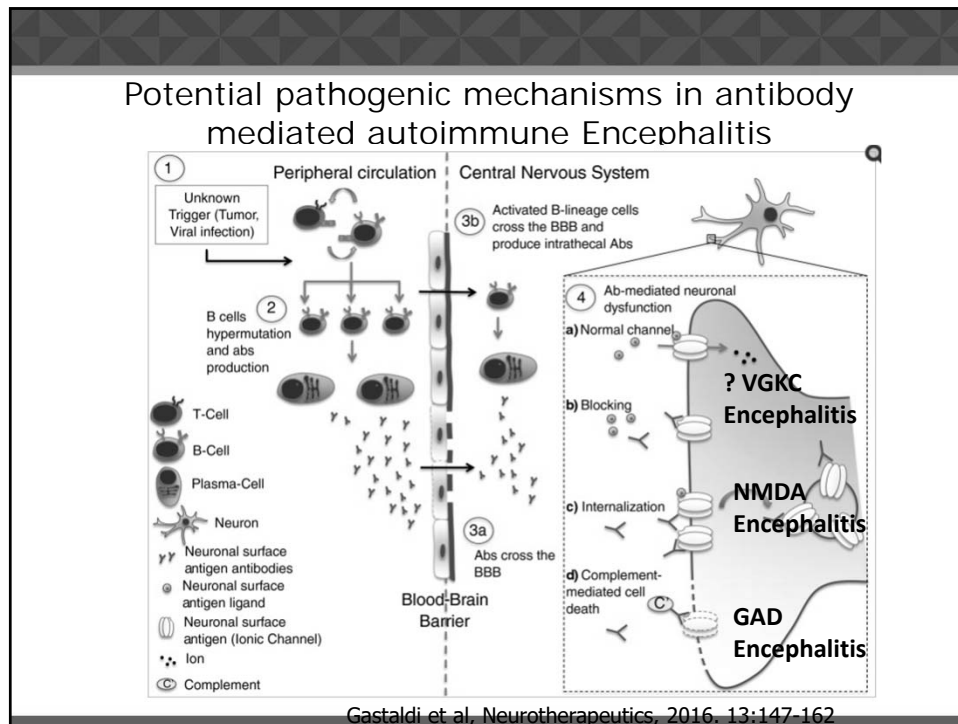
Diagnosis of possible autoimmune encephalitis can be made when all 3 of criteria met:

- Acute to 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 mm³)
 - 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

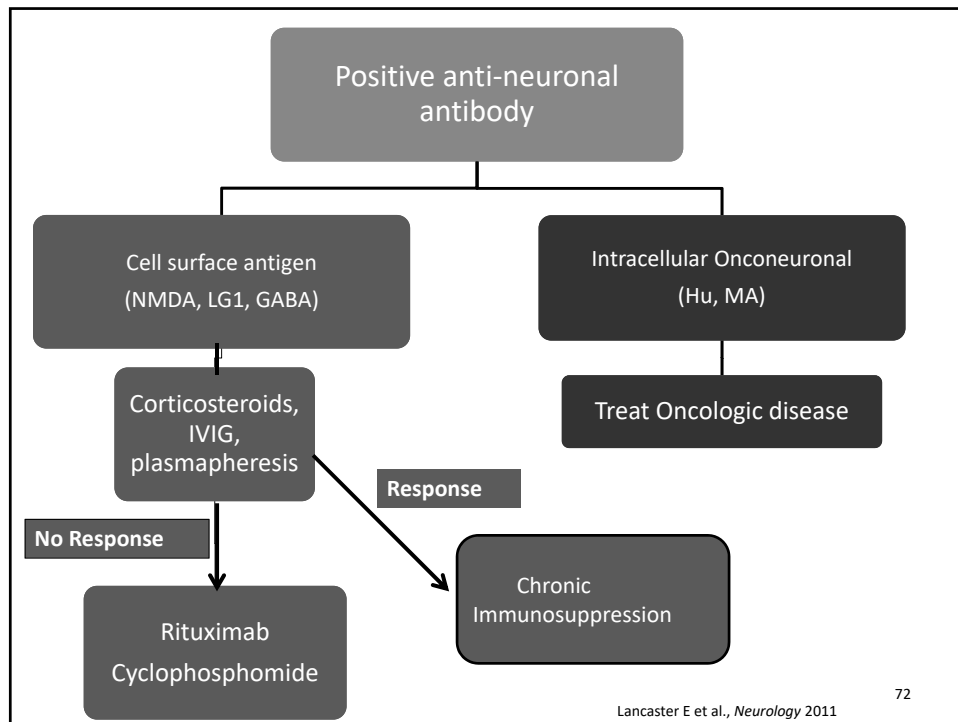
Immunotherapy Considerations

- Goal is to give the lowest risk medication for the shortest duration needed for maximum benefit/recovery
- Balance risk of disease vs risks and benefits of medications
- Certain disease types are more aggressive/likely to result in permanent injury or deficits
 - Those subtypes need more aggressive treatment at onset
- Antibody-mediated disease best understood (ex NMDA receptor encephalitis) but other parts of immune system also involved



Treatment:

- First line therapy
 - Corticosteroids
 - IVIG
 - Plasmapheresis/exchange
- Second line therapy
 - Rituximab
 - Cytoxan
 - ?Mycophenolate mofetil, Azathioprine?



First line therapy

- First-line
 - Steroids: 30mg/kg (up to 1000mg) daily for 3 to 5 days; continuing either intermittent IV dosing or change to oral steroids
 - IVIG: 2g/kg over 2 days; standard subsequent dosing 1gm/kg over 1 day once a month
 - Plasmapheresis: Q24h for 5 days, ideally before IVIG
- But...which one, when, combination????

No clear guideline

- Severity
 - ICU vs hospitalized vs outpatient
 - ?Antibody subtype (GAD vs NMDA vs Hashimoto's vs sero-negative)

Treatment Considerations

- Risk of treatment
 - Plasmapheresis higher risk
 - Adverse reactions range widely by study 10-55% of procedures.
 - Most frequent complications: hypotension, symptomatic hypocalcemia, allergic reactions, catheter-related adverse effects, and severe anaemia (Hb level <7 g/dL).
 - The excess of adverse reactions in children are mostly related to citrate toxicity, higher relative vascular volume shifts, and the need for vascular access
 - Prolonged sedation often needed due to agitation and risk of pulling central line

Treatment Considerations

- IV steroids and IVIG lower risk
 - Side effects from IVIG -aseptic meningitis, serum sickness, hemolytic anemia, behavior changes
 - Side effects steroids – disrupted sleep, agitation, transient hypertension, steroid psychosis

Treatment Considerations

- Expense
 - IVIG and plasmapheresis expense may be limiting due to insurance denial

Our practice

- Outpatient setting
 - Start with IV steroids (rarely use oral steroids)
 - Add IVIG if severe disease, positive anti-neuronal antibody, partial/incomplete response to steroids
 - Usually see improvement within days to few weeks with IVIG and steroids
- Inpatient setting
 - Often more severe presentation, faster escalation to adding IVIG
 - ICU setting, consider plasma exchange
- Certain antibodies more aggressive and second line agent started at diagnosis (GAD, NMO)

When to escalate to second line....

- Hospitalized/critically ill child
 - If declining or not improving in 10-14 days (most agreement for NMDA)
- Outpatient with clear diagnosis of AE
 - After 2-3 months of first line therapy if significant persistent symptoms; sooner if decline.

Tips prior to escalation:

- Be confident of your diagnosis
- Reassess if symptoms are sign of recovery or active disease (as best you can)
- Prepare yourself, your team and your patients for potential slow recovery

Second line

Rituximab (Antibody to CD20)

- Removes B cells and plasmablasts but not plasma cells (antibody factory)
- Does not work immediately- delayed onset of action, improvements usually 2-3 months later
- Need to continue bridging with IVIG, steroids and symptomatic therapy

Second Line

- Cyclophosphamide
 - Diffuse effects on immune system and cells in general
 - Kills dividing and non-dividing lymphocytes
 - Decrease antibody synthesis
 - Toxic (aka Cytoxan)- more limited use in pediatric AE
 - Delayed effects 1-2 months

Second Line

- Mycophenolate mofetil
 - Twice daily oral immunotherapy
 - Reduces proliferation of B and T cells, migration of inflammatory cells, macrophage mediated inflammatory damage
- Azathioprine
 - Once daily oral immunotherapy
 - Inhibits cell division (lymphocyte specificity)
 - Block T cell co-stimulation

Maintenance

- Rituximab
 - Standard dosing q 6 months.
 - Follow B cell repopulation and response to determine ultimate dosing frequency if responsive
- Mycophenolate mofetil
- Azathioprine

Keys of Treatment

- Complete your work up first!
- Immunotherapy takes time to work- weeks to months with continued recovery for 18-24 months....
- **Need to treat both inflammation and symptoms**
- **Goal is to maximize functionality- symptomatic treatment also essential**

Response to treatment?

- Risk benefit analysis of a TIME LIMITED trial of immunomodulatory intervention AFTER appropriate workup
- Response to treatment is NOT a formal diagnostic criteria but can inform case conceptualization

Response to treatment?

- Need to be thoughtful prior to starting therapy
 - What symptoms are we targeting
 - How will we measure response
 - If no response, what next

- Trends over time...

Timing is everything...

- Patient response to symptomatic control medications BEFORE immunomodulatory interventions can be **MARKEDLY DIFFERENT** than patient response AFTER immunomodulatory interventions

Trends over time

- Symptom tracking can help to elucidate change
 - Serial MOCA exams
 - Serial Folstein MMSE
 - Behavioral/mood diaries
 - School behavioral review

Timing is everything...

- Timeline of symptom “control” vs “relapse”
- Post IVIG?
 - Lasts up to 120 days
- Post IV steroids?
 - “self tapering”
- Post Rituximab?
 - 2-4 months to “sweet spot” for B cell depletion
- Plasmapheresis?
 - Quick improvements but quick declines

Timing is everything...

Who is on your treatment team?	Neurology/Rheumatology/Immunology Primary care?
What is your current immunomodulatory regimen?	-IV steroids, oral steroids, B cell modulatory agents, T cell modulatory agents, plasmapheresis, IVIG?
When was your last infusion or treatment?	-ask for specific dates and keep a log in clinic notes for follow up pattern analysis
When is your next scheduled treatment?	-clarify timeline of symptoms pre and post treatment if making any medication changes

Mooneyham, Gallentine, Van Mater. **Evaluation and Management of Autoimmune Encephalitis.** *Child Adolesc Psychiatric Clin N Am* (2017) childpsych.theclinics.com
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Trends over time

- Close monitoring of pre/post immunomodulatory interventions
- Measureable interval changes
 - Subjective
 - Concepts from global assessment of function or similar (multiple domains)
 - Objective
 - Cognitive testing

Role of Neuropsychiatric Testing

- Useful tool to document neurocognitive decline
- Differences between primary psychiatric disease and AE
 - AE
 - profound impairment across domains
 - Marked decline in IQ (30-50 points)
 - Primary psychiatric disease
 - Variable impairments across domains
 - May refuse to participate
 - IQ drop in schizophrenia ~10 points

- Symptomatic Control

Adjunctive therapy

- Psychiatry
 - Treatment of catatonia
 - Treatment of hallucinations, agitation, & paranoia
 - Treatment of circadian dysfunction
 - Treatment of depression
- Neurology
 - Treatment of seizures
 - Treatment of movement disorders
- Rehab services
 - PT, OT, ST, educational therapy

Refractory symptoms

- Immunomodulatory intervention is key to underlying process
- AND
- Symptomatic control is often still necessary

Refractory symptoms

- Symptom control
 - Sleep: Seroquel, Trazodone, Remeron
 - Steroid induced psychosis: Zyprexa, Risperdal (brief 3-5 days post IV steroids)
 - Seizures/mania: Depakote
 - Secondary mood disorder: Lithium
 - Cognitive dulling: stimulants
 - Impulsivity: alpha agonists
 - OCD features: Clomipramine

Refractory symptoms

Consider avoiding mixed dopamine agonist/antagonist

Consider avoiding NMDA receptor modulating medications

Refractory symptoms

- in acute phase of AE less responsive to psychiatric and neurologic medications
 - may require higher doses
 - may require combination of medications
 - as underlying inflammation controlled, ability to taper (sometimes very rapid de-escalation needed)

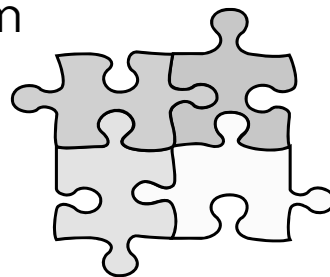
Challenges with “Psych Meds”

- Previous negative experiences with psychiatric providers and treatment
- Psychiatric treatments resisted due to the presumed “medical” etiology of the symptoms
- Family with low sense of self-efficacy in terms of their ability to cope with symptoms and treat them with behavioral approaches

- A Collaborative Approach...

Pediatric Autoimmune Brain Disease Program

- Multi-disciplinary clinic
 - Neurology
 - Rheumatology
 - Psychiatry
- We all see the patient at the same time- get one history, do our exams and then make a plan for workup and treatment together
- Present plan to patient/family all together



Benefits of a team approach

- Team determination of diagnosis and development of treatment roadmap
- Plays to the strengths of different specialties
- Keeps focus on functionality
- Reduced admission rates and length of stay
- Improved family satisfaction
- Improved physician satisfaction.

Challenges

- Diagnosing AE given breadth of differential diagnosis
- Too medically sick for psychiatric facility, to psychiatrically sick for a medical facility
- Resistant nature of seizures and psychiatric symptoms to standard treatment
- Multi-disciplinary aspects of day to day management
- Need for sustained therapy in many cases
- Slow recovery

Many Questions, less clear Answers

- Could this be an inflammatory brain disease/AE?
- What work up should you do?
- Were diagnostic criteria met? If not, what's my level of suspicion for an autoimmune process?
- When do you treat and with what?
- When should I expect to see improvements from treatment?
- How do we maximize function while waiting for immunotherapy to work?

Conclusion:

- Clinical course is the key feature with supporting diagnostics
- Response to immunotherapy is variable, if not improving indication to escalate therapy
- Recovery is slow usually over months to years- symptomatic management is essential
- Multidisciplinary team enhances care
 - initiation and escalation of treatments
 - maximizing symptomatic management
 - reducing admission rates, hospital length of stay
 - Improve family satisfaction

Acknowledgements

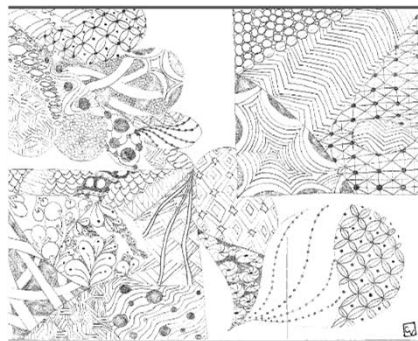
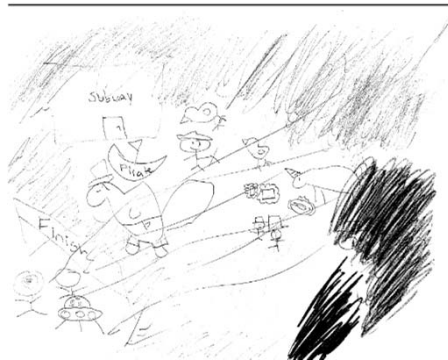
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Questions?

Pretreatment



10 days post IVIG and Steroids