Treatment of Autoimmune Brain Disorders: A Medical Perspective

Heather Van Mater, MD, MS
Pediatric Rheumatology
Duke Children's Hospital
Director, Duke Autoimmune Brain Disorders Program
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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) Aspectic 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?

http://www.ite.org/meetings/2009TransOps/TO-ITE-508/TO13/TO13.html

When to start?

Once patient meets

Possible Autoimmune Encephalitis criteria

AND

the work up is complete!

When to start?

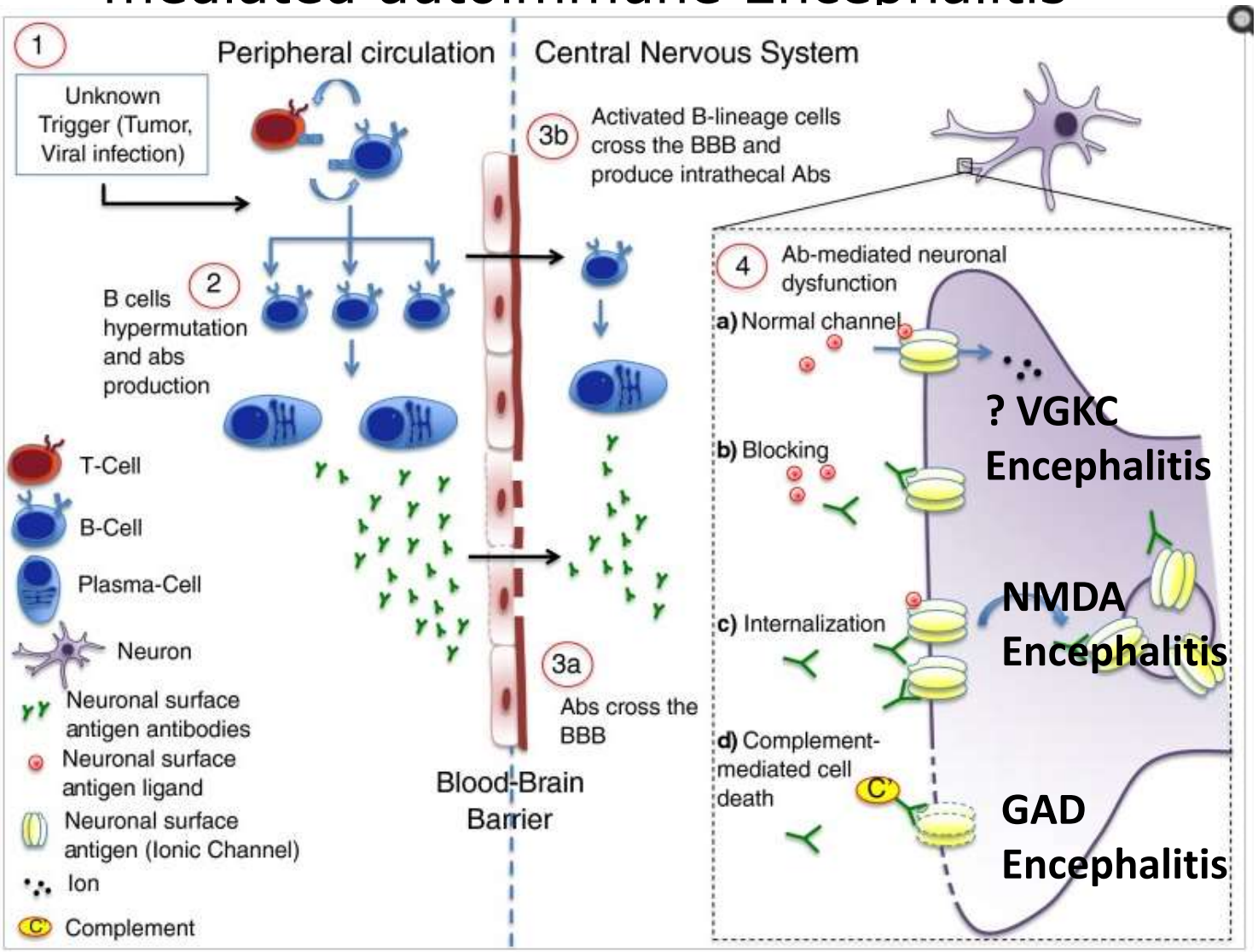
Diagnosis of possible autoimmune encephalitis can be made when all 3 of criteria met:

- 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 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

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

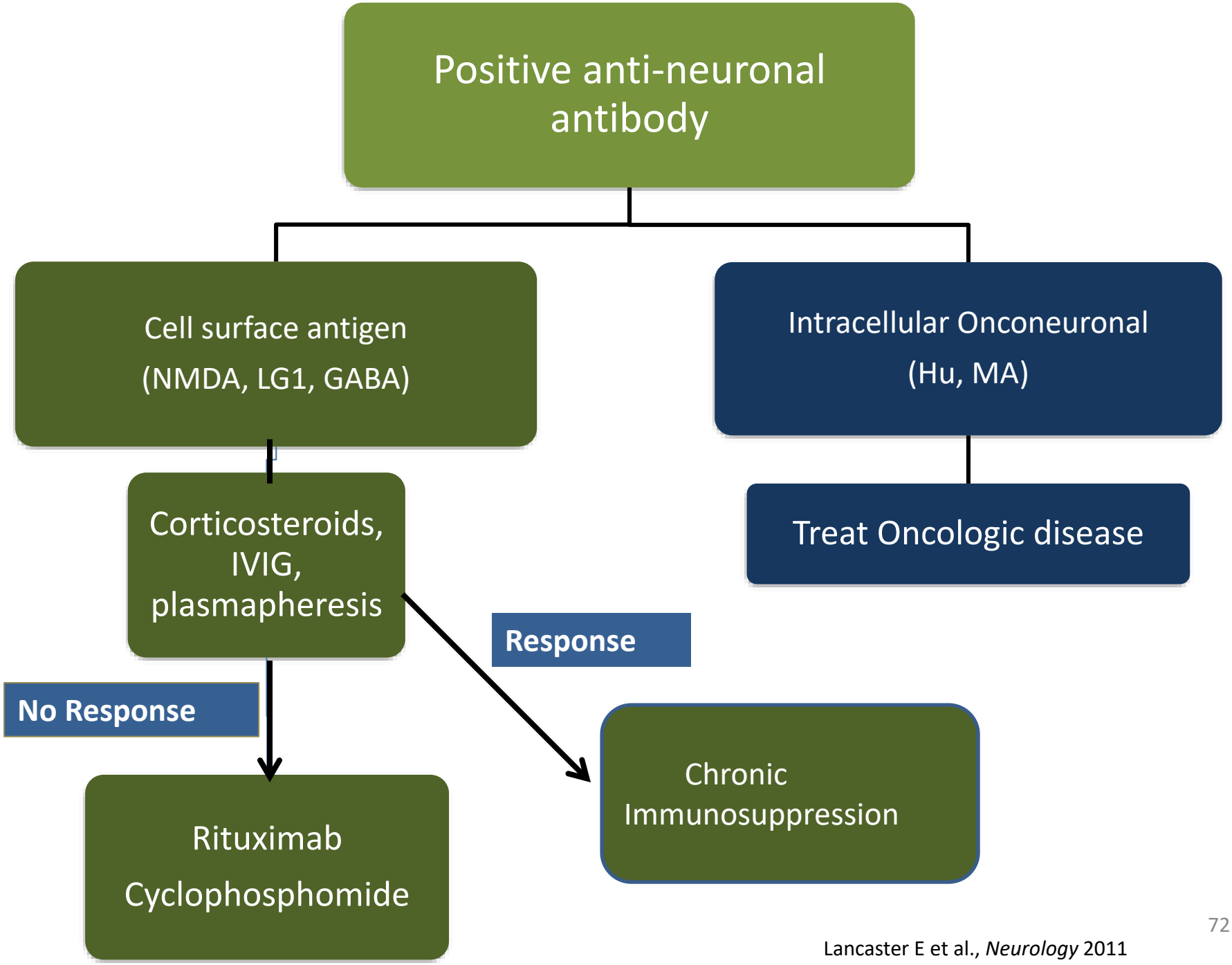
Potential pathogenic mechanisms in antibody mediated autoimmune Encephalitis



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

Treatment:

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



Lancaster E et al., *Neurology* 2011

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 (lymphoctye specificity)
  - Block T cell co-stimulation

J Clin Invest.2003 Apr 15; 111(8): 1122–1124.

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 Article in Press.** Published Online 10/20/17

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

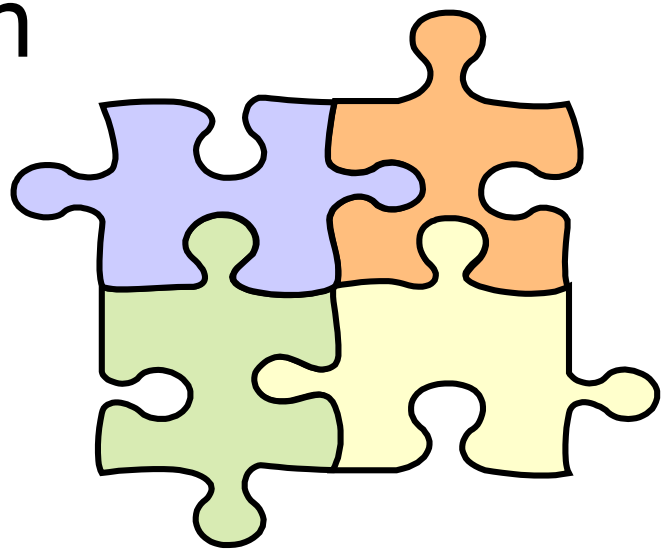
- in acute phase of AE less responsive to psychiatric and neurologic medications
  - may require higher doses
  - may require combination of medications
  - as underlying inflammation controlled, ability to taper (sometimes very rapid de-escalation needed)

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

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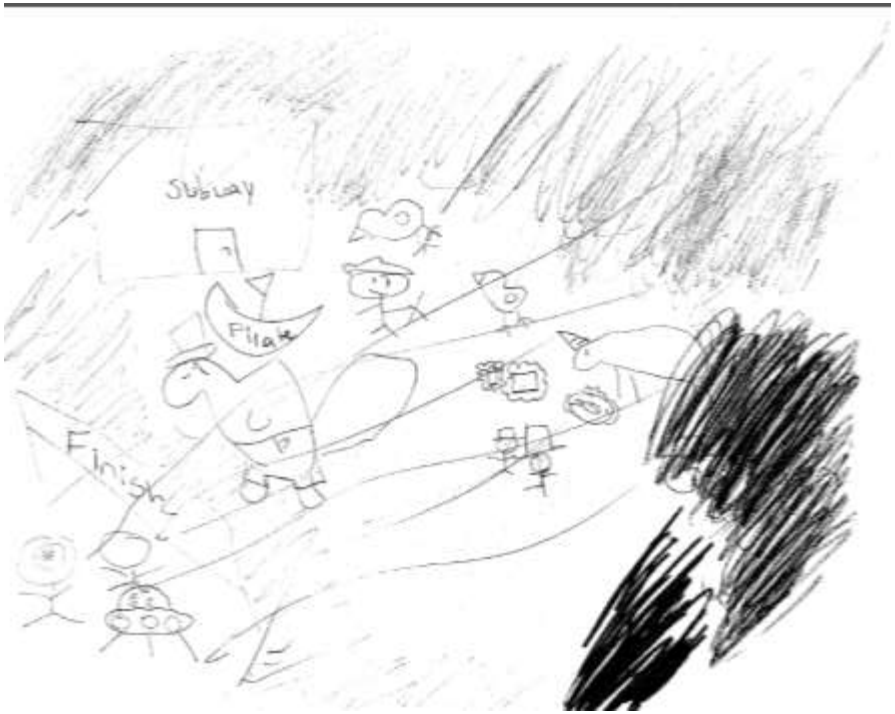
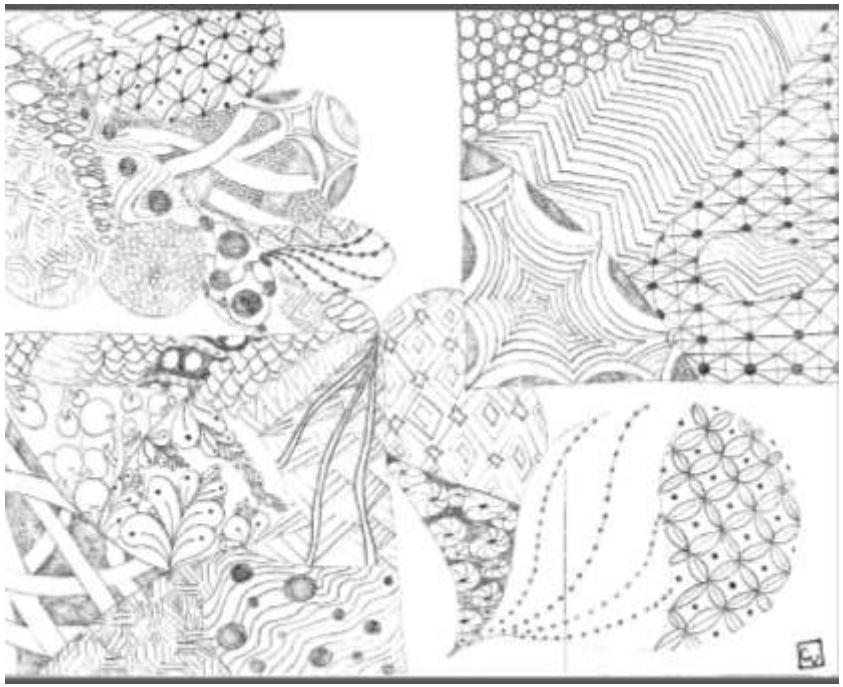
Questions?

Pretreatment





10 days post IVIG and Steroids