# Clinical Conundrums

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Duke Children's

# Goals

- Update knowledge pertaining to two general pediatric topics
- Understand recent changes in diagnostic testing

# Objectives

- Examine the presentations and diagnostic evaluations of two patients
- Discuss diagnostic and treatment challenges of each condition

# Case 1

- 12 month old FT biracial female with poor weight gain and DD presents to PCP for 12 month WCC
- Mother concerned about stools: still having 5-6/day, appear “cottage cheese-like”
- Dietary hx reveals mostly milk and juice consumption, wide variety of solid foods, no avoidance of certain foods
- No recent travel, city water source, no pets

# Case 1

- Pt has life-long hx of FTT, tracking <3rd % for weight, 25th% for ht/HC
- Mild global DD
  - Currently no words, not yet pulling to stand
- Multiple sick visits for AOM, CAP, bronchiolitis

# Case 1

- SHx
  - + maternal GC/Ch infection and smoking during pregnancy
  - Lives with married parents, 2 sibs
  - + tobacco smoke exposure
  - No pets
- FHx 3 yo sib with RAD

# Case 1

- PE: Add growth chart
  - AF, vitals WNL
  - Petite, thin extremities, pleasant
  - Dev: no words but + vocalizations, sits independently, primitive pincer, engages with examiner

# Case 1

- Abdomen without HSM, no T/R/G
- Neuro intact, non-focal, normal tone/strength
- Remainder of exam unremarkable

Case 1
Next Steps?

- Audience response

# Case 1

- Screening labs
  - CBC WBC normal, Hb 11.2, MCV 70
  - AST 465, ALT 653, APhos 246, TB nl
  - TFTs normal
- HIV, RPR, Hepatitis panel negative
- Abdominal US normal
- Endocrinology referral

# Case 1

- At 20 months, admitted for ongoing symptoms and social complexity
- Wt now at 2nd%, Length 3rd%, HC 25th%
- PE notable for thin extremities, gross motor/speech delay
- Feeding evaluation showed appropriate oral skills and caloric intake of 120 kcal/kg/day with no emesis
- 5-7 large BMs/day, “greasy” per RN staff

# Case 1

- BMP normal
- WBC 8.4, Hb 10.6, Hct 32, Plus 244, MCV 66
- AST 206, ALT 263, APhos 216, GGT 12, TB <0.1
- Alb 3.9, coag panel normal
- TFTs normal
- CRP 0.5

# Case 1

- GI consult obtained:
  - Total bile acids 7.4
  - Spot fecal fat 3g (24%)
  - Fecal elastase <50
  - ANA + 1:40 speckled
  - Anti-smooth muscle and anti-LKM Abs negative
  - Total IgG 2100, IgM 196, IgA 185
  - Tissue trans-glutaminase 12
  - $\alpha$-1 anti-trypsin 171
  - Ceruloplasmin 31
  - Plasma amino acids, urine organic acids normal
  - Giardia, crytosporidia negative

# Case 1

- Audience response: Ddx

# Case 1

- Ddx
  - Cystic fibrosis
  - Antibody-negative autoimmune hepatitis
  - Defect in bile acid synthesis
  - Metabolic disorder
- Ruled out: celiac, Wilsons, $\alpha$-1AT

# Case 1

- Sweat chloride normal
- Panc enzyme supplementation initiated, pt began to gain weight and have formed stools
- Subsequent CBCs showing neutropenia, leading to suspicion for Schwachman-Diamond syndrome

# Malabsorption

- Typically characterized by malodorous greasy stools, poor weight gain/growth, chronic diarrhea, abd pain/distention, anemia
- >10 g/kg/d stool volume in infants/toddlers, >200 g/d in older children
- >3 loose or watery BMs/day
- Not all have chronic diarrhea!

# Malabsorption

- Severe:
  - Vit A def: hyperkeratosis, night blindness
  - Vit B12/folate def: neuropathy, megaloblasts
  - Vit D def: osteomalacia, rickets
  - Vit E def: ataxia, ocular palsy, hemolytic anemia
  - Vit K def: bruising, bleeding, petechiae
  - Protein loss: edema, decreased muscle mass, infection

# Malabsorption: Etiologies

| | Congenital | Acquired |
|---|---|---|
| Carb | • CF/SDS (↓ amylase)<br>• Gluc-Glact txp def<br>• Sucrase-isomaltase<br>• Microvillus inc dz<br>• Lactase def | • Mucosal BB damage |
| Protein | • CF/SDS (↓ protease)<br>• Enterokinase | • Nonspecific |
| Lipid | • CF/SDS (↓ lipase)<br>• Primary bile acid malabsorption<br>• Prim intest lymphangectasia | • Secondary to liver/GB/pancreatic dz<br>• Secondary intest lymphangectasia |

# Malabsorption: Screening

- Blood
  - CBC: leukocytosis, neutropenia, anemia, thrombocytosis
  - CMP, LFTs
  - ESR
  - TTG and total IgA

- Stool
  - WBC, occult blood, calprotectin: inflammation
  - O&P, Giardia antigen, C diff antigen
  - Elastase: pancreatic insufficiency
  - Stool pH, reducing subs: carb malabsorption
  - $\alpha$-1AT: protein loss

# Malabsorption: Stool Studies

- Spot Fecal Fat
- Calprotectin
- Elastase

# SDS

- Autosomal recessive disorder caused by mutations in the SBDS gene
- Triad
  - Exocrine pancreatic dysfunction
  - Bony metaphyseal dysostosis
  - Degrees of BM dysfunction (neutropenia)
- Up to 1/3 with MDS or AML
- Multifactorial immune dysfunction

# Case 2

# Case 2

- 8 yo  with PMH ADHD presenting with spell of altered mental status witnessed by mother at home
- 2 hours after unwitnessed fall onto linoleum floor, mother found him lying supine on the floor with legs in the air, crying and agitated
- Mother also noted that his body felt limp
- ROS + one episode NBNB emesis; - fever, URI, diarrhea, known ingestions/exposures

# Case 2: History

- PMH and PSH otherwise negative
- No medications, allergies
- SH 2nd grade, doing well, many close friends, □ □, denies drug exposure, married parents, father active military, mother student
- FH unremarkable

# Case 2: PE

- Vitals AF, HR 125, otherwise normal
- Growth parameters 25th %
- Gen alert, mildly anxious, conversive and appropriate
- Neuro notable for mild amnesia to event, mild anxiety, slightly increased tone in UE bilaterally (? cooperation/anxiety) but otherwise entirely intact
- Remainder normal with no signs of trauma

# Case 2: Additional Information?

- Word cloud

# Case 2: Labs/Studies

- Head CT normal
- CBC normal
- CMP normal
- Urine drug screen negative
- Serum drug screen negative

# Case 2: Continuation

- One week later, patient represented to ED with maternal concerns for intermittent agitation and arm stiffening
- New concern for hallucinations and periodic unresponsiveness
- PE now remarkable for agitation/combativeness, no verbalization, bilateral UE hypertonicity

# Case 2: Labs/studies

- CBC, CMP again unremarkable
- Rapid RSV, influenza negative
- EKG NSR with questionable LVH

# Case 2: Progression

- While in ED, patient noted to have GT/C seizure for which he was given IV lorazepam
- Transferred to Duke

# Differential Dx?

- Word cloud ddx

# Case 2: Further Evaluation

- Very broad diagnostic evaluation ensued, most of which was uninformative
- CSF autoimmune encephalopathy panel returned positive for anti-N-methyl-D-aspartate receptor and glutamic acid decarboxylase antibodies

# Autoimmune Encephalitis

- Relatively new group of diseases characterized by acute onset neurologic and psychiatric symptoms
- Mediated by auto-antibodies that irreversibly bind to neuronal cell surface/synaptic proteins
- Best characterized is anti-NMDA receptor group

# AE Features

| Neurologic | Psychiatric |
| --- | --- |
| • Prodrome (HA, fever, viral)<br>• Memory deficit<br>• Abnormal Behavior/Cognition<br>• Speech Disorder<br>• Dyskinesias<br>• Autonomic dysfunction<br>• Seizures<br>• Central hypoventilation<br>• Cerebellar ataxia/hemiparesis | • Anxiety<br>• Agitation<br>• Bizarre behaviors<br>• Hallucinations<br>• Delusions<br>• Disorganized thinking |

# AE Diagnosis: Exclusion

| | |
|---|---|
| **Infectious** | EBV, VZV, HHV-6, CMV, HIV, HSV, entero, arbo, Bartonella, other bacterial, Lyme/spirochetes, fungal, TB |
| **Toxic-Metabolic** | Drugs, CO, IEM/mitochondrial |
| **Demyelinating/inflammatory** | MS, NMO, ADEM, neurosarcoidosis |
| **Rheumatologic/Vascular** | Lupus cerebritis, Hashiomotos, Sjogrens, Bechets, CNS vasculitis |
| **Psychiatric** | Schizophrenia, Psychosis, Bipolar, Conversion |

# AE Diagnosis

**Diagnostic criteria for anti-NMDA receptor encephalitis**

**Probable anti-NMDA receptor encephalitis***

All three criteria must be met:

1. Rapid onset (<3 months) of at least four of the six following major groups of symptoms: ¶
   - Abnormal (psychiatric) behavior or cognitive dysfunction
   - Speech dysfunction
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation
2. At least one of the following laboratory results:
   - Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands
3. Reasonable exclusion of other disorders

**Definite anti-NMDA receptor encephalitis***

1. IgG anti-GluN1 antibodies[Δ] in the presence of one or more of the six major groups of symptoms, after reasonable exclusion of other disorders

*Reproduced from: Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15:391.*

# AE Diagnosis: Additional Studies

- Brain MRI
  - signal hyperintensities on FLAIR or T2-weighted images in affected brain regions (eg, medial temporal lobes and/or brainstem); subcortical regions and the cerebellum are sometimes affected
- EEG
  - “extreme delta brush” characteristic for anti-NMDAR
- Chest/abd/gonadal imaging to eval for tumor

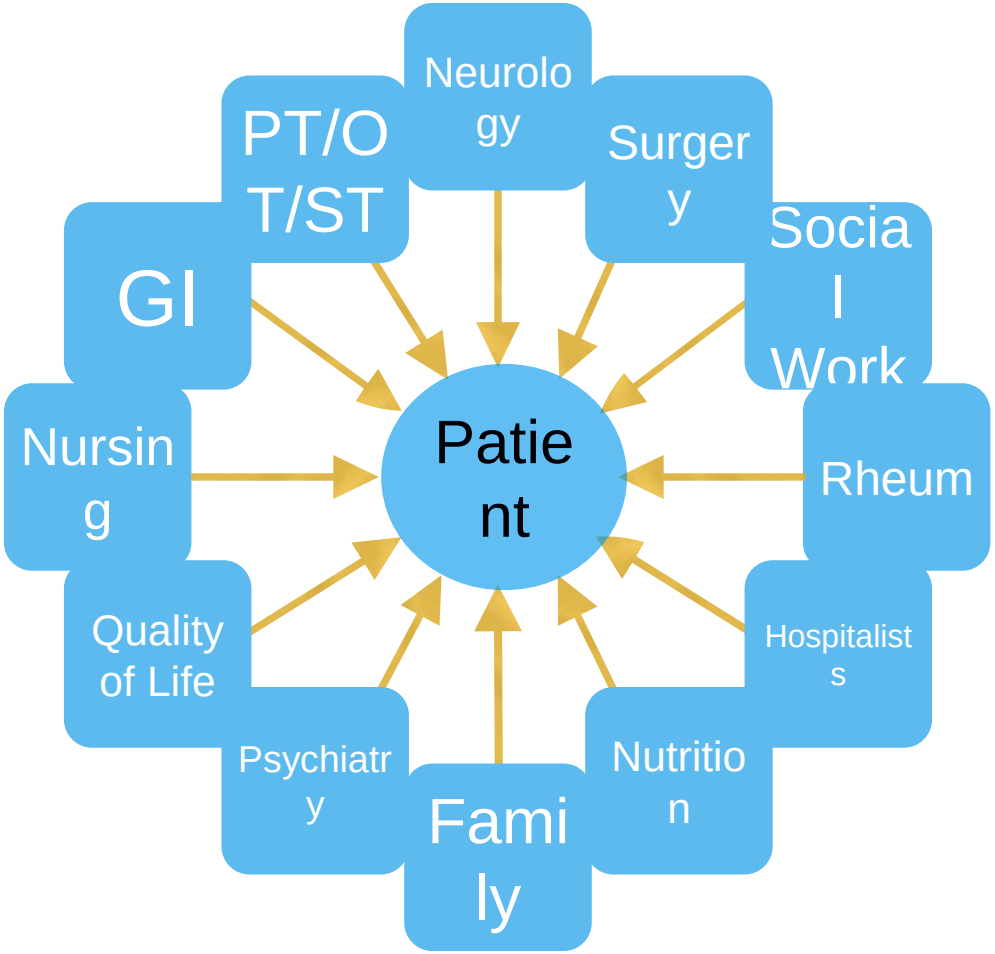
# AE: Treatment

- Immune suppression and antibody clearance
  - High-dose corticosteroids
  - IVIG
  - Immunomodulators
  - Plasmaphoresis
- 85% make full recovery, 15% relapse

# AE: Complications

- Agitated catatonia
  - benzodiazepines
- Delerium/hallucinations
  - avoid antipsychotics!
- Dyskinesia
  - trihexyphenidyl
- Seizures
  - depakote, lacosamine
- Insomnia
  - clonidine, trazodone, temazepam, melatonin, hydroxyzine
- Dysautonomia
- Orofacial dyskinesia
- Weight loss
- Vomiting
- Constipation
- Transaminitis
- Urinary retention
- Deconditioning

# AE: Multidisciplinary Treatment



# Case 2: Resolution

- Ultimately hospitalized for 78 days
- Treated with 5 day burst high-dose IV corticosteroids and IVIG
  - Repeated corticosteroid dosing q1-2 wks
  - Repeated IVIG x 3
- Rituximab given HD#7
- Slow, gradual improvement

# References


- Ammoury RF and Croffie JM. Malabsorptive Disorders of Childhood. *Pediatrics in Review* 2010;31;407
- Online Mendelian Inheritance in Man. https://www.omim.org/entry/260400, accessed 6/1/18