Altered States of Consciousness: Enzymes Gone Awry

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A toddler with trouble sitting up

Leslie

- 13 month old girl was well until 3 d prior to presentation when she developed URI symptoms, fever to 101°F and intermittent difficulty with standing and sitting up. Parents also reported that she had been “dazed” and more sleepy than usual.

History

- Birth: 7# product of 37 wk gestation delivered by C/section for maternal hypertension
- Development: sits up unassisted, cruises. says 6 words, waves bye-bye, feeds self. However, recently has had periods when she cannot stand or sit at all. When the parents attempt to help her, she “flops” over.
- No hospitalizations, surgeries, or medicines
- Family hx: retardation in 2 paternal uncles

Physical examination

- General: awake but not alert at the beginning of the exam but was alert by the end. Otherwise normal except
- Neuro: initially unable to sit unassisted and with profound head lag. By end of exam, able to push herself to sitting position
  - CNs: decreased lateral gaze in the right eye
  - Hypotonia throughout
What were we thinking?
- Intermittent ataxia
  - Migraine, Epilepsy
  - TIA
  - Hartnup disease
  - Wilson’s disease
  - Hereditary paroxysmal ataxia
  - MSUD
  - Pyruvate dehydrogenase deficiency
- Altered mental status
  - DPT: dehydration, poisoning, trauma
  - OPV: occult trauma, postictal, VP shunt
  - HIB: hypoxia or hyperthermia, intussusception, brain masses
  - MMR: meningitis, metabolic, Reye’s

What causes them?
- Enzyme deficiencies
- Co-factor deficiencies
  - Result in problems with absorption, transport, metabolism, etc.
  - Most are autosomal recessive
  - Occasionally x-linked
  - Incidence 1 in 2500 newborns

Inborn errors of metabolism
- Amino acid disorders
- Organic acidoses
- Urea cycle disorders
- Carbohydrate metabolism disorders
- Mitochondrial disorders
- Mitochondrial fatty acid oxidation disorders
- Peroxisomal disorders
- Lysosomal storage disorders
- Purine and pyrimidine disorders
- Porphyrias
- Metal metabolism disorders

When should you worry?
- Newborn period
  - Acute neurological decline
    - Lethargy
    - Coma
    - Decreased feeding, FTT
    - Vomiting, diarrhea, dehydration
    - Seizures
  - Acidosis (especially if elevated anion gap)
  - Tachypnea
  - Hypo (or hyper) glycemia
  - Hyperammonemia
- Up to the seventh decade of life
  - “Recurrent syndromes”
    - Lethargy
    - Emesis; often with dehydration
    - Failure to thrive, poor feeding
    - Unusual odors
      - Sweat (MSUD), sweaty feet (isovaleric acidemia), musty (PKU, tyrosinemia)
    - Dystonia, choreoathetosis, myoclonus, hypotonia, unexplained seizures
    - Hepatosplenomegaly
    - MR or CP without a clear etiology
### General features of IEM
- **History**
  - Aversion to specific foods
  - Untoward reaction to childhood illnesses
  - Psychomotor retardation
  - Growth failure
  - Pertinent family history--consanguinity
- **Physical findings**
  - Rapid breathing
  - Exfoliative dermatitis
  - Abnormal hair
  - Abnormal eye exam
  - Seizures and/or coma often with hypotonia
  - Unusual odor
  - Hepatomegaly
  - Cataracts
  - Microcephaly

### IEM: ED presentation
- Review of 53 pediatric patients who presented to the ED and ultimately were diagnosed with IEM
  - 85% presented with neurological signs
  - 58% presented with GI complaints
  - 51% presented with both neuro and GI
- Calvo et al PEC, 2000

### What should you do?
- Think about inborn errors
- Obtain labs acutely
  - CBC d/p, urinalysis
  - Chemistries (lytes, abg, glucose, U/A, ammonia, lactate, LFTs, PT)
- Metabolic labs
  - Plasma, urine and CSF(?) amino acids
  - Urine organic acids, urine orotic acid
- Freeze urine and plasma for later analyses

### Leslie’s labs
- CT scan: bilateral symmetric changes of decreased signal intensity in the globus pallidus, and dorsal brain stem
- CSF: 3 WBCs gluc & prot nl
- Chem 7: normal
- Lactate 1.5mmol/l (normal 0.2-2.0 venous)
- Ammonia 59umol/l (normal 22- 48)
- Isoleucine 768 mmol/l (range 10-86)
- Leucine 2203mmol/l (range 30-142)
- Valine 1832mmol/l (range 50-242)
- Urine organic acids: elevated 2-hydroxyisovaleric acid

### Diagnosis
- Maple syrup urine disease: branched chain ketoaciduria
  - Incidence 1:185,000 births (1:176 in Mennonites in Pa.)
  - Caused by deficiency of branched chain alpha-ketoacid dehydrogenase (BCKD) complex, the second enzyme of the metabolic pathway of the 3 branch-chain aa (leucine, isoleucine, valine)
  - Characterized by psychomotor retardation, feeding problems, maple syrup odor to the urine

### Maple syrup urine disease
- Genetics: autosomal recessive with 5 distinct phenotypes
  - Classical: present within 48h of birth
  - Intermediate: present at any age
  - Intermittant: present with ketoacidosis during episodes of catabolic stress
  - Thiamine responsive
  - E3-deficient
Making the diagnosis of MSUD

- Plasma amino acids
  - Will have elevated branched chain amino acids
- Urine organic acids
  - Elevated branched chain ketoacids
- BCKD enzyme activity can be measured in lymphocytes or cultured fibroblasts—this is not necessary to make the diagnosis

MSUD treatment

- Prognosis poor if classic MSUD untreated
- Rapid recognition and treatment is essential
- Dietary therapy necessary to promote normal growth and development
- Prompt treatment of episodes of acute metabolic decompensation is necessary
- Normal outcome is possible although unusual

Too many rum smoothies?

Mary

- 3yo girl presented to OSH with 2d history of ataxia and slurred speech. Her parents initially attributed the behavior to her having been sipping "rum smoothies" but when it lasted more than 18 hours, they came in. Work-up included CT scan, LP and UDS. All results normal. Sent home. Presented again 5 days later with persistent symptoms.

Mary

- Medical history: received varicella vaccine 8 days prior to onset of symptoms.
- Dietary history: multiple formula changes, currently eats little protein (parents are vegetarians)
- PE: ataxic
- Laboratory: Ammonia=186
- Diagnosis: OTC deficiency

Genetic hyperammonemias

- Acidosis absent: Primary urea cycle disorders
- Acidosis present and/or ketosis: Organic academia, lactic academia or mitochondrial errors
  - Elevated anion gap acidosis
  - Excess urinary ketones
  - Secondary hyperammonemia
  - Secondary carnitine deficiency
  - Bone marrow suppression with neutropenia
Genetic hyperammonemias

- Inheritance:
  - X-linked—OTCD
    - Variable X-inactivation
    - No male to male transmission
    - 50% sons and 50% daughters are affected
  - Autosomal recessive—all conditions except for OTCD
    - Carrier parents
    - 25% recurrence

Genetic hyperammonemias

- Presentation
  - Classic presentation: CNS depression beginning at days to weeks of life
  - Late onset presentation: reflects residual enzyme function
    - Symptoms:
      - Vomiting, mental status changes, FTT, hypotonia, developmental delay, self-selected low protein diet
      - Decompensation may occur after significant metabolic stress

Treatment when IEM suspected

- Stop all oral intake
- Clear ammonia—
  - Dialysis required for AMS or very high ammonia
- Stimulate anabolism
  - Glucose, Insulin, Supportive care
- Correct hypoglycemia, acidosis
- Mechanical ventilation to prevent hypoxia, and unnecessary metabolic expenditure
- Consult genetics service

A teenager on a camping trip

Ginger

- 19yo previously healthy woman presented to an outlying hospital with altered mental status. She had been camping with friends when she became ill. No history of bites, stings or injuries. The friends admitted that she had multiple “shots” of tequila the evening prior to the onset of her symptoms

Ginger

- PE: 100 20 70/20 98.6
  - General: drowsy but oriented
  - Neuro: ataxic gait
  - Received a liter of NS. BP improved
  - CT scan (head) normal
  - Electrolytes: CO₂ 18 Anion gap 19
  - Uric acid=11.2
  - U/A neg. UPT neg
  - UDS-alcohol and marijuana
Ginger

- Admitted to inpatient unit at 5:30 AM
- Noted to be “restless” at 9:30 AM
- Found to be pulseless and apneic at 9:45 AM
- Could not be resuscitated

Wilhelm JEM, 2006

Ginger

- Post mortem exam
  - Fatty change in the liver
  - Plasma acylcarnitine profile showed marked increase in octanyl carnitine consistent with medium chain acyl-coenzyme A dehydrogenase (MCAD) deficiency

Of note: discussion with parents after the patient’s death revealed that the patient was hospitalized at 2 yr of life for “Reye’s syndrome”

MCAD deficiency

- Most common of the 10 inherited disorders of fatty acid metabolism
  - If undiagnosed, mortality rate of 25%
- Autosomal recessive transmission
- MCAD is necessary for mitochondrial beta-oxidation of fatty acids
  - Classic presentation: hypoketotic hypoglycemia

MCAD deficiency

- Classic presentations
  - SIDs/“near-miss SIDs”
  - Vomiting and lethargy after a period of fasting in a child 3-15 months of age
    - Few present after 4 years of life
  - Fasting, febrile illness, stressors, or alcohol consumption may trigger a Reye’s syndrome like illness

Deaths due to IEM

- When death appears imminent in a patient with suspected IEM,
  - Obtain and freeze urine and plasma for testing.
  - Consider obtaining skin specimen
    - Use sterile technique
    - Store at room temperature in tissue culture medium or NS
  - Alert pathologist to your clinical suspicion

A neonate with jaundice
Steven
7 do baby presented to pmd's office with 1-2 d history of vomiting and lethargy. On PE, he was noted to be jaundiced.
Sent to the ED where an evaluation for sepsis done and was transferred to a hospital equipped to handle ill neonates. He had a cardiopulmonary arrest shortly before arrival and could not be resuscitated.

Results of the newborn screen were available a week after the baby’s death and showed that the infant had galactosemia.
Parents sued the hospital where the baby was born for failure to diagnose the IEM
Jury found in favor of the defense
Selbst PEC 2006.

The newborn screen
- Vary by state
- http://genes-r-us.uthscsa.edu

Texas newborn screening
- CAH
- Hypothyroidism
- Galactosemia
- PKU
- Sickle cell disease
- Fatty acid disorders (5)
- Organic acid disorders (9)
- Amino acid disorders (6)

Carbohydrate disorders
- Deficiencies of enzymes in the metabolic pathways of
  - Galactose
  - Fructose
  - Glycogen
- Classic presentation: lethargy, hypoglycemia or encephalopathy during periods of decreased CHO intake or after prolonged fasting. May also have HSM

Galactosemia
- Three distinct enzyme deficiencies
  - Autosomal recessive
  - Galactose-1-phosphate uridytransferase (GALT) is the most common and only one picked up on newborn screen
- Presentation: V, D, jaundice, HSM, lethargy, hypotonia, cataracts
- Septicemia (E. Coli) is common in those with GALT
Carbohydrate disorders
- Laboratory findings
  - Nonglucose reducing substances in the urine
  - Metabolic acidosis

Elizabeth’s daughter
- Caroline is a 9 yo girl with FTT, microcephaly, developmental delay and seizures who was thought to have ataxic cerebral palsy.
- Evaluation at age 6 years revealed a central nervous system folate metabolism disorder. She was started on leukovorin (folinic acid) with improvement of symptoms.

Neurotransmitter disorders
- Group of neurometabolic conditions caused by abnormal neurotransmitter metabolism or transport
- Require high index of suspicion and specialized CSF analysis for diagnosis
- Favorable clinical response in patients identified and treated before age 6

IEM: bottom line
- Think about the possibility of IEM
  - Neonates with acute neurological decline, acidosis, abnormal glucose metabolism
  - Any one who presents with
    - Episodic symptoms,
    - FTT,
    - unusual odors,
    - dystonia, unexplained seizures, MR, or CP without clear etiology

IEM: bottom line
- Obtain appropriate labs on presentation
  - Lytes, abg, glucose, LFTs, NH₃, plasma AA, urine OA, acylcarnitine profile, lactate, pyruvate, U/A, CSF studies
- Consider hemodialysis if ammonia is very high
- In acute situations: stop protein, build anabolism, consult genetics