Neurological manifestations of FODs and Organic Acidemias: recognition, monitoring and management

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Goals

Discuss the major neurological features of FAOs and OAs
- Encephalopathy
- Seizures
- Changes in muscle tone
- Muscle disease
- Neuropathy
- Movement disorders
- Developmental delay/MR
Models of brain injury in inborn errors

- Global exposure, yet selective injury
- Substrate intoxication vs deficiency
- Selective location
  - White matter, gray matter, BG, cerebellum
- Organic acidopathies
  - Basal ganglia
  - White matter
Blood brain barrier
ER: Endoplasmic Reticulum
Golgi: Golgi body
AMD: Axonal Membrane Depolarization
Fatty Oxidation Disorders (FODs)

Genetic disorders in which the body cannot breakdown fatty acids to make energy

- Enzyme deficiency
- Inherited disorder
Fatty acid oxidation defects

Risk: cause recurrent disturbances of brain or muscle function

- The neurological symptoms of impaired brain function are due to:
  - Hypoglycemia (low glucose)
  - Hypoketonemia (low ketone bodies)
  - Effects of potentially toxic organic acids (breakdown products when enzymes are missing)

- Symptoms occur during fasting
Fatty acid oxidation defects

Symptoms
- Drowsiness
- Stupor (extreme sleepiness, not arousable easily, but not in coma)
- Coma occur during acute metabolic crises
- Seizures
- Long term neurological effects
  - Muscle tone
  - Cognition/thinking-developmental delay/MR
Organic acidurias

Result From:
- Missing mitochondrial enzymes that metabolize CoA activated carboxylic acids
  - come from amino acid breakdown

Neurological Symptoms
- Encephalopathy
  - Changes in level of consciousness
  - Seizures
- Episodic metabolic acidosis
  - caused by build up of toxic metabolites
  - Disturbance of mitochondrial energy production
  - Seizures, strokes, movement disorders
- Long term neurological effects
  - Muscle tone
  - Cognition/thinking-developmental delay/MR
Neurological complications

- **Fatty acid oxidation disorders**
  - Tone abnormalities
    - Hypotonia: low muscle tone
  - Seizures/coma
    - due to hypoglycemia
  - Developmental delay or mental retardation
  - Muscle disease
    - VLCAD
    - VLCHAD
    - LCHAD
  - Neuropathy
    - TFP deficiency
    - LCHAD

- **Organic acidemias**
  - Tone abnormalities
    - Hypotonia
    - Hypertonia
  - Seizures/strokes/coma
  - Developmental delay or mental retardation
  - Movement disorders: funny postures, writhing movements and jerking movements
  - Certain OAs
    - neuropathy
Short and Long term Neurological consequences of FAOs and OAs

- Hypotonia
  - Low muscle tone
  - Results in delayed
    - Gross motor (large muscles, used for ex. Walking)
    - Fine motor (hands, eye hand coordination)
    - Speech milestones (talking, understanding language)
  - Usually trunk muscles (muscles close to the body)
  - Improves with therapy
Short and Long term Neurological consequences of FAOs and OAs

- Hypertonia
  - High resting muscle tone (at rest, muscles are tight)
  - Muscles are contracted and stiff
  - Prevents movements
  - Using limb muscles
  - Stretching therapies
  - Medications
  - Surgeries
    - Tendon releases and transfers
Short and Long term Neurological consequences of FAOs and OAs

Movement disorders

- Fixed postures
- Interfere with purposeful movement
- Writhing or rapid movements
- May occur when performing purposeful movement
Short and Long term Neurological consequences of FAOs and OAs

- **Seizures**
  - Single event that may be provoked
    - Hypoglycemia
    - Hyperammonemia
  - Repetitive events
    - Focal
    - Generalized
Short and Long term Neurological consequences of FAOs and OAs

- Developmental delay/mental retardation
  - Variable degrees
  - Disorder affects brain
    - Hypoglycemia
    - Seizures
    - Repeated injury
Short and Long term Neurological consequences of FAOs

- Muscle weakness
  - At rest
  - After exercise
Hypotonia

- Medical term used to describe decreased muscle tone
  - the amount of resistance to movement in a muscle
- It is not the same as muscle weakness, although the two conditions can co-exist
- Not a specific medical disorder
- It can be a condition on its own or it can be associated with another problem where there is progressive loss of muscle tone
Hypotonia can be caused by a variety of conditions
- Central nervous system (brain and spinal cord)
- Muscle disorders
- Genetic disorders

It is usually first noticed during infancy
- Floppy infant
- Poor head control
- Weak suck and swallow
Hypotonia

Hypotonia (decreased muscle tone)
Clinical aspects of hypotonia

- Can involve only the trunk or trunk and extremities
- Delayed Motor skills (requires strength and movement against gravity)
- Hypermobile or hyperflexible joints
- Drooling and speech difficulties
Clinical manifestations of hypotonia

- Poor tendon reflexes
- Decreased strength
- Decreased activity tolerance
- Rounded shoulder posture and curved back when sitting
Infantile hypotonia

- Floppy, rag doll
- Difficulty with feeding
  - Mouth muscles cannot maintain a proper suck-swallow pattern or a good breastfeeding latch
- Hypotonic infants are late in
  - Lifting their heads while lying on their stomachs
  - Rolling over
  - Lifting themselves into a sitting position
  - Sitting without falling over
  - Balancing
  - Crawling
  - Walking independently
Hypotonia and motor delays

- Delayed developmental milestones
  - degree of delay can vary widely
- Motor skills are particularly susceptible to the low-tone disability
Hypotonia and motor delays

They can be divided into two areas

- gross motor skills
- fine motor skills
- Fine motor skills delays
  - grasping a toy
  - transferring a small object from hand to hand
  - pointing out objects
  - following movement with the eyes
  - self feeding
Speech delays and hypotonia

- **Speak later than their peers**
  - appear to understand a large vocabulary
  - can follow simple commands
- **Difficulties with muscles in the mouth and jaw**
  - poor pronunciation
  - discourage experimentation with word combinations and sentence-forming
- **Feeding difficulties**
  - Chewing
  - Textures
  - Mouth play
Hypotonia versus weakness

The low muscle tone associated with hypotonia is often confused with low muscle strength

- Muscle tone is the ability of the muscle to respond to a stretch
- The child with low tone has muscles that are slow to initiate a muscle contraction
  - contract very slowly in response to a stimulus
  - cannot maintain a contraction
- Muscles remain loose and very stretchy
Workup for hypotonia

- Computerized tomography (CT) scans
- Magnetic resonance imaging (MRI) scans
- Blood tests
  - CPK
- Electromyography (EMG)
- Muscle and nerve biopsy
Hypotonia

- Often evaluated by physical and occupational therapists
  - series of exercises designed to evaluate developmental progress
  - observation of physical interactions

Hypotonic child has difficulty knowing where the body is in space
  - develop recognizable coping mechanisms
    - locking the knees while attempting to walk
    - tendency to observe the physical activity of those around them for a long time before attempting to imitate
Different names for hypotonia

- Low Muscle Tone
- Benign Congenital Hypotonia
- Congenital Hypotonia
- Congenital Muscle Hypotonia
- Congenital Muscle Weakness
- Amyotonia Congenita
- Floppy Baby Syndrome
- Infantile Hypotonia
Management and treatment

No known treatment or cure for most (or perhaps all) causes of hypotonia

The outcome depends on the underlying disease

In some cases, muscle tone improves over time

Patient may learn or devise coping mechanisms that enable him to overcome the most disabling aspects of the disorder
Management of hypotonia

- If the underlying cause is known, treatment is tailored to the specific disease, followed by symptomatic and supportive therapy for the hypotonia.
- In very severe cases, treatment may be primarily supportive.
Management of hypotonia

- Physical therapy can improve fine motor control and overall body strength
- Occupational therapy to assist with fine motor skill development and hand control, and speech-language therapy can help breathing, speech, and swallowing difficulties
- Therapy for infants and young children may also include sensory stimulation programs
Management of hypotonia

- Ankle/foot orthoses are sometimes used for weak ankle muscles.
- Toddlers and children with speech difficulties may benefit greatly by using sign language or picture exchange.
Treatment

Once a diagnosis has been made
- underlying condition is treated first
- followed by symptomatic and supportive therapy for the hypotonia
Hypertonia

- Abnormal increase in the tightness of muscle tone
- Reduced ability of a muscle to stretch
  - increased stiffness
- Accompanied by spasticity
Causes of hypertonia

- Damage to upper motor neurons
  - Causes hypertonia
  - Spasticity (overactive reflexes)
  - Rigidity (constant muscle contractions)
Hypertonia

Other names for hypertonnia
- Cerebral palsy
- Hemiparesis
- Quadriparesis
- Hemiplegia
- Diplegia
Hypertonia
Damage of motor tracts in hypertonia
Hypertonia

Diagnostic tests

- CT or MRI scan of the brain
- EEG to measure electrical activity in the brain

may also be necessary
Management of hypertonia

- Physical therapy can encourage stretching and prevent contractures
- Occupational therapy to assist with fine motor skill development and hand control, and speech-language therapy can help breathing, speech, and swallowing difficulties
- Ankle/foot orthoses are used to prevent contractures at the heel cords
- Toddlers and children with speech difficulties may benefit greatly by using sign language or picture exchange
Use of orthotics

- **Prevent Deformity**
  - This is done by maintaining ROM (Range Of Motion), maintaining correct alignment, and limiting potentially damaging motions.

- **Improve function**
  - This is done by preventing deformity, providing stability

- **Facilitate Development**
  - This is done through an ongoing process of evaluation and working with Physicians, Therapists, and family to provide the best design for achieving rehab and developmental goals
AFOs for hypo/hypertonia

- UCBL
  - Custom made insert for controlling a hyper-mobile pes-planus or cavus
  - supports the arches of the foot and maintains the relative position of the hindfoot, midfoot, and forefoot
The D-DAFO for hypertonia

dynamic, total contact orthosis works well for spasticity

- maintains the correct alignment of the bones in the foot and ankle

  - a full length D-DAFO blocks plantar flexion and allows dorsi-flexion

  - low profile D-DAFO allows plantar flexion and dorsiflexion
Articulated AFOs

- Allow for flexion at the ankle and have an adjustable/removable plantar flexion stop
- can add dorsiflexion assist or check straps.
Spells, seizures, and epilepsy

A “spell” may be a seizure or may be something else
- Movement disorder
- GERD
- Sleep disorder

A single seizure is not yet epilepsy

The medical syndrome of recurrent, unprovoked seizures is called epilepsy
Things that go bump in the night:  
*Spells, seizures, and epilepsies*

A seizure

- Temporary abnormal electrophysiologic phenomenon of the brain
  - Results in abnormal synchronization of electrical neuronal activity

- Can appear as
  - Alteration in mental state/awareness
  - Tonic or clonic movements
  - Convulsions
  - Various other psychic symptoms (such as déjà vu or jamais vu)
Seizures

- Cause involuntary changes in
  - Body movement
  - Function
  - Sensation
  - Awareness
  - Behavior

- Can last from
  - Few seconds
  - Status epilepticus, a continuous seizure that will not stop without intervention

- Seizure is often associated with a sudden and involuntary contraction of a group of muscles
A seizure can also be as subtle as

- Marching numbness of a part of the body
- A brief loss of memory
- Sparkling or flashes
- Sensing an unpleasant odor
- A strange sensation in the stomach
- Sensation of fear
Seizures are typically classified as
- Motor
- Sensory
- Autonomic
- Emotional/cognitive
Seizures

- Symptoms depend on where in the brain the seizure activity occurs
  - Focal onset, stays focal or generalizes
  - Generalized at onset
  - Convulsive
  - nonconvulsive

- In children, seizures often happen in sleep or the transition from sleep to wake

- A person having a tonic-clonic seizure may cry out, lose consciousness and fall to the ground, and convulse, often violently
Seizures

- Complex partial seizure
  - Person may appear confused or dazed
  - not be able to respond to questions or direction

- Sometimes, the only clue that a person is having an absence seizure
  - Rapid blinking
  - Mouthing movements
  - Few seconds of staring into space
Hypoglycemia and seizures

- Hypoglycemia
  - Lower than normal level of glucose (sugar) in the blood

- Why is this important?
  - Brain metabolism depends primarily on glucose (sugar) for fuel in most circumstances
  - A limited amount of glucose can be made from glycogen stored in astrocytes, but it is used up within minutes
  - Brain is dependent on a continual supply of glucose diffusing from the blood into central nervous system and into the neurons themselves
Hypoglycemia

Caused by a continuing demand for glucose by brain and other organs

- Results from the primary biochemical defect of fatty-acid oxidation since fats cannot be broken down efficiently

Treatment

- Avoidance of catabolism (more break down)
  - Requires the use of fatty acids except in FAOs
  - L-Carnitine supplementation
  - Some patients may benefit from medium-chain triglyceride supplementation as a source of fat
Hypoglycemia and seizures

- If the amount of glucose supplied by the blood falls, the brain is one of the first organs affected.
- In most people, reduction of mental abilities occur when the glucose falls below 65 mg/dl (3.6 mM).
Hypoglycemia and seizures

- Impairment of action and judgement usually becomes obvious below 40 mg/dl (2.2 mM)

- Seizures may occur as the glucose falls further
  - As blood glucose levels fall below 10 mg/dl (0.55 mM), most neurons become electrically silent and nonfunctional, resulting in coma
Hypoglycemia and seizures

Brief or mild hypoglycemia produces no lasting effects on the brain
– Can temporarily alter brain responses to additional hypoglycemia

Prolonged, severe hypoglycemia can produce lasting damage of a wide range
– Impairment of cognitive function, motor control, or even consciousness
Hypoglycemia and seizures

The likelihood of permanent brain damage from any given instance of severe hypoglycemia is difficult to estimate. It depends on a many factors:

- Age
- Underlying disorder
- Recent blood and brain glucose concurrent
- Problems such as hypoxia
- Availability of alternative fuels
Hypoglycemia, symptoms

- Abnormal thinking, impaired judgment
- Anxiety, moodiness, depression, crying
- Irritability, combativeness
- Personality change, emotional lability

- Fatigue, weakness, apathy, lethargy, daydreaming, sleep
- Confusion, amnesia, dizziness, delirium
- Staring, "glassy" look, blurred vision, double vision
Hypoglycemia, symptoms

- Automatic behavior, also known as automatism
- Difficulty speaking, slurred speech
- Ataxia, incoordination, sometimes mistaken for "drunkenness"
- Focal or general motor deficit, paralysis, hemiparesis
- Paresthesia, headache
- Stupor, coma, abnormal breathing
- Generalized or focal seizures
Management of hypoglycemic seizures

- Failure to administer glucose would be harmful to the patient

- Recurrent seizures
  - Anti-epilepsy drugs
    - Give single drug at lowest concentration if possible
    - Careful with certain conditions
  - Drug treatment geared towards whether focal, generalized, etc.
    - Trileptal, Keppra, Zonergran, Lamictal, Depakote, Klonopin, Dilantin, Tegretol
Dystonia
- Abnormal fixed posture of an extremity (arms or legs, neck)
- Sustained muscle contraction
- Resulting in abnormal posture

Chorea
- Fast, dance like movements of the distal extremities (fingers and toes)

Athetosis
- Slow, writhing movements of the extremities
Movement disorders - Organic acidemias

- Patient may have combination of movement disorders at baseline or with special circumstances
  - Stress
  - Illness
  - Attempt at purposeful movement

- Anatomy
  - Damage to deep gray nuclei
    - Caudate, putamen, globus pallidus
    - Release of inhibition
The Basal Ganglia

The basal ganglia connect to the cortex and thalamus and organize muscle-driven “motor” movements of the body.
FAOs and Muscle disease

- SCAD
- VLCAD
- LCHAD

Symptoms
- Weakness
- Pain/cramps
- Exercise intolerance
- Red urine
- Muscle breakdown
- Rhabdomyolysis
Rhabdomyolysis

- Elevations of CPK
  - Muscle enzyme
  - Leaks out of the muscle when the muscle membrane is damaged
FAOs with muscle disease

- SCAD
  - Hypotonia
  - metabolic acidosis
  - NBS:
    - elevated C4
    - UOA have elevated ethylmalonic acid
  - Common mild variants of ? Significance
FAQs with muscle disease

LCHAD
- Cardiomyopathy
- hypotonia,
- rhabdomyolysis
- moms have HELLP syndrome
- NBS

Acylcarnitine profile with elevated C14-OH, C16-OH, C18-OH and C18:1-OH
FAOs with muscle disease

- VLCAD
  - Cardiomyopathy
  - hepatomegaly
  - SIDS
  - Rhabdomyolysis
- Acylcarnitine profile:
  - Elevations of C14:1 and C14:1/ C12:1
General management guidelines - medical

- Fatty acid oxidation
  - Provide brain fuel
    - Glucose
    - Calories
    - Sick day management

- Organic acidurias
  - Provide brain fuel
    - Calories
    - Glucose and nonprotein/fat
    - Sick day management
General management guidelines - medical

- Malignant hyperthermia
  - Risk with anesthesia for surgery
    - G tube
    - Orthopedic surgery to correct hypertonia
    - Dental work
    - Etc.
Management of metabolic disorders

- Mechanical assistance with basic life functions
  - breathing and feeding
  - physical therapy to prevent muscle atrophy and maintain joint mobility

- Treatments to improve neurological status
  - medication for a seizure disorder
  - medicines or supplements to stabilize a metabolic disorder
  - surgery to help relieve the pressure from hydrocephalus (increased fluid in the brain).
General management guidelines - therapies

- Physical therapy
  - Large muscles, gross motor skills
- Occupational therapy
  - Fine motor skills
- Speech therapy
  - Speech articulation, communication
- Feeding therapy
  - May be done by either speech or occupational therapist
Thank you for your attention

Questions? ? ? ?