Neurological complications of FODs and organic acidemias: what parents need to know about diagnosis, monitoring and management

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Goals

- Discuss the major neurological features of FAOs and OAs
  - Seizures
  - Muscle disease
  - Developmental delay/MR
- Discuss signs and symptoms that should alert family members to seek neurological care
Fatty Oxidation Disorders (FODs)

• Genetic disorders in which the body is unable to oxidize (breakdown) fatty acids to make energy
  – Enzyme deficiency
  – Inherited disorder
  – Due to deficiency there are specific neurological signs and symptoms
    • Brain
    • Muscle
Presentation

Hypotonia and weakness
- Lethargy
- Hypoglycemia with absence or ‘trace’ ketones
- developmental delay
- peripheral neuropathy
- retinitis pigmentosa
- seizures
- hepatomegaly with liver dysfunction (rarely liver failure or cirrhosis)
- coagulopathy
- cardiomyopathy
- ‘Reye’ like syndrome
- coma
- sudden death
Fatty acid oxidation disorders

- Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
- Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
- Short-chain acyl-CoA dehydrogenase (SCAD) deficiency
- Multiple acyl-CoA dehydrogenase (MAD) deficiency (= Glutaric aciduria type II, GA II)
- Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
- Trifunctional protein deficiency
- Carnitine palmitoyl-transferase I (CPT I) deficiency
- Carnitine palmitoyl-transferase II (CPT II) deficiency
- Carnitine acylcarnitine translocase deficiency
- Primary (systemic) carnitine deficiency
How does it cause symptoms

• We all run on energy!!
• Energy from fat keeps us going
  – When our bodies run low of their main source of energy, sugar (glucose)
  – Between meals
• Our bodies rely on fat when we don’t eat for a period of time such as an overnight fast
• When an enzyme is missing or not working well
  – The body cannot use fat for energy and must rely solely on glucose
How does it cause symptoms

• Glucose is a good source of energy but there is a limited amount available
• Once the glucose is gone, the body tries to use fat without success
• This leads to low blood sugar, called hypoglycemia, and to the build up of harmful substances in the blood
  – The brain prefers glucose, but can run on breakdown from fats (ketone bodies)
Fatty acid oxidation defects

- Risk: cause recurrent disturbances of brain function if there is not enough energy
- The brain needs energy to function
  - When the brain is starved for energy it reacts
    - Seizures!!
    - Drowsiness
    - Reversible early on, then irreversible
  - Symptoms occur during fasting
Fatty acid oxidation defects

• Symptoms
  – Drowsiness
  – Stupor and coma occur during acute metabolic crises
  – Seizures
  – Long term neurological effects
    • Recurrent seizures can cause memory problems
    • Problems in Muscle tone, strength, nerves
    • Problems with Cognition/thinking
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, 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
Hypoglycemia and seizures

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

• Why is this important?
  – Brain metabolism depends primarily on glucose 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 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

• 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

- 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

- The likelihood of permanent brain damage from any given instance of severe hypoglycemia is difficult to estimate.
- Depends on a many factors:
  - Age
  - Underlying disorder
  - Recent blood and brain glucose concurrent
  - Problems such as hypoxia
  - Availability of alternative fuels
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
What is a seizure?

- A seizure results from a brief, strong surge of electrical activity in the brain
  - Seizures can last from several seconds to a few minutes or even longer
- The clinical signs or symptoms of seizures depend
  - the location of the epileptic discharges in the brain (where it starts)
  - the extent/pattern of propagation of the epileptic discharges in the brain (where it goes)
Seizures

• 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

• Convulsions and loss of consciousness are the most typical types of seizures most people can recognize

• Events that are less often recognized as seizures include
  – Blank stares
  – Lip smacking
  – Intermittent eye movements
  – Jerking movements of the extremities
Seizures

• Seizures are typically classified as
  – Motor
  – Sensory
  – Autonomic
  – Emotional/cognitive
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
Seizures

• Symptoms depend on where in the brain the disturbance in electrical activity occurs.
• 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.
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 manifest as
    - Alteration in mental state/awareness
    - Tonic or clonic movements
    - Convulsions
    - Various other psychic symptoms (such as déjà vu or jamais vu)
Spells, seizures, and epilepsy

- The medical syndrome of recurrent, unprovoked seizures is termed epilepsy
- A single seizure is not yet epilepsy
- A “spell” may be a seizure or may be something else
  - Movement disorder
  - GERD
  - Sleep disorder
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
Diagnosis of seizures

• EEG classification of seizure type or age of onset or type of seizures
• An EEG machine records brain waves detected by electrodes taped/glued to the head
  – Electrical signals from neurons are recorded as wave forms or lines by the machine
  – Brain waves during or between seizures may show specific patterns in terms of location (generalized, focal), duration, and characteristics help determine whether or not someone has epilepsy
Treatment

- Treatment
  - Dietary restriction
    - of the chain length that cannot be broken down
  - Prevention of catabolism
  - Supplementation
    - carnitine and or vitamin to act as a co-factors for enzymes
Organic acidurias:

• Result From:
  – Deficiencies of mitochondrial enzymes that metabolize CoA activated carboxylic acids
    • Derived from amino acid breakdown.

• Neurological Symptoms
  – Chronic: Encephalopathy
    • Changes in level of consciousness
    • Seizures
    • Chronic developmental delay
  – Episodic/acute: metabolic acidosis
    • Caused by build up of toxic metabolites
    • Disturbance of mitochondrial energy production
    • Require prompt treatment
Organic acidurias

- Treatment
  - Dietary restriction
    - of the amino acids (protein) that cannot be broken down
  - Prevention protein
    - catabolism
  - Supplementation
    - carnitine and or glycine to form less toxic intermediate conjugates
    - biotin/vitamin to act as a co-factors for mitochondrial carboxylase enzymes
Neurological complications

• Fatty acid oxidation disorders
  – Tone abnormalities
    • Hypotonia
  – Seizures
    • due to hypoglycemia
  – Developmental delay or mental retardation
  – Muscle disease
    • VLCAD
    • VLCHAD
    • LCHAD

• Organic acidemias
  – Tone abnormalities
    • Hypotonia
    • Hypertonia
  – Seizures
  – Developmental delay or mental retardation
  – Movement disorders
Short and Long term Neurological consequences of FAOs and OAs

• Hypotonia
  – Low muscle tone
  – Results in delayed gross, fine and speech milestones
  – Usually trunk muscles
  – Improves with therapy
Short and Long term Neurological consequences of FAOs and OAs

• Hypertonia
  – High resting muscle tone
  – 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 be induced by purposeful movement
  - Usually disappear in sleep
  - Caution: some medications can make them worse
Short and Long term Neurological consequences of FAOs and OAs

• Seizures
  – Single event that may be provoked
    • Hypoglycemia
    • Hyperammononemia
  – 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
    • Underlying structural or biochemical changes in brain
      – Research needed
Short and Long term Neurological consequences of FAOs

• Muscle weakness
  – At rest
  – After exercise
Hypotonia

- Decreased muscle tone
  - the amount of resistance to movement in a muscle
- It is not the same as muscle weakness, although one can have both
- Not a specific medical disorder
  - It can be a condition on its own
  - It can be associated with another problem where there is progressive loss of muscle tone
Hypotonia

• Cause
  – 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
  - Walking, pulling up against gravity

- Fine motor skills
  - 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 obey simple commands
• Difficulties with muscles in the mouth and jaw
  – inhibit proper pronunciation
  – discourage experimentation with word combination 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 to assess developmental progress, or observation of physical interactions

• Hypotonic child has difficulty with spatial location
  – 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,
  - 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
• 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
Hypotonia

• Diagnostic tests
  – CT or MRI scan of the brain
  – EMG to evaluate nerve and muscle function
  – EEG to measure electrical activity in the brain may also be necessary
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
  – Brain
  – Spinal cord

• Clinical features
  – Spasticity (overactive reflexes)
  – Rigidity (constant muscle contractions)
Hypertonia

• Other names for hypertonia
  – 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

• Things to watch for
  – contractures
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
Movement disorders-Organic acidemias

- **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
FAOs and Muscle disease

- SCAD
- VLCAD
- LCHAD

- Symptoms
  - Weakness
  - Pain/cramps
  - Exercise intolerance
  - Red urine
  - Muscle breakdown
  - rhabdomyolysis
FAOs with muscle disease

• SCAD
  – Hypotonia
  – metabolic acidosis
  – NBS:
    • elevated C4
    • UOA have elevated ethylmalonic acid
  – Common mild variants of ? Significance
**FAOs 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.
Metabolic crisis

- extreme sleepiness
- behavior changes
- irritable mood
- poor appetite
- Other symptoms then follow:
  - fever
  - nausea
  - diarrhea
  - vomiting
  - hypoglycemia
Consequences of metabolic crises

• Repeated episodes of metabolic crisis can cause brain damage
• This can result in learning problems or mental retardation
• Symptoms of a metabolic crisis often happen after having nothing to eat for more than a few hours
• Symptoms are also more likely when a child with a metabolic condition gets sick or has an infection
Avoidance of metabolic crises

- **Avoid going a long time without food**
- Babies and young children need to eat often to avoid problems
- They should not go without food for more than 4 to 6 hours
- Some babies may need to eat even more often than this
- It is important that babies be fed during the night.
- They need to be woken up to eat if they do not wake up on their own.
Avoidance of metabolic crises

• Children with CTD should have a starchy snack before bed and another during the night
• They may need another snack first thing in the morning
• Raw cornstarch mixed with water, milk, or other drink is a good source of long-lasting energy.
• Your dietician can give you ideas for good night-time snacks
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? ? ?