

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
 - 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
 - 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

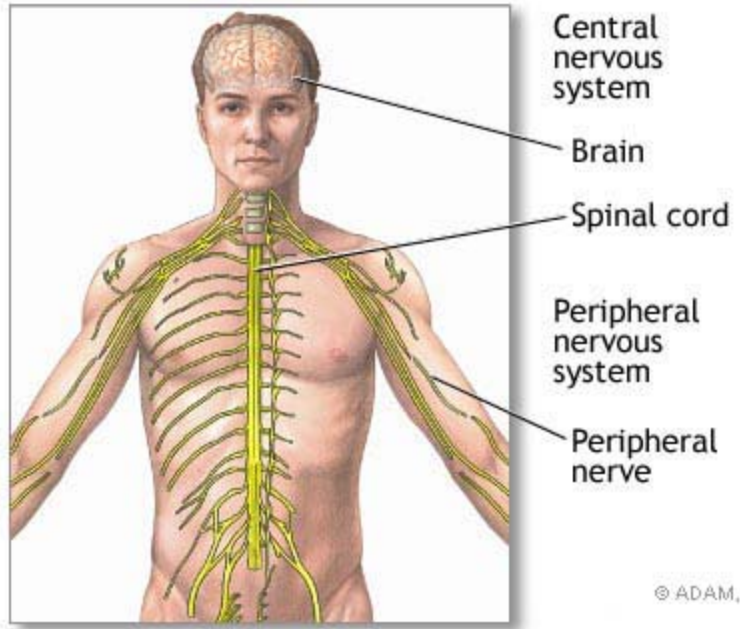
- Cause
 - Central nervous system (brain and spinal cord)
 - Muscle disorders
 - Genetic disorders
- It is usually first noticed during infancy
 - Floppy infant
 - Poor head control
 - Weak suck and swallow

Hypotonia

Hypotonia
(decreased
muscle tone)



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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)

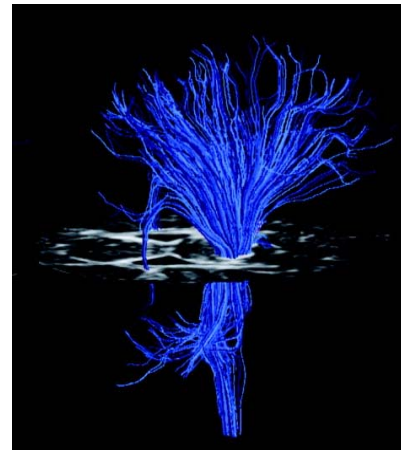
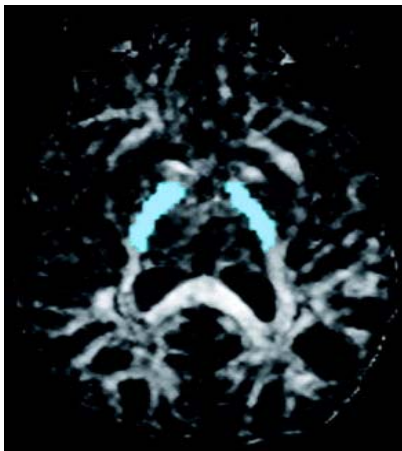
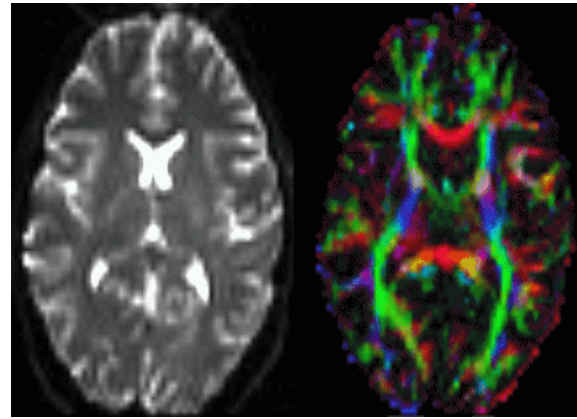
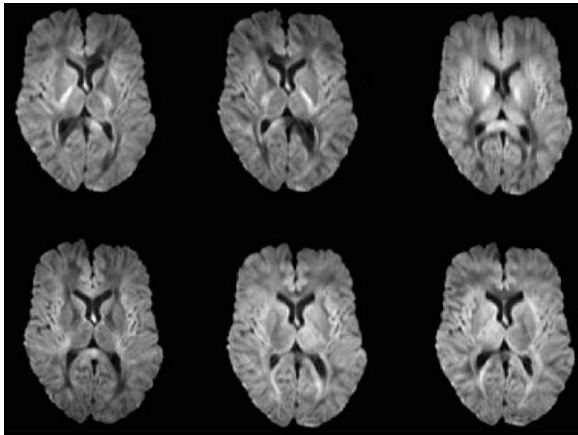
Hypertonia

- 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 nighttime 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? ? ?