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

Andrea Gropman, M.D., FAAP, FACMG
Associate Professor, George Washington University of the Health Sciences
Attending, Children's National Medical Center

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 abnormalites
    - 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

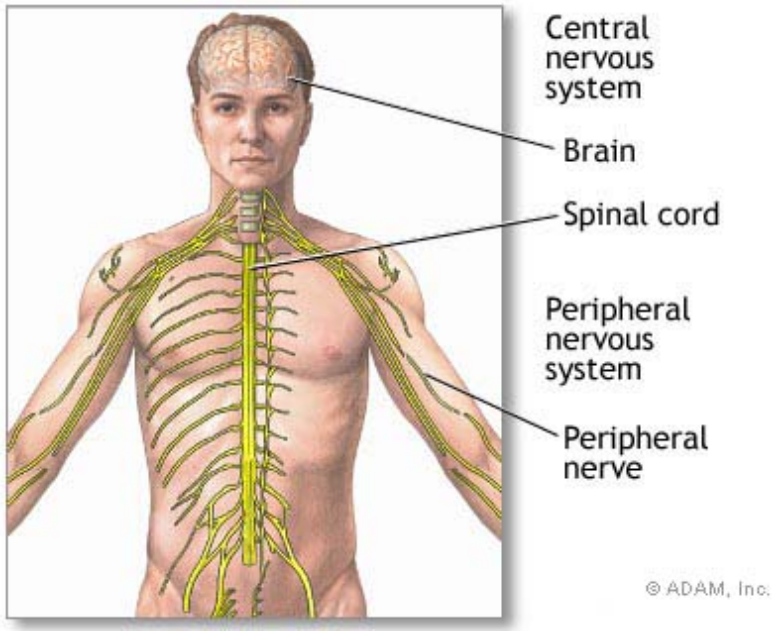
- Decreased muscle tone
  - the amount of resistance to movement in a muscle
- It is not the same as muscle weakness, although one can have both
- Not a specific medical disorder
  - It can be a condition on its own
  - It can be associated with another problem where there is progressive loss of muscle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


Central
nervous
system
Brain
Spinal cord
Peripheral
nervous
system
Peripheral
nerve
© ADAM, Inc.

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

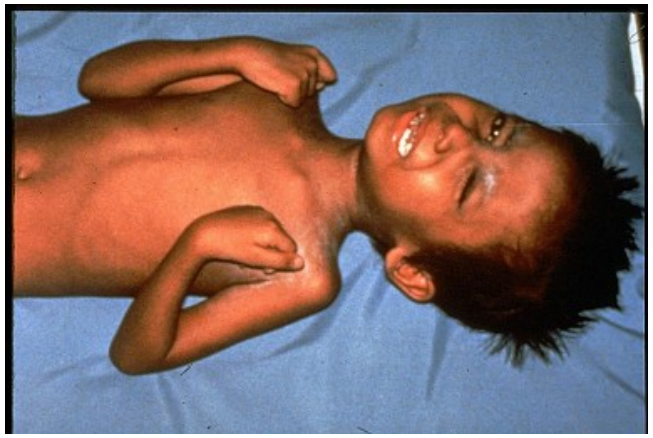
Causes of hypertonia

- Damage to upper motor neurons
  - Brain
  - Spinal cord
- Clinical features
  - Spasticity (overactive reflexes)
  - Rigidity (constant muscle contractions)

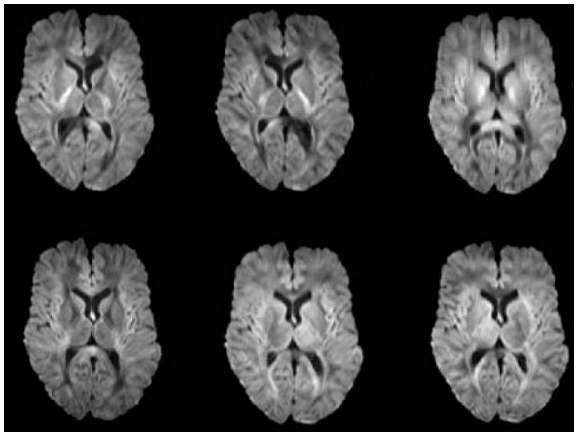
Hypertonia

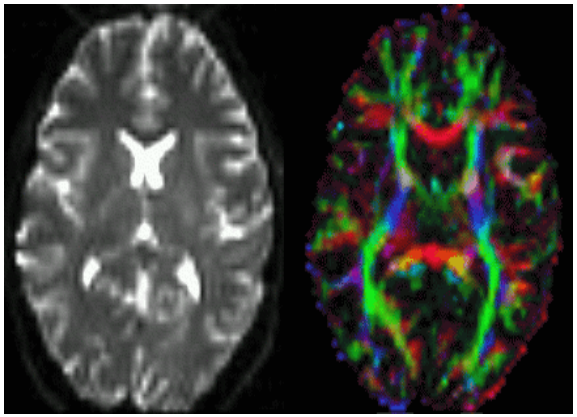
- Other names for hypertonia
  - Cerebral palsy
  - Hemiparesis
  - Quadriparesis
  - Hemiplegia
  - Diplegia

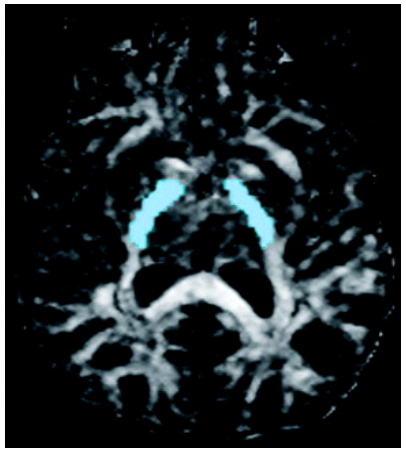
Hypertonia

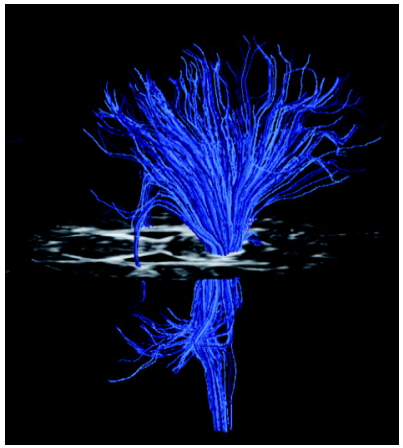


Damage of motor tracts in hypertonia









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 C14:1and 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? ? ?