Anesthetic Issues in Children with Neurologic Diseases

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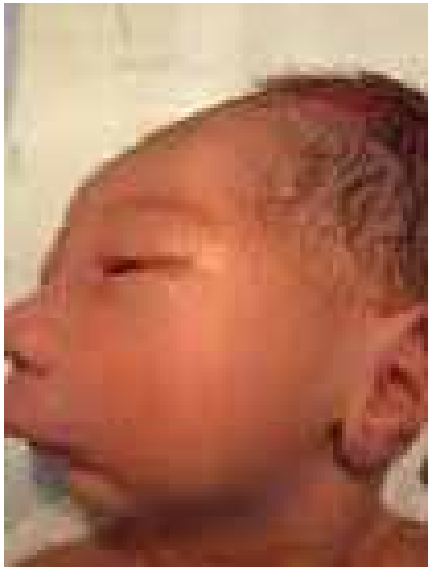
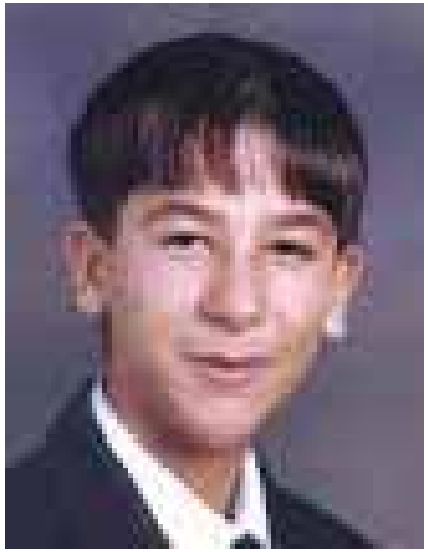
Nothing to Declare

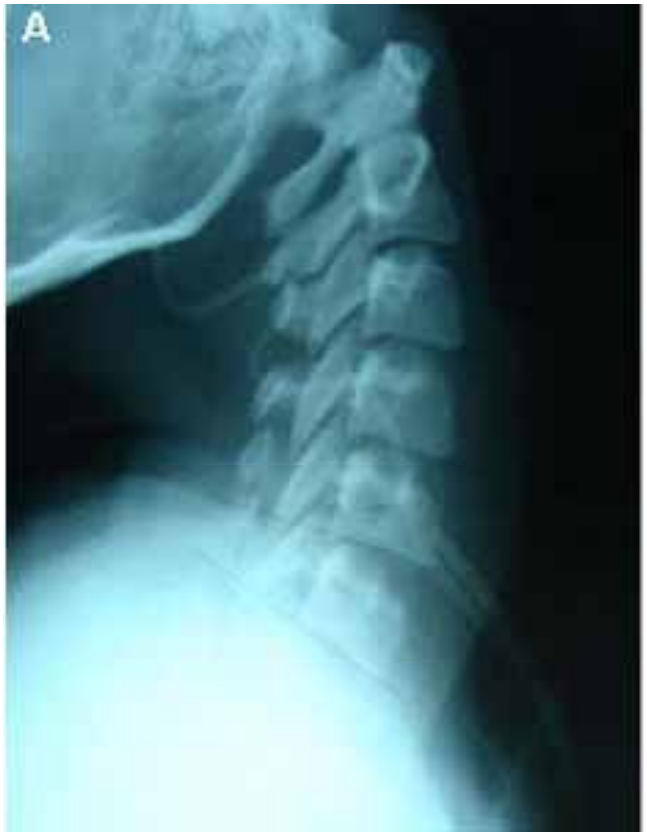
Generalities

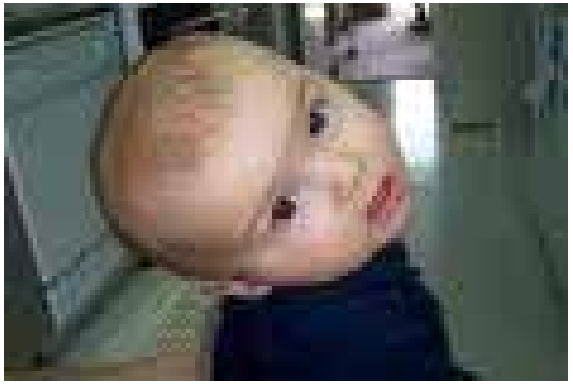
- Common problems in children with various neurologic diseases:
  - Cortical issues (intelligence, behavior, etc.)
  - Visual or hearing disturbances
  - Oropharyngeal, pulmonary mechanical problems
  - Cervical instability or torticollis
  - Reflux
  - Contractures, weakness/hypotonia
  - Movement disorders
  - Seizures and antiseizure medications

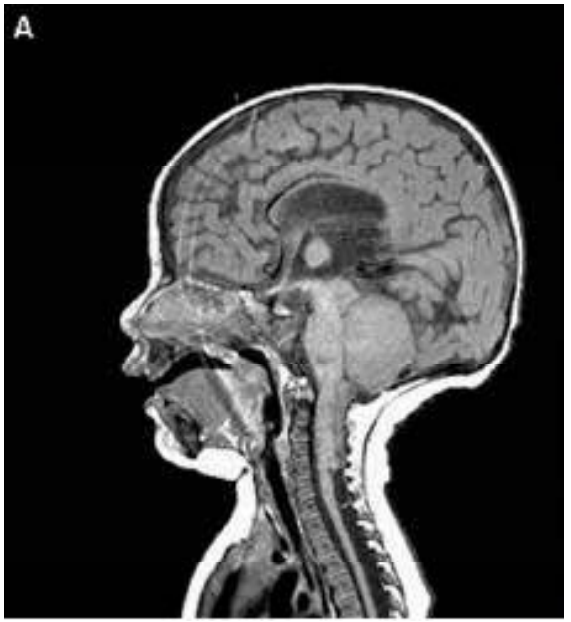
Intubation-related risks











Approach to individuals with epilepsy

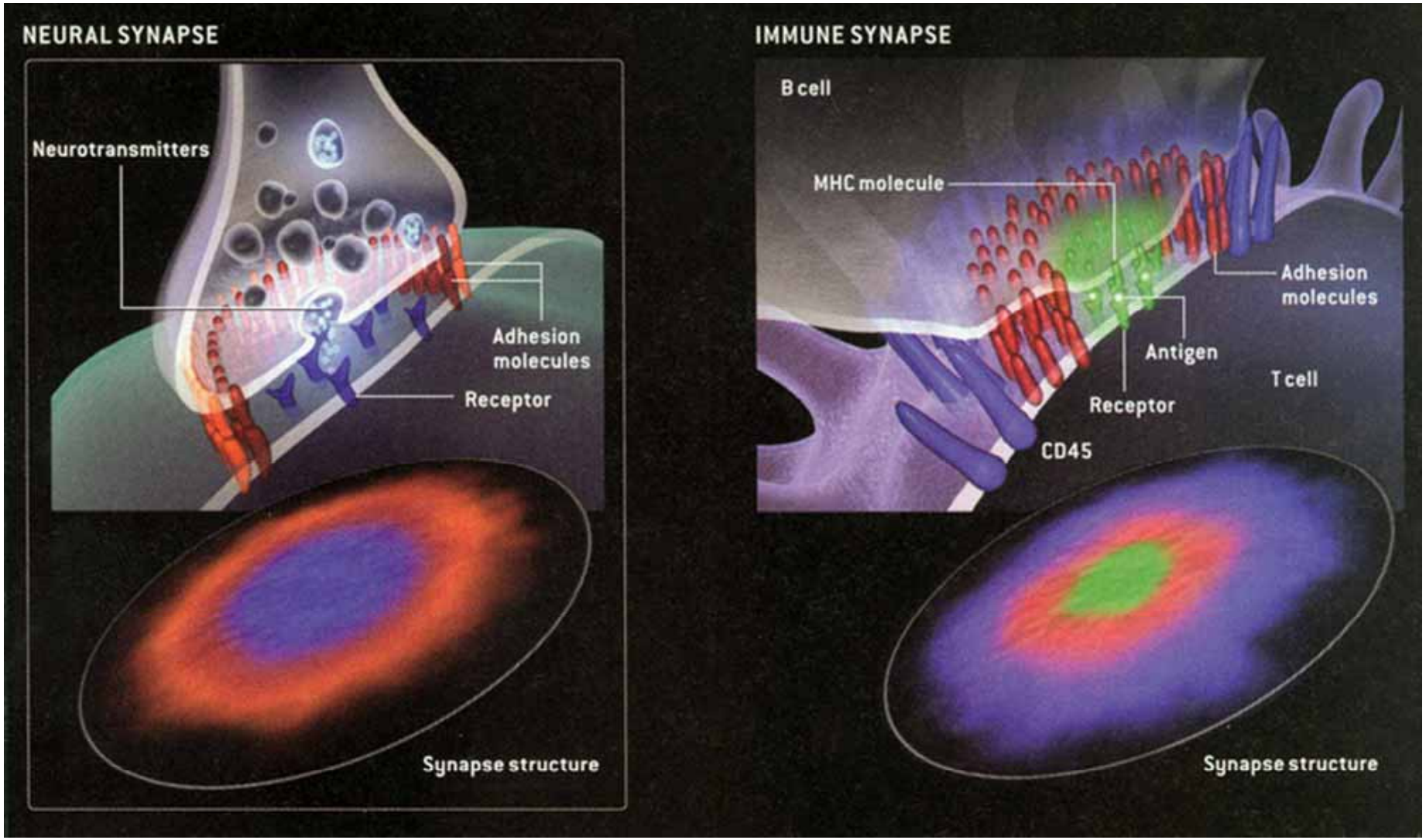
- Avoid prolonged preoperative fast
- 18+ ASDs—avoid holding doses pre/post
  - Depends on half-time drug elimination
  - Oral with small sip/rectal/IV
  - Anesthetic choice/dose: consider ASD etc. med
- Care with hyperventilation/hypocarbia
  - Reduction of CBF v worsening metab/EEG
  - Care in interpretation of cause or nature of twitching, tonicity, shivering, confusion

Anesthetics with effects on seizure threshold (sometimes…)

• Enflurane	Proconvulsant
• Etomidate	Proconvulsant
• Sevoflurane	Proconvulsant
• Fentanyl	Pro- or anticonvulsant
• Ketamine	Pro- or anticonvulsant*
• Lidocaine	Pro- or anticonvulsant
• Methohexital	Proconvulsant
• Morphine	Pro- or anticonvulsant
• Propofol	Pro- or anticonvulsant*
• Etc.	

* Particularly useful treating BDZ-resistant status epilepticus

Receptor trafficking



Inhalational Anesthetics (1)

- Enflurane: *proconvulsant*
  - Organic/inorganic flourinated metabolites
  - *No Epilepsy*: Facial/appendicular myoclonus
    - No associated convulsive EEG abnormalities
    - Deep levels have been associated with GTC szs
  - *Epilepsy*: concn-related worsening szs + EEG abn
    - HV (to decrease CFB/ICP) worsens enflurane effect
    - DZP, thiopental may *worsen* enflurane effects
    - Nitrous not known to have + or – influence
    - Post-op GTC/myoclonic szs may persist for days

Inhalational Anesthetics (2)

- Isoflurane
  - Little proconvulsive--except co-admin of nitrous?)
  - *Valuable anticonvulsant effects* (esp. BDZ-resistant status)
  - Good choice in status epilepticus
  - Concerns re caspase-3 activation/NMDA-r endocytosis
    - Pertinent to Alzheimer (including Down syndrome-associated and…?
- Desflurane
  - Similar to isoflurane
  - Faster emergence
    - Valuable in individuals with *metabolic diseases* where special dietary frequent accomodations must be made
    - However greater tendency to peri-emergent coughing

Inhalational Anesthetics (3)

- Sevoflurane
  - Induction-related movements
    - May be non-epileptic
    - Focal or generalized epileptic seizures may occur
      - Children especially vulnerable, epileptic >> normal
      - Especially with rapid induction, higher doses
      - Rapid + controlled HV may provoke in 80% cf 20% without HV
      - May have associated CNS-related autonomic changes
      - Nitrous or bolus MDZ may suppress sevoflurane-related seizures
- Nitrous: Little proconvulsive *or anticonvulsive* activity
  - Extensive experience, valuable in epilepsy surgery
- Halothane: *anticonvulsive*
  - Except with co-administered nitrous?
    - Transient post-op vertex sharp waves 2-7 days

Barbiturate Anesthetics (1)

- Phenobarbital
  - Very anticonvulsive, high doses well-tolerated
    - Up to at least 120mg/kg over time well tolerated
    - Long duration of effects
    - Loss of effect with receptor trafficking (as with BDZ)
- Pentobarbital
  - Brainstem in addition to cortical anticonvulsive
    - Shorter duration, cardiopulmonary support early
    - Loss of effect with receptor trafficking (as with BDZ)?

Barbiturate Anesthetics (2)

- Thiopental
  - Powerful anticonvulsive effects in Tx range
    - Valuable for status epilepticus, local anesthetic related szs
    - Probably safe for induction in mitochondrial diseases
- Methohexital
  - Excitatory during induction:
    - Tremor, muscle twitch, hypertonus, hiccough with nl EEG
  - Epilepsy (PC): Szs/EEG abn may occur (IV, IM, rectal admin)
    - Low doses may activate PC (>70% cases?)
    - No such effect in primary generalized epilepsies?
    - High doses—electrocerebral silence possible
  - Methohexital suppression test to find TLE focus

Other Anesthetics(1)

- Etomidate
  - Useful in neurological diseases with cardiovascular instability
  - Non-epileptic individuals
    - Longer convulsive phase after electroconvulsive Tx than with propofol
    - Involuntary myoclonic mvts 10-70% of patients
      - » May suggest szs, may be violent
      - » Co-administration opioid or short acting BDZ avoids problem
      - » But: epileptiform in 20% heart valve replacement cases
  - Epileptic individuals
    - Some risk for provocation of focal or secondary GTC szs
      - » 0.2mg/kg sz focus activation (<30s onset)

Other Anesthetics (2)

- Ketamine
  - Epilepsy: 37% risk sz/obtundation 2-4mg/kg IV(focal/2^{o} genl)??
    - Treat with BDZ or barb rather than increasing ketamine dose
      - » *Some studies show little ketamine risk in well-treated epilepsy but given alternative agents may be best to avoid if epilepsy.*
  - Dissociative state with delirium possible (may suggest “PC Sz”)
  - With prolonged use cerebellar injury possible

Propofol

- Cortical depressant for anesthesia/treatment of seizure
  - CNS subcortical excitatory phenomena in10% of patients
  - When used in electroconvulsive Tx shortens convulsive phase
  - Avoid in well-controlled epilepsy (driver's license risk?)
- Status epilepticus: 5-10 mg/kg/hr infusion
  - May bolus with 1.0-3.0 mg/kg over 5 min; ***beware hypotension***
    - Titrated to achieve suppression-burst or isoelectric EEG
    - Intubation and pressor support required
    - Central arterial blood pressure monitoring recommended
  - Monitor acid-base balance: at risk for severe metabolic acidosis.
    - Children may be particularly subject to this
  - May wish to replace with other agents once control of SE is achieved.
    - Taper at rates no faster than 5% per hour
- Alternatives:
  - Inhalation anesthesia (isoflurane)

Propofol infusion syndrome (1)

- Rare but may be fatal; critically ill children > adults (21/14 as of 2003)
    - Mostly acute neurological or inflammatory illnesses—receiving catecholamines/steroids as well as longterm high dose propofol.
    - Cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure.
    - CNS activation with ↑catecholamines and glucocorticoids

Vasile et al., Intensive Care Med. 2003 Sep;29(9):1417-25

Propofol infusion syndrome (2)

- Systemic inflammation / cytokine production priming cardiac/ peripheral muscle dysfunction ± necrosis.
  - ***Potent inhibitor of Complex I of electron chain***
    - Impairs free fatty acid utilization: LCFA transport via CPT as well as beta oxidation
    - Mismatch of energy supply and demand
    - Avoid utilization in mitochondrial neurologic disease
    - Avoid prolonged (>48 h) propofol sedation at doses higher than 5 mg/kg/h especially if acute neurological or inflammatory illnesses.
    - In such cases, alternative sedative agents should be considered. If unsuitable, strict monitoring of signs of muscle necrosis advisable.

*Vasile et al., Intensive Care Med. 2003 Sep;29(9):1417-25

A few more things about propofol

- Prolonged infusion-related acid-base disturbances
  - Fever, muscle membrane dysfunction, CK>20,000, occ rhabdomylolysis, some fatalities—especially <20yo
- Movement abnormalities especially in induction phase:
  - May provoke myoclonus in myotonic dystrophy
  - Twitches, athetosis, chorea, dystonia, opisthotonus are also described in individuals who do not have myotonic dystrophy
  - May reappear in postoperative period
- Conscious dental sedation:
  - Even with epilepsy not provocative of seizures
- Bolus anesthetic doses may activate epileptic foci
  - Occ seizure recurrence for up to 23 d postop—metabolite?
  - Cardiac surgery with propofol + calcium + MDZ reduces post-op risk of seizures

Medications said to induce mitochondrial damage (1)

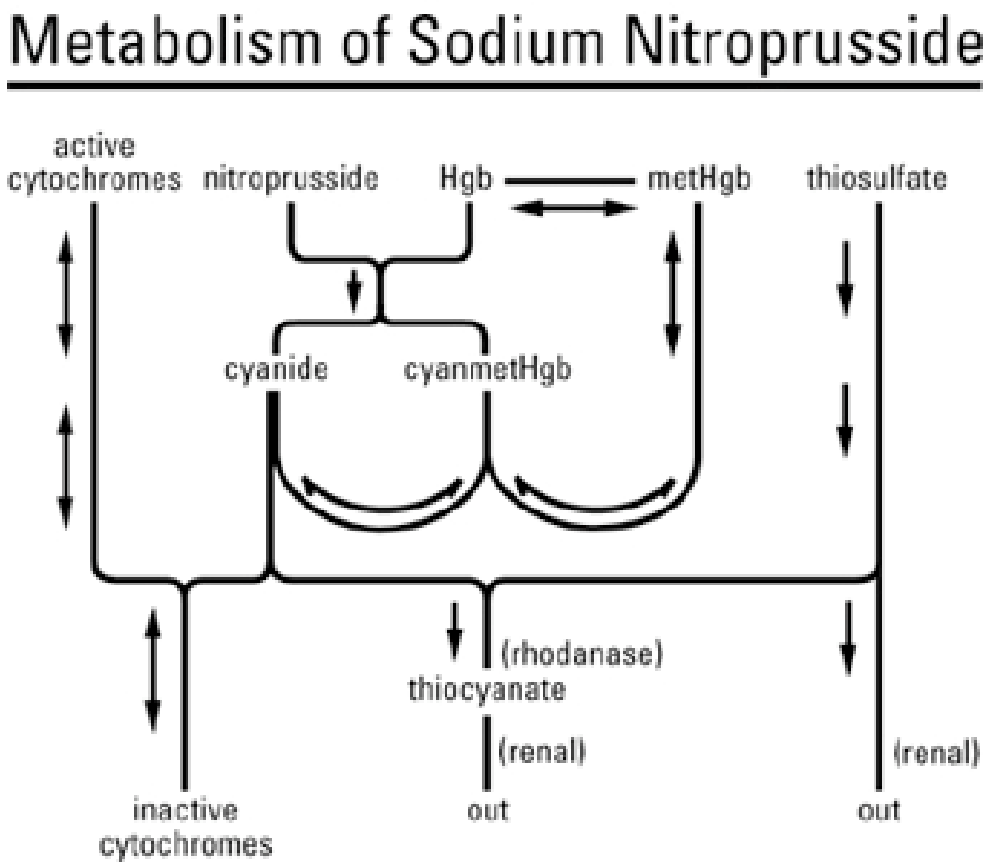
Drug class	Drugs
• Alcoholism treatments	Disulfiram
• Analgesic/anti-inflammatory	Aspirin, acetaminophen, diclofenac, fenoprofen, indomethacin
• Anesthetics	***Isoflurane, halothane, propofol***
• Angina medications	Perhexiline, amiodarone Diethylaminoethoxyhexesterol
• Antiarrhythmic	Amiodarone
• Antibiotics	Tetracycline, antimycin A
• Antidepressants	Amitriptyline, amoxapine, citalopram fluoxetine
• Antiemetics	***Haloperidol***
• Antipsychotics	Chlorpromazine, fluphenazine, ***haloperidol***, risperidone, quetiapine, clozapine, olanzapine
• Anxiety medications	Alprazolam, diazepam
• Barbiturates	***All barbiturates***

Medications said to induce mitochondrial damage (2)

Drug Class	Drugs
• Cholesterol medications	Statins (atorvastatin, fluvastatin, etc)
• Bile acid medications	Cholestyramine, clofibrate, ciprofibrate, etc
• Cancer chemotherapeutics	Mitomycin C, profiromycin, adriamycin
• Dementia medications	Tacrine, Galantamine
• Diabetes medications	Metformin, troglitazone, rosiglitazone, etc.
• HIV/AIDS medications	Atripla, Combivirm, Emtrivam, etc.
• Epilepsy/Seizure meds	Valproic acid
• Mood stabilizers	Lithium
• Parkinson's meds	Tolcapone, also Stalevom)

Nitroprusside

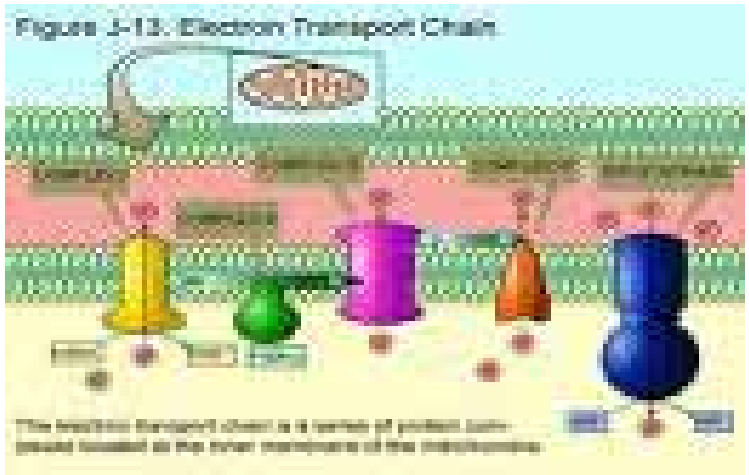
- Some cyanide in blood of many individuals:
  - Smoking
  - Industrial exposures
  - Mining wastes
  - Cassava (tapioca)
  - Almonds
  - Apple, apricot pits
  - Spies, wealthy relatives
- Mitochondrial Dx:
  - May wish to use labetolol instead for hypotensive anesthetic approaches

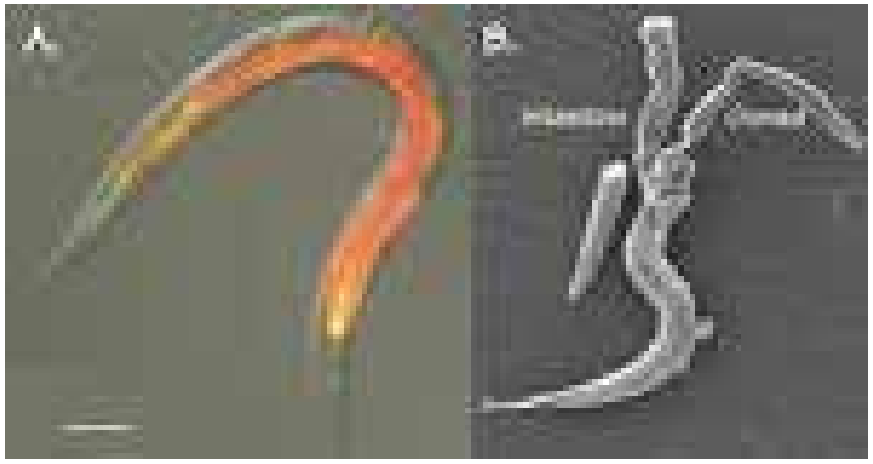


C. elegans mitochondrial diseases

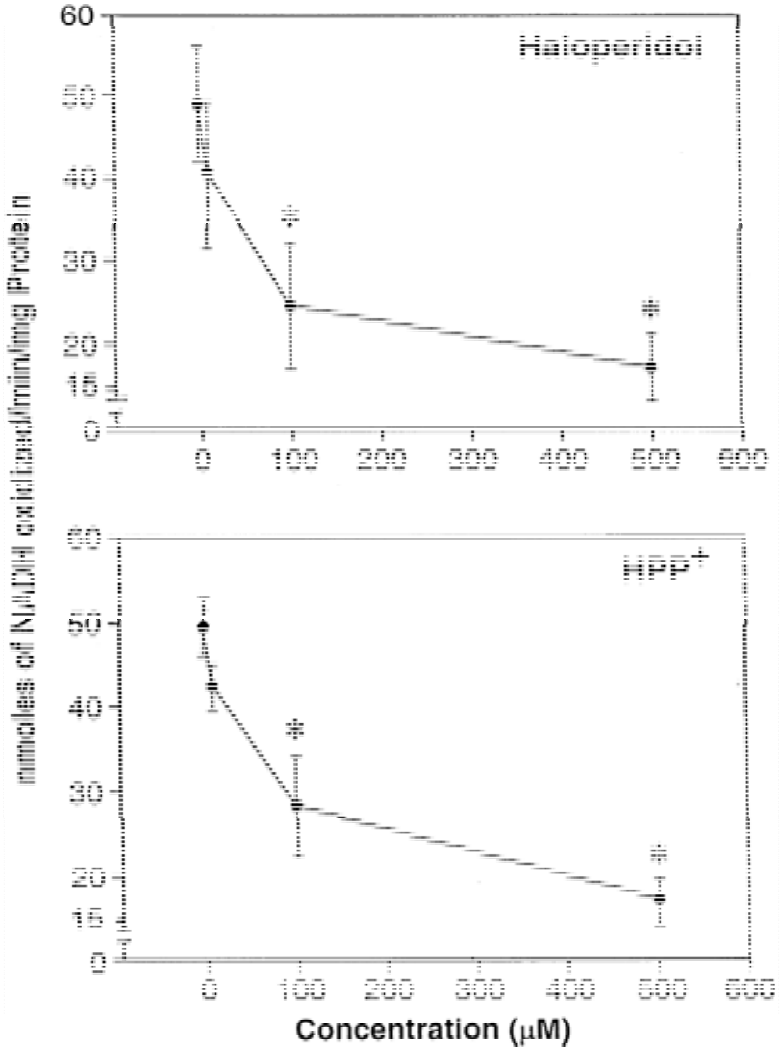
(Hartman et al, 2001)

- Complex I (gas-1 mutation)
  - Hypersensitive to volatile anesthetics
    - Halothane, diethylether, isoflurane, (propofol?)
- Complex II (mev-1 mutation)
  - Hypersensitivity to oxidative damage/hypermutability
    - Paraquat-induced free radicals or hyperoxia
- Either: incr free-radical sensitivity (↓ubiquinone)





Haloperidol v Complex I



Antiemetics

- Haloperidol effects on Complex I
- Movement disorders
  - May resemble seizures
  - Produce wasteful energy expenditure
  - Esp. Dopamine antagonists
    - Extrapyramidal effects, e.g. dystonia
    - Phenothiazines (prochlorperazine)
    - Butyrophenones (droperidol)

Muscle relaxants

- Hepatic enzyme inducing anti-Sz meds
  - Lower than expected duration of liver-metabolized muscle relaxants
  - The effect may be marked
    - Esp. Aminosteroidal compounds
      - Vecuronium, Pancuronium less so with rocuronium)
    - Not benzylisoquinolinium compounds
      - Atracurium, mivacurium

Leigh Disease

(Subacute necrotizing encephalomyelopathy)

- AR: ↓PDH complex and electron chain
- Weakness, Szs, ataxia, ophthalmoplegia
- Progressive symmetric necrosis BG, brainstem, periacqueductal gray

Leigh Disease
Anesthetic Considerations*

- Avoid stress that may ↑energy demand
  - No fasting interval >8 hours
  - Avoid/treat *suspected* infection, fever, acidemia (no lactated fluids)
  - Avoid ↓glucose, hypoxia, hypercarbia, cardiomyopathy
  - Assure optimal pulmonary function at time of surgery
  - Leigh disease probably not associated with MHyperthermia
- Barbs and volatile anesthetics may compromise mitochondrial respiratory function—thiopental induction may be safe
  - Be cautious with succinylcholine (↑K+?), rocuronium, atracurium
  - Avoid halothane, propofol, nitroprusside, chloral hydrate, BDZs
  - Avoid narcotics--clonazepam for postoperative pain control

*Baum and O'Flaherty 2007; Shear and Tobias Paed Anaesth 14:792, 2004

Malignant Hyperthermia (1)

- Inherited myopathy-related vulnerability
  - Muscle constitutes 40% of body weight!
- Volatile anesthetics or succinylcholine
  - Other stresses may contribute to vulnerability
- MH mortality formerly 70%
  - Dantrolene (RyR1 receptor inhibitor) with supportive care has reduced mortality to 5%

Malignant Hyperthermia (2)

- Classic: AD myopathic ryanodine receptor (RyR1) (30+ mutations)
  - Abnormal caffeine-halothane muscle contraction test (MCT)
    - Cause of trismus/generalized rigidity
  - MCT positive patients tolerate anesthetic challenges
  - Vulnerability to ↑ membrane permeability
  - Sarcoplasmic reticular calcium release
  - ***Control*** of Abn calcium fluxes produces
    - Compensatory ↑ metabolic rate/heat, H+ ion release acidemia
    - Differs from myopathic membrane leaks ***without*** compensatory response
  - Child > adult susceptibility
    - any time during/shortly after anesthetic

Malignant Hyperthermia (3)

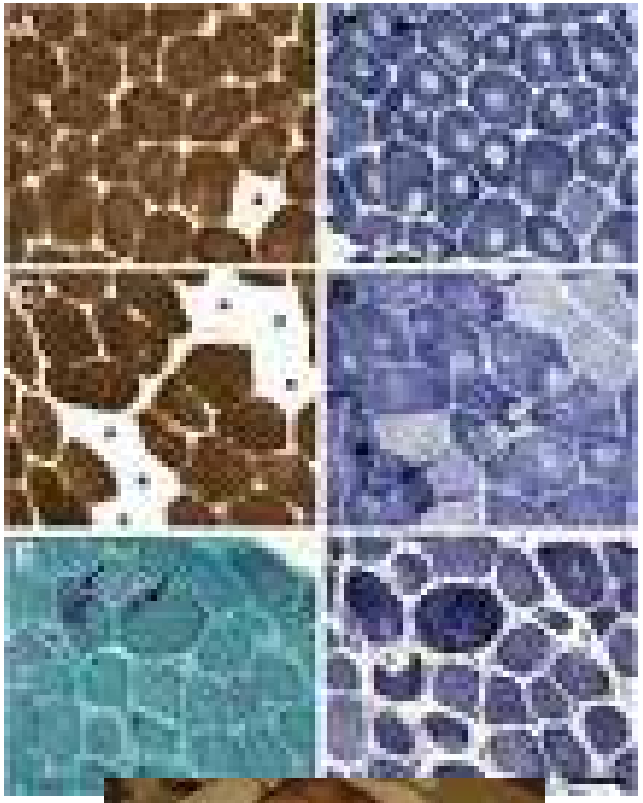
- Variant: rhabdomyelitic ↑K+, CK, Myoglobin
  - ***50% Co-occurs*** in setting of RyR1 hyperthermia/abnl MCT
  - 50% occurs in isolation where RyR1 and MCT are normal
    - Fever of later onset than true malignant hyperthermia
    - Especially myopathies with membrane breakdown
    - Rapid occurrence after succinylcholine bolus
      - » Contraindicated in myopathic patients
    - May occur with volatile anesthetics (slower onset)
    - Best approach if risk:
      - » Nitrous + IV opiates/sedative, propofol maintenance

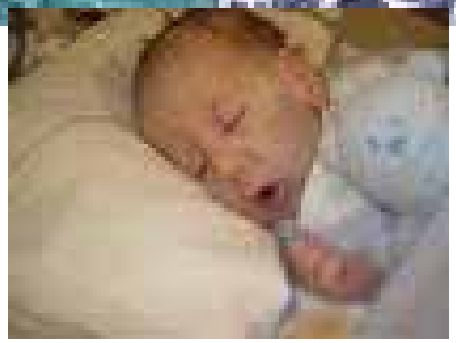
MH-associated conditions

- King-Denborough Syndrome
  - Ptosis, strabismus, kyphosis, cryptorchid, short
- Succinylcholine induced trismus
  - Most children have this but subclinical in 95%
  - Small number may manifest “jaws of steel” pheonomenon
- SCN4A-related ↑K+ periodic paralysis (17Q)
  - Also K+ aggravated myotonia, paramyotonia congenita
- ***Central Core Disease***
- ***Duchenne / Becker dystrophinopathies***

Central Core Disease
(19q13.1=RyR1 gene locus)

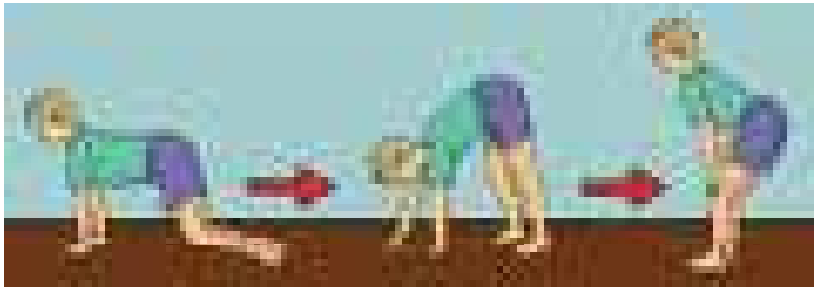
- AD congenital myopathy
  - Mandibular hypoplasia, short neck
  - Contractures
  - Proximal muscle weakness
  - Non- or slowly progressive (19q13.1)
    - Ryanodine receptor-1 Ca channel gene: "true" RyR1 MH
    - Abnl mitochondria/sarcoplasmic reticulum
    - Loss of central skeletal muscle fibers
    - ↑Type 1 muscle fiber calcium
    - Abnl muscle contraction testing

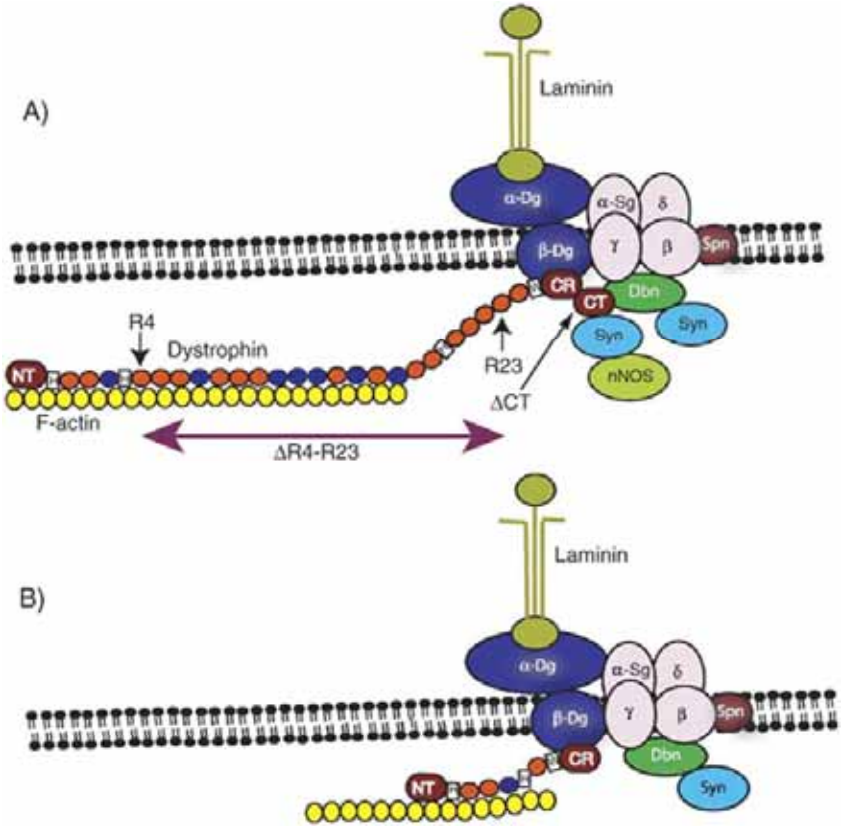




Duchenne dystrophinopathy

- X-linked boys
  - Membrane instability
  - Calcium leakage
  - Inflammatory fibrosis
- ±Congenital adrenal hypoplasia
- Abnl ECG in 90%
  - Tall R to right, deep Q to left
- Dilated cardiomyopathy
  - Severity many differ from striated muscle
  - Cardiomyopathy in adult female carriers





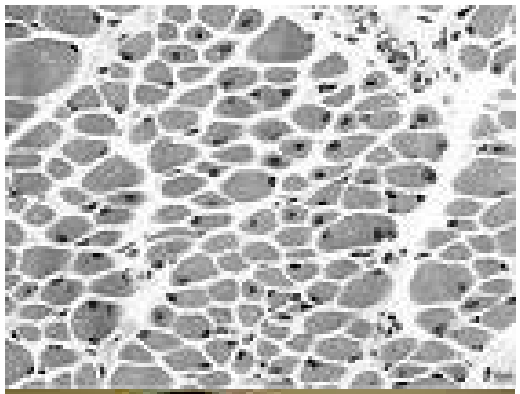
Duchenne dystrophinopathy
Anesthetic considerations

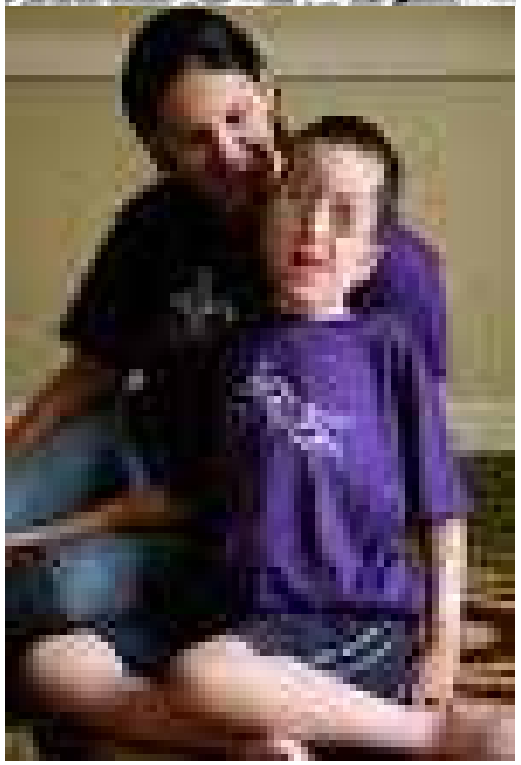
- Acute rhabdomyolysis ± hyperkalemia
  - Not “true” (RyR1-related) malignant hyperthermia
  - May occur after succhinylcholine with ↑K+ rhabdomyolysis—sometimes associated with cardiac arrest
    - Pre-Dx occurrence led to succinylcholine warning for children
    - Multilead ECG monitoring important even for biopsy
    - Occasional ↑K+ arrest at or after anesthetic emergence
    - Late DMD: fibrotic heart block
  - Inhalation anesthetics sometimes cause similar problems:
    - Halothane, isoflurane, enflurane, sevoflurane
    - May be latency of several hours for myoglobinuria—especially if muscle very fibrotic;
  - Occasionally similar picture seen in Becker’s
  - Don’t neglect possible adrenal insufficiency

Myotubular (Centrotubular) Myopathy
Anesthetic considerations

- X-linked (myotubularin)
  - Unless ventilated usually fatal in infants
  - AR (infantile) or AD (adult) varieties
- Much less MH risk than central core
  - ±hyperkalemia to succinylcholine
  - ↓ swallow, aspiration risk
  - Low risk nondepolarizing agents
    - may not need: muscles markedly weak

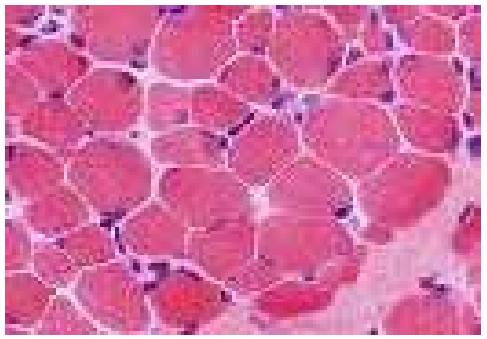
--Pierson et al, J Neuropathy: 2006

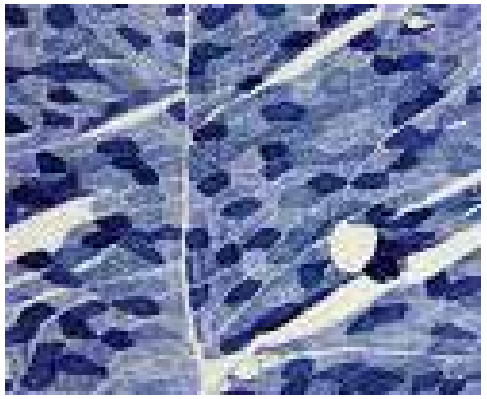




Nemaline Rod Myopathy

- Three clinically similar types:
  - Type 1 (AD: tropomyosin-3)
  - Type 2 (AR: nebulin)
  - Type 3: (AD: alpha-actin 1)
- Subsarcolemmal rods of fast-twitch fibers (Z-disc derived)
- Variable axioproximal weakness
- ± faciopharyngeal/distal limbs
- ± cardiomyopathy (rare)





Nemaline Rod Myopathy
Anesthetic considerations*

- Micrognathia/malocclusion:
  - Laryngoscopy/tracheal intubation difficulties
  - Aspiration risk
- Pulmonary > cardiac risk
  - May require prolonged postoperative ventilation
  - Postoperative pain worsens breathing
  - No reports of malignant hyperthermia or succinylcholine-related hyperkalemia (but little information available)
- High level spinal anesthesia may be risky
- Muscle relaxants may not be necessary (weak)
  - …and may be risky

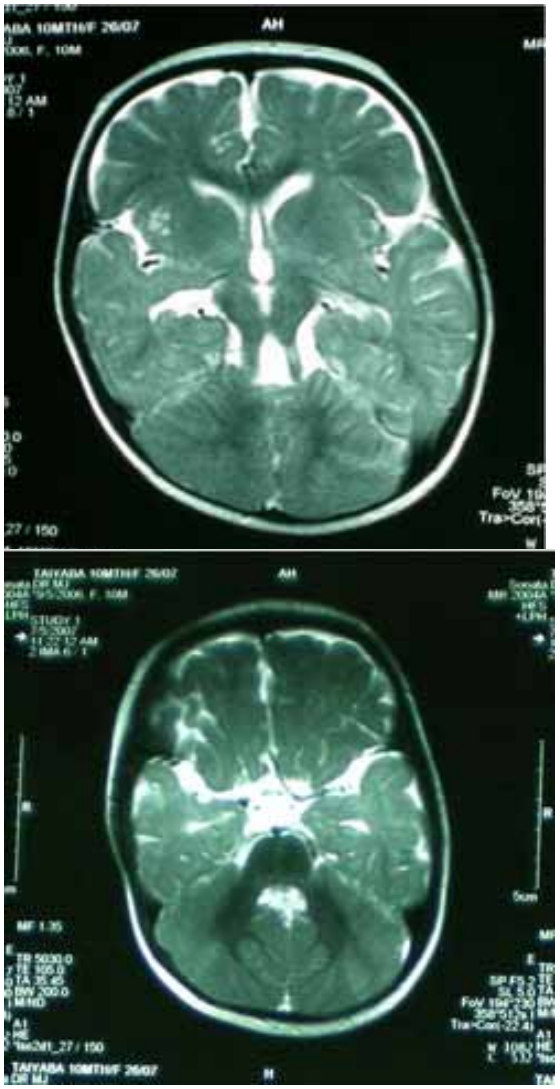
*Cunliffe and Burrows, Can Anaesth Soc J 1985

Approach to anesthesiological issues in muscle disease (CN)

- Tell your patients to inform the anesthesiologist they have heritable muscle disease
    - Especially important in the emergency room
- Rely on the anesthesiologist to know what to do if a complication rhabdomyolysis, MH, postoperative weakness) develops
    - Also rely on the ER anesthesiologist to enforce a sensible approach to anesthetic or paralytic medications in order to obtain scans—which are usually beside the point in evaluation and treatment of status epilepticus

Joubert Syndrome

- AR, severe psychomotor delay
- Infantile nystagmus, ataxia
- Tachypnea/panting/apnea
    - ***Improves with development or caffeine***
    - Apnea may entail cardiac arrest
- Various oropharyngeal abnormalities
- Occipital myelomeningocele sometimes
    - May also have caudal epidural deformation
- Characteristic scan:
    - Cerebellar vermal dysplasia/agenesis
    - “Molar tooth” deformity of peduncles
    - Lg 4th ventricle “batwing” or “umbrella”
    - Agenesis corpus callosum



Joubert Syndrome
Anesthetic considerations*

- Direct laryngoscopy may be difficult
  - Micrognathia, large tongue, short/stiff neck, epiglottic deformities, etc.
- Apneas usually 15 secs or so duration:
  - Nitrous oxide, opioids, etc. may prolong these for as much as several hours postoperatively
  - Regional anaesthesia recommended if possible
  - Caudal epidural anesthesia may be challenging but spinal anesthesia may prove useful
  - IV propofol has been used uneventfully
- Improves after infancy or with caffeine

*Vodopich and Gordon, 2004

Central hypoventilation syndrome (Ondine's Curse)

- AR/AD* (PHOX2B etc. genes)
  - Usually neonatal onset
    - May be have low tone, somnolence
    - Mile to moderate developmental delay
    - Apnea occurs in non-REM sleep
      - » Anesthetics, narcotics may ↑ apnea
    - May have cardiac arrhythmias
    - SIADH-related risk for hyponatremic seizures
    - Neuroblastoma or ganglioneuroma in some
    - Hirschsprung disease in 50%: aspiration risk
      - » Suggests neural crest migration disorder
  - Tracheostomy, PPV in sleep
    - Low CO2 responsiveness—O_2 may provoke apnea

SMARD1
(SMA with respiratory disease)

- AR (11q13-q21/IGHMBP2 gene defects in some)
    - IGHMBP2 mutationin some—resembles SMN1 protein
- Completely normal CNS function
- May present in infancy resembling infantile GBS
- Progressive untreatable distal → central peripheral and diaphragmatic/respiratory muscle paralysis
- Large myelinated peripheral nerve abns in some

SMARD1

(SMA with respiratory disease: Distal HMN VI)

- Ethical issues resembling those of respiratory failure in Duchenne muscular dystrophy
- Without breathing support death <1yo
  - After intubation total ventilatory dependency, survival for decades possible

Approaches: severe breathing paralysis

- Maintain lung capacity
    - Stack breathing, etc.
- Flu prophylaxis, viral precautions
- Mucolytics, steroids, bronchodilators??
- Incentive spirometry, breath stacking early
- Aerosolyzed nebulizers
- Cough inexsufflator
- Antibiotics ***if secondary*** bacterial pneumonia
- BiPAP if VC falls below 40%

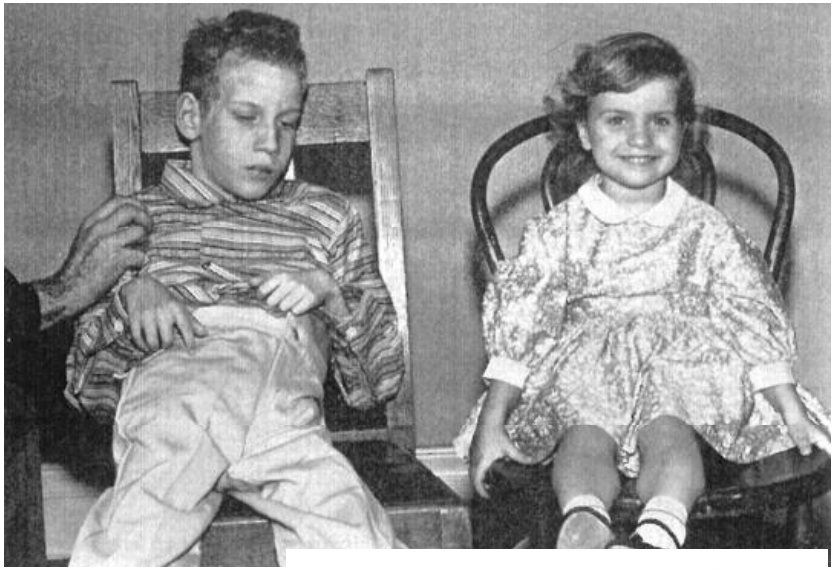
BiPAP

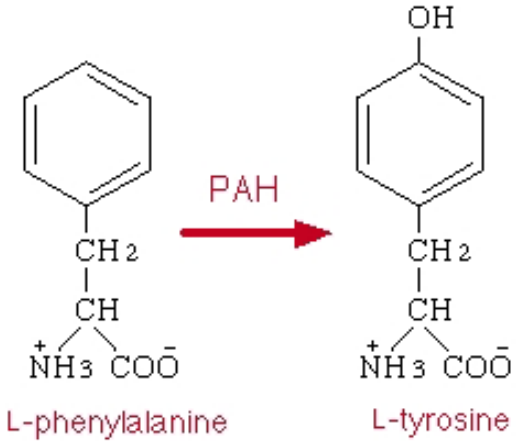
Generalities concerning neurometabolic diseases

- Things that may be required:
  - Continuation of dietary restrictions if needed
  - Avoidance of hypoglycemia
  - Avoidance of catabolic state (e.g. PKU)
  - Avoidance of GI protein load (e.g. blood)
  - Avoidance of hemolysis (e.g.PGK deficiency)
  - Awareness of cardiac status (e.g. Pompe, DMD)
  - Avoidance of rhabdomyolysis
  - Fluid titrations if renal disease

Phenylketonuria
Anesthetic considerations

- Must continue PA restriction perioperatively
  - If untreated:
    - Vomiting risk
    - Megaloblastic anemia?
- Avoid prolonged fast
    - Catabolic ↑ phenylalanine
- Anesthetics
    - Avoid proconvulsants
    - Antiseizure meds v anesthetics
    - Nitrous oxide inactivation of b12-dependant methionine synthase→post-op paraparesis?

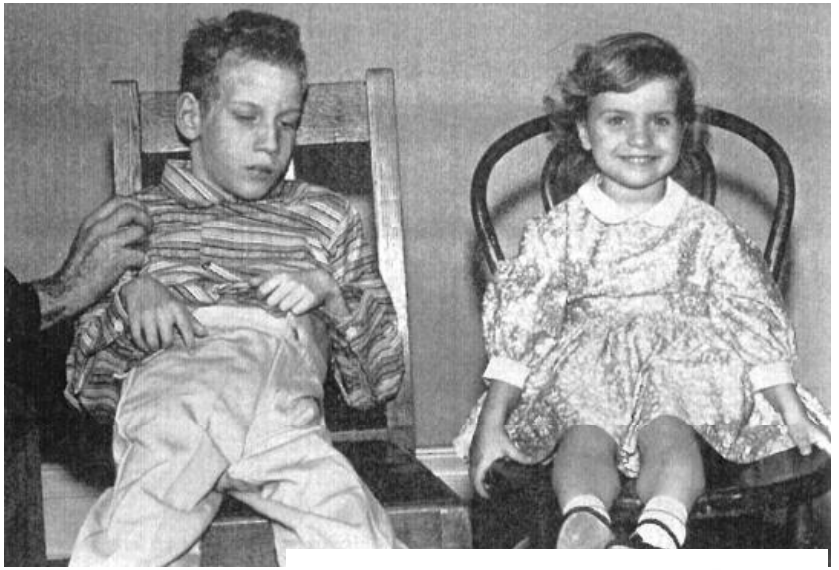


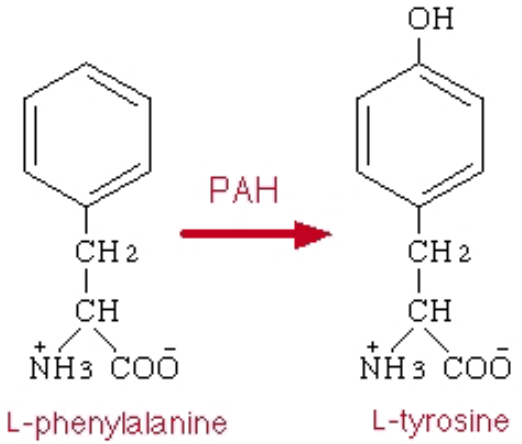


The enzyme phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine.

Phenylketonuria

- AR chromosome 12
  - ↓phenylalanine hydroxylase ***or***
  - ↓tetrahydrobiopterin in 1-2% *
  - 1/10,000 US / 1/2600 Turkey
  - Heterozygosity v mycotoxins
- Rx: restrict phenylalanine
  - Protein restriction
  - Doesn't work if BH4 deficiency
  - May develop 2○ ↓B12
- If untreated:
  - Musty odor
  - Blue eyes/light hair/exczema
  - MR, vomiting episodes, szs
  - Spasticity, PD (if ↓BH4)



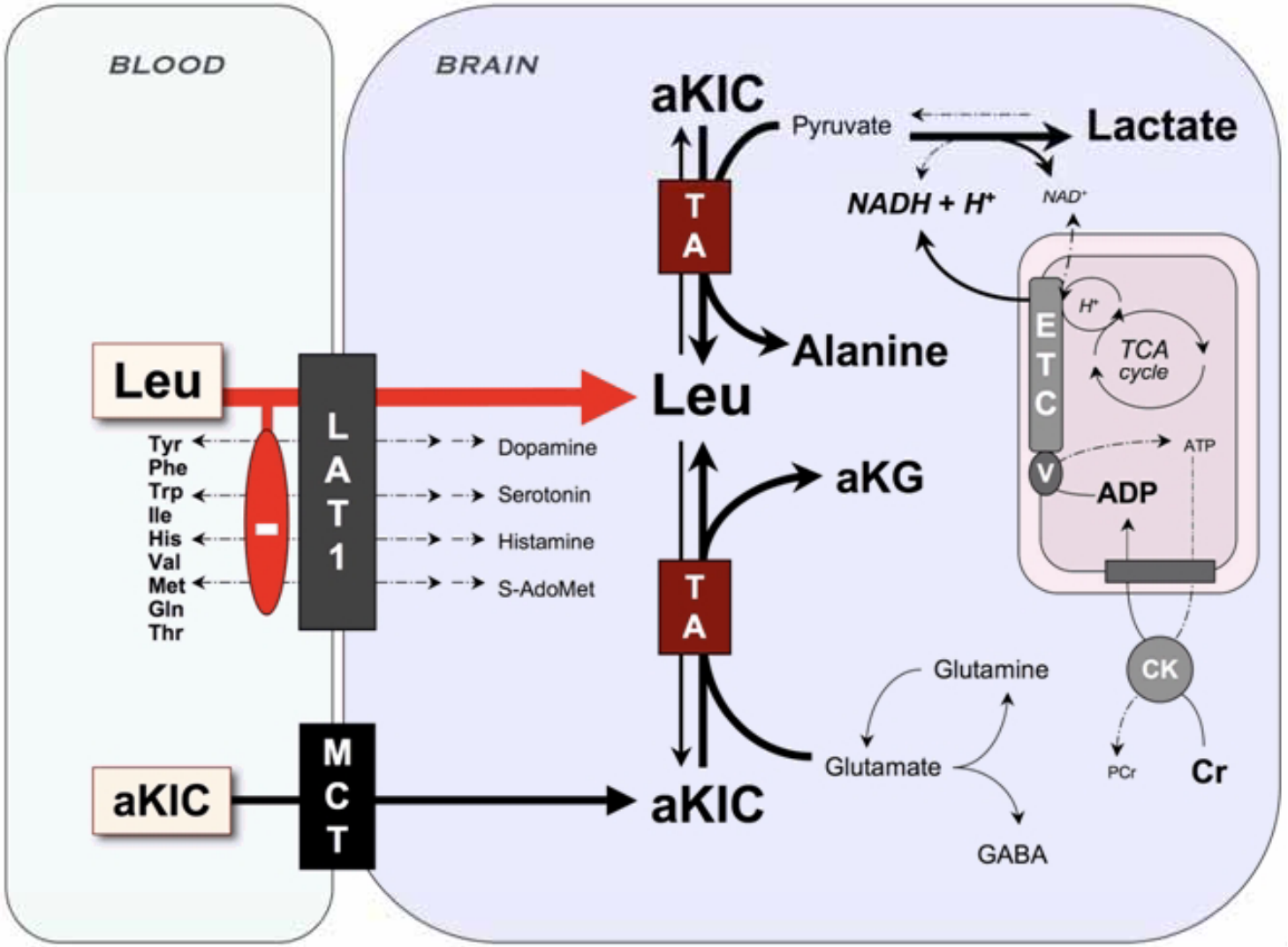


The enzyme phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine.

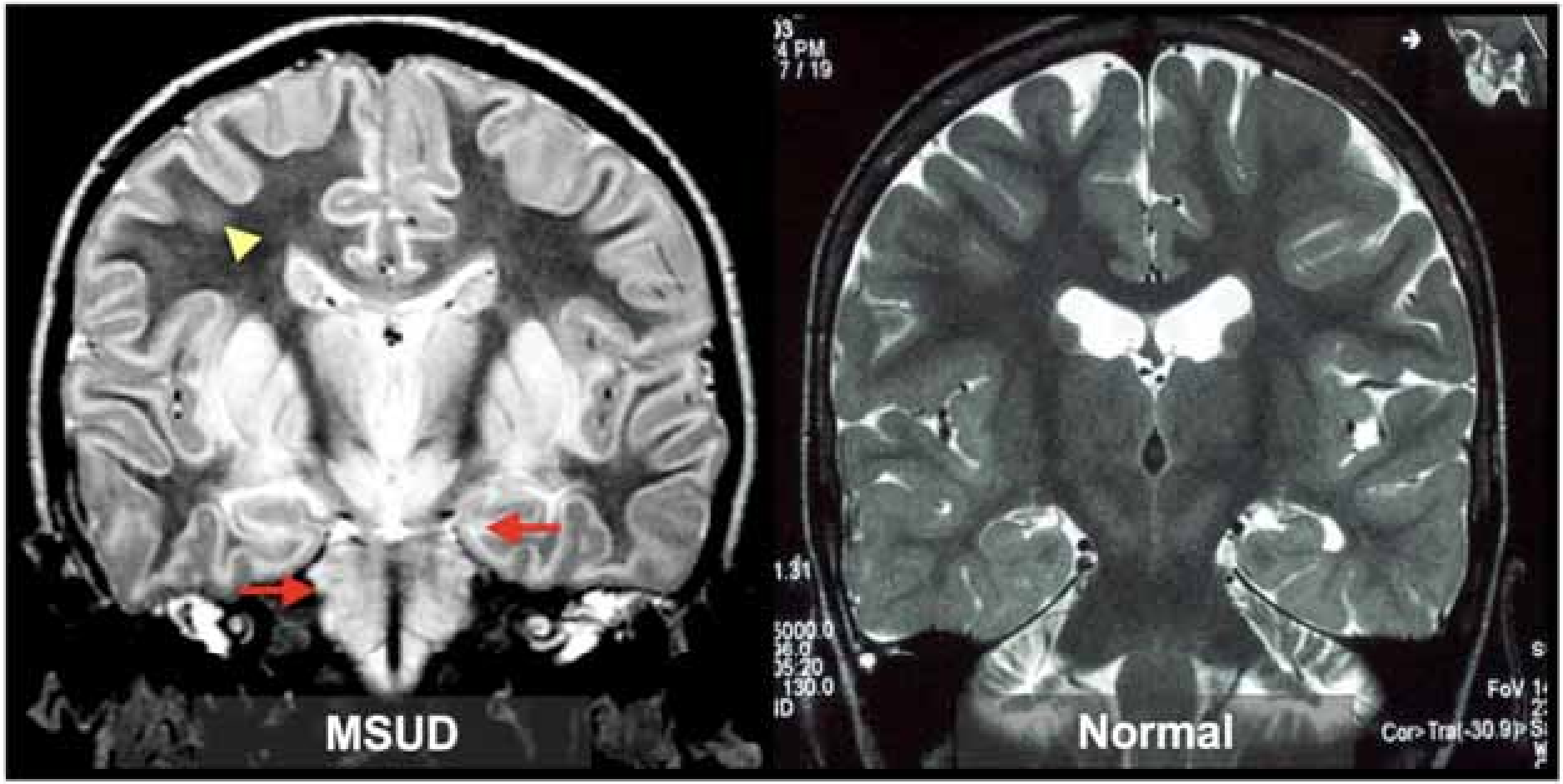
Maple syrup urine disease (AR)

- AR—BCKAD genes, chromosome 19
  - Mitochondrial branched-chain keto acid DH
    - Some thiamine-responsive forms
  - Maple syrup: isoleucine ketoadduct (ear/navel)
  - Untreated: severe encephalopathy (Guthrie patch!)
- Decompensation:
  - Surgical stress / intercurrent illness / fast
  - Ataxia, lethargy, coma, cerebral edema, apnea, opisthotonus
  - Pancreatitis risk

Maple Syrup Urine Disease



Maple Syrup Urine Disease



Maple Syrup Urine Disease

Anesthetic Considerations

- No prolonged fasting (pre-, intra- or postop)
  - Risks of hypoglycemia, ketoacidemia
    - Associated opisthotonus, focal dystonia may occur
    - 1/3 of daily dose dietary AA supplement just prior to surgery—post-operatively IV supplementation
- IV fluids with glucose, fat emulsion
  - Hypertonic glucose may ↑CO_2 and provoke NorEpi release
- Risk for cerebral edema if overhydrate
  - Especially in older patients
- Orogastric/throat packs for oral/GI blood
  - Excess protein load→metabolic failure

A UVA Colleague has written: