Porphyria

Porphyrias are a group of inborn errors of metabolism characterized by overproduction of porphyrins and their precursors; in humans heme is the most important porphyrin, essential to both hemoglobin and cytochromes (P450 isozymes are important for drug metabolism); neurologic involvement is most significant for anesthesia (CNS, peripheral NS and autonomic NS)

ANESTHETIC CONSIDERATIONS:

- Aspiration risk (bulbar dysfunction)
- CNS dysfunction
  - Altered LOC, seizures, coma
  - Cranial and peripheral neuropathies
  - Autonomic instability
- Neuromuscular weakness:
  - Respiratory insufficiency (due to neuromuscular weakness)
  - Bulbar dysfunction and risk of aspiration
- Chronic renal failure with severe volume depletion and electrolyte abnormalities
  - Hypokalemia, hyponatremia (SIADH)
- Avoidance of pharmacologic and physiologic triggers of acute porphyrias

ANESTHETIC GOALS:

- Adequate optimization
  - Avoid prolonged fast
- Avoid triggers:
  - Barbiturates, etomidate, steroids, ?lidocaine
  - Fasting, progesterone, estrogen, infection
  - Smoking, alcohol, marijuana, ecstasy, amphetamines, cocaine
- Be prepared to treat an acute crisis → fluids, glucose, hemin (panhematin), cimetidine

HISTORY

- History of illness and course of disease
  - Previous triggers
  - Previous anesthetic records
- Presence of Acute porphyries (can have life threatening neurovisceral sequelae):
  - acute intermittent porphyria (AIP)
  - variegate porphyria (VP)
  - hereditary coproporphyria (HCP)
- Cutaneous porphyrias (photosensitivity and chronic blistering skin lesions):
  - Porphyria cutanea tarda
  - Erythropoietic protoporphyria
  - Hepatoerythropoietic porphyria
  - Congenital erythropoietic porphyria
- Type: diagnosis is partly based upon 3 major complications
  - Neurovisceral complaints
  - Photosensitivity
  - Hemolytic anemia
- Symptoms and signs of AIP
  - CNS: mental symptoms, seizure, sensory loss, pain
  - CVS: tachycardia,
  - Resp: respiratory paralysis
  - GI: abdominal pain, vomiting, constipation, diarrhea

PHYSICAL

- **CNS** - neurological changes (i.e. skeletal muscle strength and cranial nerve function that may predict respiratory failure, requiring postoperative ventilation, and increased risk of aspiration
- **HEENT** - A/W may be difficult if bulbar symptoms present
- **CVS** - looking for hypertension and tachycardia
- **GI** - may have abdominal pain and a normal exam
- **DERM** - skin changes may be subtle (or obvious in acute state)

INVESTIGATIONS

- **Labs**
  - CBC (anemia may precipitate acute porphyria)
  - Electrolytes, glucose (hyponatremia, disorders of K^+ / Mg^{++} commonly observed)
  - BUN, Cr (chronic kidney disease in AIP)
- **Imaging**
  - ECG (chronic hypertension in AIP – LVH)
  - CXR / PFTs / ABG: (indicated if respiratory failure or aspiration a concern)

OPTIMIZATION

- Correction of Anemia
- Avoid prolonged fasting (carbohydrate loading in AIP)
- Cimetidine has been suggested as prophylaxis (inhibits ALA synthethase activity)

- Anxiolysis recommended
- Aspiration prophylaxis if bulbar dysfunction a concern
- Treatment overview:
    - General
        - Volume resuscitation is recommended
        - Beta blockers generally used for hypertension
        - Carbohydrate loading is the treatment of choice for acute porphyria
    - Specific
        - Hemin (supplements intracellular heme pool → suppresses ALA synthetase: may cause thrombophlebitis, renal failure & coagulopathy)
            - Heme arginate is alternative with better side effect profile
        - Somatostatin decreases ALA synthetase
        - Plasmapheresis

ANESTHETIC OPTIONS

- Use of regional is somewhat controversial given the potential for pre-existing peripheral neuropathy
    - May be preferred technique, document existing deficits
    - Caution with block extension in those with respiratory weakness, autonomic dysfunction
    - Some controversy with lidocaine use – it is porphyrinogenic in vitro, but safely used in vivo
    - Bupivacaine may be better choice
- With GA, must avoid triggering agents
    - Propofol appears to be induction agent of choice, though maintenance is controversial
    - Succinylcholine is safe
    - Rocuronium has limited information but is likely safe
    - Narcotics appear safe, as is nitrous (N_2O)
    - Limited information available for newer volatiles (though would expect desflurane to be safe given insolubility & limited metabolism)
    - Relatively long history of safety with isoflurane
    - Neostigmine / glycopyrrolate recommended for NMB reversal

ANESTHETIC SETUP

- **Drugs**
    - Avoid drugs listed below
- **Equipment**
    - Routine CAS
    - Temperature
    - Nerve Stimulator
    - Arterial line for acute porphyria (given autonomic dysfunction)
    - Acute attacks should have serial monitoring of urine porphyrinogens

MANAGEMENT OF ANESTHESIA

- **Induction**
    - Avoid triggering drugs
        - Propofol
            - Certainly safe as induction agent
            - Prolonged infusions can increase porphyrins, thus should probably avoid infusions
        - Ketamine
            - Probably safe and has been used in humans during remission
            - Does increase ALA synthetase therefore should only be used if clinically warranted
- **Maintenance**
    - Volatiles / N_2O
    - Neuromuscular blockers
        - Succinylcholine safe
        - Pancuronium has been listed as unsafe by some authors, however, the majority of NDMR (including pancuronium) are probably safe
        - Should probably avoid extended use of NDMR if possible
- **Emergence**
    - Opioids
    - Acetaminophen
    - NSAIDs (except ketorolac)

DISPOSITION & MONITORING

- HDU for monitoring

COMPLICATIONS

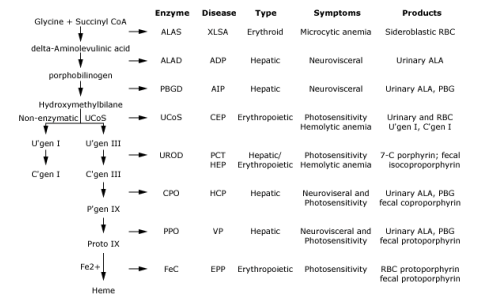
- Be prepared to treat acute attack:
    - Stop precipitant
    - Ensure adequate hydration
    - Carbohydrate load: D10W infusion
    - Hematin: 3-4 mg/kg IV over 20 minutes is the only treatment for an acute crisis (it is presumed that hematin supplements the intracellular pool of heme and suppresses ALA synthetase activity)
    - Pain may require treatment with opioids
    - Beta blockers safe for tachycardia and hypertension

- Seizures: regular anticonvulsants unsafe, use benzodiazepines
- Treat electrolyte disturbances aggressively
- Somatostatin decreases the rate of ALA synthetase formation and combined with plasmapheresis may reduce pain and induce remission

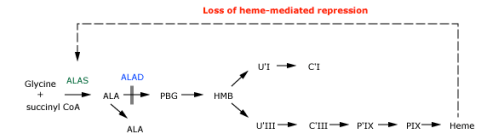
PATHOPHYSIOLOGY

- The hepatic isoform of the first enzyme in the heme pathway, ALA synthetase (ALAS), is subject to feedback inhibition by the final product
  - Thus, metabolic inhibition (d/t high levels of heme) along the pathway leads to reduced production of heme, and, in turn, depression of ALAS activity
- In porphyria there is an increased production of heme precursors in an effort to overcome the metabolic block, and contributes to the accumulation of intermediates prior to the deficient enzymatic step
  - This abnormality continues until sufficient heme synthesis is restored, or exogenous heme is administered as treatment
- Patients with acute hepatic porphyrias may not become symptomatic unless they are exposed to certain drugs, liver damage, hormonal changes during the menstrual cycle, stress, or starvation, which result in the induction of ALAS
  - Recognition and avoidance of such precipitating events is a key part of the treatment / prevention program for porphyria
- All of the heme intermediates are potentially toxic
  - Their overproduction causes the characteristic neurovisceral and / or photosensitizing symptoms
- Although the mechanism is unclear, the porphyrias associated with increased production of delta-aminolevulinic acid (ALA) and / or porphobilinogen (PBG) are associated with neurovisceral complaints
- Porphyrins cause photosensitization and skin damage through exposure to ultraviolet light, with subsequent production of tissue-damaging free radicals
- Solubility determines the excretion pattern of the metabolites
  - Water soluble precursors are excreted mainly in the urine (ALA, PBG, and uroporphyrin), protoporphyrin is excreted mainly in the feces, and coproporphyrin is excreted in both

Classification of the porphyrias



Enzyme defect in ALA dehydratase porphyria



Depiction of the enzymatic defect in 5-aminolevulinic acid (ALA) dehydratase porphyria (ADP). This disorder is characterized by a defect in the enzyme ALA dehydratase (ALAD), leading to the accumulation and excretion of ALA. The reduced production of heme also contributes via loss of heme-mediated repression of ALA synthase (ALAS), the enzyme that promotes the formation of ALA from glycine and succinyl CoA.

- Drugs (see Uptodate for Huge list)
  - Unsafe
    - Barbiturates
    - Etomidate
    - Diclofenac
    - ACE inhibitors
    - Ca channel blockers
    - Metoclopramide and benzodiazepines
    - Cephalosporins
    - Lidocaine?
      - In animals has precipitated attacks
      - Has been used for neuraxial in humans and for arrythmias IV (limited experience)
    - Steroids
  - Safe
    - Propofol
      - Certainly safe as induction agent
      - Prolonged infusions can increase porphyrins, thus should probably avoid infusions
    - Ketamine
      - Probably safe and has been used in humans
      - However, does increases ALA synthetase
      - Should only use if clinically warranted
    - Volatiles / N_2O

- Neuromuscular blockers
  - SCh safe
  - Pancuronium has been listed as unsafe by some authors, however, the majority of NDMR (including pancuronium) are probably safe
  - Should probably avoid extended use of NDMR if possible
- Opioids
- Acetaminophen
- NSAIDs

REFERENCES

- BMJ. Diagnosis and Management of Porphyrias. Volume 320(7250), 17 June 2000, pp 1647-1651
- Uptodate 14.3
- Stoelting, Co-Existing Disease p 455-460
- Barash, 4th Ed on CD
- Miller, 6th Ed p 1097-98