Managing Pruritus and Sleep Disorders Related to Liver Disease

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Objectives

- Understand the mechanisms for pruritus
- Review the treatments for pruritus in liver disease
- Understand liver issues that might relate to poor sleep
Pruritus

• Severe itching of the skin

• “In both [types of icterus]...the whole body is itchy...the bilous particles become prickly.”
  -Arataeus, the Cappadocian (circa 160 A.D.)

• Common symptom of liver disease with poor bile flow (cholestasis)

• Cholestatic liver diseases
  – Primary sclerosing cholangitis
  – Primary biliary cirrhosis
  – Cholestasis of pregnancy
  – Bile duct obstruction from tumors or gallstones
  – Hepatitis C
Causes of Pruritus

- Liver disease – cholestatic liver disease
- Skin diseases – dermatitis, psoriasis, urticaria
- Kidney disease – end-stage renal disease
- Blood disease – iron deficiency, lymphoma
- Endocrine diseases – diabetes, thyroid disease
- Infectious diseases – scabies, HIV, fungal
- Autoimmune disorders – scleroderma, Sjogren’s
- Neurologic disorders – multiple sclerosis, stroke
- Psychogenic disorders – depression, anorexia
Cholestatic Pruritus

• Occurs in 20-30% of patients with cholestatic liver disease
• Fluctuates in severity
• Generally worse at bedtime
• Potential to drive significant others crazy
Etiology of Cholestatic Pruritus

- Bile acids
- Endogenous opioids
- Lysophosphatidic acid and autotaxin
Function of Bile Acids

• Elimination of cholesterol from the body
• Elimination of bilirubin (metabolism of red blood cells)
• Absorption of fat soluble vitamins
• May have role in triglyceride and glucose metabolism and liver growth
Role of Bile Acids in Pruritus

• 1960’s demonstrated that bile acid binders relieved itching
  – Assumed retention of bile acids in the skin
• Poor correlation of bile acids in skin and itching
Role of Endogenous Opioids

• Noted that narcotic medications makes pruritus worse
• Agonist activity at the mu opioid receptor can cause pruritus in normal people
• Endogenous opioid levels are elevated in cholestatic liver disease
  – Improvement in pruritus with blocking opioid receptor
Lysophosphatidic acid (LPA)

- Autotaxin (ATX) required for angiogenesis and neuronal development
- ATX important in generation of LPA
- LPA is small, potent bioactive phospholipid with variety of effects in many cell types
  - Cytoskeletal (re)organization and cell migration
  - Cytokine production
  - Platelet activation
- Plays crucial role in neuropathic pain
  - Reprogramming of gene expression in different types of nerve fibers
Role of LPA in Cholestatic Pruritus

• Levels of LPA are markedly increased in serum of patients with cholestatic pruritus
  – Serum levels closely correlate with itch intensity
  – Intradermal injection induces scratch behavior in mice

ATX activity generates LPA

(A) ATX activity [nmol/min] vs. Itch intensity [VAS]

(B) Scratching activity [number of bouts / 15min]
Interaction of ATX/LPA and Bile Salts

- PBC patients with severe pruritus
- Nasobiliary drainage for 2-7 days leading to reduction in pruritus
- Interestingly lead to reduction in ATX activity
- Finding not due to reduction of ATX in bile
Future Novel Treatment Strategies

- ATX inhibitors
- LPA receptor blockers
Simple Treatments for Pruritus

• Skin moisturizers (especially in Denver!)
  – Dry skin can cause or exacerbate
• Avoid hot showers
• Avoid narcotics
• Cool environment
• Avoid stress
• Avoid physical interventions
  – Itch-scratch cycle
• Topical therapy
  – Sarna lotion
  – Hydrocortisone cream
  – Ice packs
  – Topical anesthetics
  – Antihistamines
First Line Therapy for Cholestatic Pruritus: Relieve Biliary Obstruction
Treatments of Cholestatic Pruritus

- Bile acid resin binders
  - Cholestyramine
  - Colestipol
- Ursodiol
  - Useful in intrahepatic cholestasis of pregnancy
- Rifampin
- Phenobarbital
- Opioid antagonists
  - Naloxone
  - Naltrexone
- Serotonin-receptor antagonists (sertroline)
- Plasmaphoresis/MARS
- Steroids
- UV light
Bile Acid Binders
Cholestryramine/Colestipol

• Non-absorbable resin binding bile acids
• Used to treat elevated cholesterol, bile acid diarrhea after cholecystectomy
• Initial dose 4 gms 1-2 times daily ➔ 3x/day
• Side effects:
  – Nausea, bloating, constipation
  – Binds other medications (digoxin, urso, warfarin, propranolol, thiazide diuretics)
  • Take 2-4 hours before/after other meds
Rifampin

• Anti-tuberculous drug
• Mechanism of action unclear
  – Competes with bile acids for hepatic uptake
  – Induce enzymes in liver promoting reduction of toxic bile acids
• Initial dose: 300 -600 mg/day
• Side effects: acute hepatitis so caution in advanced liver disease
• Drug interactions
Opioid antagonists

• Blocking opioid receptor – central action
• Doses:
  – Naloxone 0.4mg IV then 0.2mcg/kg/min x 24 hrs
  – Naltrexone 12.5-50 mg daily
  – Nalmefene 60-120 mg daily
• Can’t take with narcotics or history of chronic pain
AASLD Guidelines for Treating Pruritus

1. Bile acid sequestrants
2. Rifampin 150-300mg twice daily
3. Naltrexone 50 mg daily
4. Sertraline 75-100 mg daily

Liver transplantation is indication for severe, incapacitating and refractory pruritus
Sleep Disorders

"No wonder you have insomnia . . . lying there awake all night."
International Classification of Sleep Disorders

- Insomnia
  - Difficulty initiating or maintaining sleep
- Sleep related breathing disorders
  - Obstructive sleep apnea, hypoventilation
- Central disorders of hypersomnolence
  - Medications, stroke, heart failure, renal failure
- Circadian rhythm sleep-wake disorders
  - Shift work, jet lag, hepatic encephalopathy
- Parasomnias
  - Undesirable physical or emotional experiences during sleep
- Sleep related movement disorders
  - Restless leg syndrome
- Other sleep disorders
Sleep Disorders in Cirrhosis

- Sleep disorders common with cirrhosis
  - 2/3\(^{rd}\) report sleep-wake abnormalities
    - Disturbed night sleep
    - Delayed sleep
    - Excessive day-time sleepiness
  - 70% cirrhosis classified as “poor sleepers” using validated Pittsburg Sleep Quality Index
  - Often associated with hepatic encephalopathy (HE)
  - Half of patients do not have HE (undiagnosed?)

- Significant impact on quality of life and physiological well-being
Cirrhosis Associations with Sleep Disorders

- Higher prevalence of SD with more advanced CTP score
- Low albumin levels
  - Free forms of albumin-bound toxins may cross blood-brain barrier
- Patients with cirrhosis go to bed later, sleep later
- Animal models show derangements in sleep patterns
# Sleep Timing and Sleep Quality Screening Questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>What time do you usually go to bed?</td>
<td></td>
</tr>
<tr>
<td>What time do you usually start trying to sleep?</td>
<td></td>
</tr>
<tr>
<td>How long does it take you to fall asleep on average?</td>
<td></td>
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<tr>
<td>How many times do you usually wake up?</td>
<td></td>
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<tr>
<td>What time do you usually wake up <em>in the morning</em>?</td>
<td></td>
</tr>
<tr>
<td>What time do you usually get up?</td>
<td></td>
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</tbody>
</table>

**How would you rate your usual quality of sleep?**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Best sleep ever</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
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<td>8</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>Worst sleep ever</td>
</tr>
</tbody>
</table>
Comparison of STSQS Questionnaire with Pittsburg Sleep Quality Index

-Box plots showing the STSQS sleep quality scores for different groups.

- Healthy volunteers with PSQI total score ≤ 5 (n=14)
- Patients with cirrhosis with PSQI total score ≤ 5 (n=27)
- Healthy volunteers with PSQI total score > 5 (n=4)
- Patients with cirrhosis with PSQI total score > 5 (n=54)

Significant differences are indicated by p-values: p<0.01 and p<0.001.
Hepatic Encephalopathy

- Neuropsychiatric complication of cirrhosis
- Result of:
  - Portosystemic shunting
  - Liver insufficiency
- Failure to metabolize neurotoxic substances
  - Ammonia
Failure to metabolize ammonia

Toxins

Pathogenesis of Hepatic Encephalopathy

Ammonia shunting
Hepatic Encephalopathy is a Clinical Diagnosis

- Clinical history and exam are most important
- Ammonia levels are unreliable
  - Poor correlation with diagnosis or severity
- Measurement of ammonia levels are not necessary
- Clinical research tools
  - Number connection test
Poor Correlation of Ammonia Levels With Presence or Severity of Encephalopathy

Ong et al., Am J Med 2003; 114:188
Minimal Hepatic Encephalopathy

- Attention and cognitive deficits
- Visual-spatial perception impairment
- Defects in visual constructive ability
- Impaired driving ability
Treatment of Hepatic Encephalopathy

• Identify and treat precipitating and reversible factors:
  – Infection
  – GI bleeding
  – Renal failure
  – Sedatives
  – Constipation

• Lactulose – goal 3 bowel movements/day

• Rifaximin – non-absorbable antibiotic

• L-ornithine L-aspartate

• Zinc
Recommendations For Improved Sleep Hygiene

- Do not eat 3 hour prior to bed
- Unwind from day’s tensions 1 hour before bed
- Avoid screen time (TV, iPhone, computer) before bed
- Warm milk (tryptophan) or herbal tea
- Keep bedroom cool
- Soft sheets
- Bed is for sleep only!
  - Don’t fall asleep in 20 minutes get out of bed and read or do something relaxing
- Avoid naps during day (20-30 minutes early afternoon is okay)
- No alcohol
- No caffeine after noon
- Exercise daily (not in the evening)
END