NEONATAL CHOLESTASIS

張堯婷
CONTENTS

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NASPGHAN Definition

- Conjugated bilirubin concentration >1.0 mg/dL if the total serum bilirubin is <5.0 mg/dL

Or

- Conjugated bilirubin concentration >20 % of the total serum bilirubin if the total serum bilirubin is >5.0 mg/dL

(Moyer et al J PEDIATR GASTROENTEROL NUTR 2004;39:115)
IAP Definition

- Conjugated hyperbilirubinemia > 1.5-2 mg/dL in a newborn/infant with passage of high coloured urine with or without acholic stools.

(Consensus report on neonatal cholestasis syndrome, INDIAN PEDIATRICS 2000; 37: 845-851)
ETIOLOGIES
INTRAHEPATIC ETIOLOGIES

Hepatocellular causes
(Neonatal hepatitis)

- Idiopathic: INH
- Toxic
- Genetic/Chromosomal
- Infectious
- Metabolic
- Others

Bile duct injury

- Intrahepatic bile duct hypoplasia or paucity
INTRAHEPATIC ETIOLOGIES - INH

• IDIOPATHIC NEONATAL HEPATITIS
  ▪ Generally normal stools or clay stools with onset at one month-old
  ▪ Low birth weight
  ▪ Male predominance
  ▪ Familial cases (15-20%)
INTRAHEPATIC ETIOLOGIES - Toxic

- TPN-associated cholestasis

- Drug-induced cholestasis
  - Anticonvulsants
  - Antibiotics
  - Immunosuppressive Agents
  - Psychotropic Drugs
  - Drugs Against HIV
  - Acetaminophen
INTRAHEPATIC ETIOLOGIES - Infectious

- Bacterial sepsis
  - E. coli
  - Listeriosis
  - Staph. aureus
- TORCHES
- Echo virus
- Hepatitis B and C
INTRAHEPATIC ETIOLOGIES - Metabolic

- Disorders of Carbohydrate Metabolism
- Disorders of Amino Acid Metabolism
- Disorders of Lipid Metabolism
- Disorders of Bile Acid Metabolism
- Peroxisomal Disorders
- Endocrine Disorders
- Miscellaneous Metabolic Disorders
• Disorders of Carbohydrate Metabolism
  ▪ Galactosemia
  ▪ Fructosemia
  ▪ Glycogen Storage Disease Type IV

• Disorders of Amino Acid Metabolism
  ▪ Tyrosinemia
  ▪ Hypermethioninemia
INTRAHEPATIC ETIOLOGIES - Metabolic

- Disorders of Lipid Metabolism
  - Niemann-Pick disease
  - Gaucher disease
- Disorders of Bile Acid Metabolism
  - 3β-hydroxysteroid dehydrogenase/isomerase
  - Trihydroxycoprostanic acidemia
- Peroxisomal Disorders
  - Zellweger syndrome
INTRAHEPATIC ETIOLOGIES - Metabolic

- Endocrine Disorders
  - Hypothyroidism
  - Idiopathic hypopituitarism
- Miscellaneous Metabolic Disorders
  - Alpha-1-antitrypsin deficiency
  - Cystic fibrosis
  - Neonatal iron storage disease
EXTRAHEPATIC ETIOLOGIES

- Extrahepatic biliary atresia
- Choledochal cyst
- Bile duct stenosis
- Spontaneous perforation of the bile duct
- Cholelithiasis
- Inspissated bile/mucus plug
- Extrinsic compression of the bile duct
CLINICAL PRESENTATION AND DIAGNOSIS
CLINICAL PRESENTATION

- Jaundice
- Scleral icterus
- Hepatomegaly
- Clay stools
- Dark urine
- Other signs and symptoms depend on specific disease process
Jaundice, dark urine with or without acholic stools at 14 days of age
Urine bilirubin +, serum bilirubin (conjugated)
Give vitamin K 5 mg IM
Refer to a specialized center
LFT, administer vitamins
Assess general clinical condition

Sick*
- Urine for reducing sugars**
- Blood and urine cultures
- Malaria parasite
- TORCH serology
- Urinary succinylacetone
- Serum ferritin

Not Sick
Look at stool color X 3 days

Pale stools
(Urgency to investigate for biliary atresia)
- Ultrasonography
- Liver biopsy
- ± HIDA scan

Pigmented stools
(Ultrasonography
Liver biopsy)

Biliary atresia on liver biopsy or
Liver biopsy equivocal, no excretion on HIDA scan
Laparotomy and Perop choangiography ® Kasai

Hepatitis on liver biopsy with or without excretion on HIDA scan ® treat as Neonatal hepatitis
DIAGNOSIS - NASPGHAN

Jaundiced infant 2 to 8 weeks old

1. Is the patient acutely ill? Require urgent care?
   - Yes
     - Manage the acute illness
     - Consider urinary tract or other infection, glucosuria, tyrosinemia, hypopituitarism, fructosemia, iron storage disease, metabolic disorders, acute common duct obstruction, hemolysis

   - No
     - Is there direct hyperbilirubinemia?
       - Yes
         - Evaluate further (See AAP guideline)
       - No
         - Measure serum direct bilirubin
           - Normal
           - Indirect hyperbilirubinemia
             - Evaluate further (See AAP guideline)
           - Abnormal
             - Cholestatic Jaundice
               - History
               - Physical exam
               - Urinalysis
               - Urine culture
Evaluate further

Findings of specific disease?
Yes → 11
No → 13

Is the newborn screen positive for galactosemia or hypothyroidism?
Yes → 13
No → 12

Refer for further management

Does bilirubin normalize by 6 weeks of age?
Yes → 14
No → 15

No hyperbilirubinemia

Consult Pediatric GI
CBC, platelet count
Total and direct bilirubin, ALT, AST, alkaline phosphatase, glucose
Prothrombin time, albumin
α-1 antitrypsin
Urine reducing substances
Abdominal ultrasound

10 → 11
12 → 13
14 → 15
16
• Pi typing
• Further management

17

Yes

Low

α-1 antitrypsin?

18

No

Yes

Consider:
• Percutaneous liver biopsy
• Scintiscan
• Duodenal aspirate
• ERCP

20

Is there evidence of biliary obstruction?

21

Yes

• Consult Pediatric Surgery
• Operative cholangiogram

22

No

Medical evaluation:
• Infection
• Metabolic disorders
• Genetic disorders
• Other

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TREATMENT
TREATMENT - Medical Management

- Nutritional support
- Treatment of pruritus
- Choleretics and bile acid-binders
- Management of portal hypertension and its consequences
## Nutritional support

<table>
<thead>
<tr>
<th>IMPAIRMENT</th>
<th>MANAGEMENT (NASPGHAN)</th>
<th>MANAGEMENT IAP</th>
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<tbody>
<tr>
<td>Fat soluble vit malabsorption</td>
<td>10,000-15,000 IU/d AQUASOL-A</td>
<td>50,000 IU i.m –diagnosis 10,000 IU monthly</td>
</tr>
<tr>
<td>Vit A deficiency</td>
<td>50-400 IU/d; oral alfa tocopherol</td>
<td>50-200 mg/d orally</td>
</tr>
<tr>
<td>Vit E deficiency</td>
<td>5000 -8000IU/d of D2 3-5 mcg/kg/d of 25 HCC</td>
<td>30,000 IU i.m –diagnosis &amp; monthly</td>
</tr>
<tr>
<td>Vit K deficiency</td>
<td>2.5 -5.0 mg alternate day as water soluble derivative of menadione.</td>
<td>5 mg/d im x3 days,5 mg wkly. Perform PT monthly.</td>
</tr>
<tr>
<td>Microutrient deficiency</td>
<td>Ca, P, Zn supplementation</td>
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</tr>
<tr>
<td>Water soluble Vit def.</td>
<td>2 times RDA supplementation</td>
<td>2-5 times RDA supplementation</td>
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</table>
Treatment of pruritus

- Bile acid-binders: cholestyramine (4-8 g/day)
- Ursodeoxycholic acid (15-20 mg/kg/day)
- Phenobarbital (5mg/kg/day)
- Diphenhydramine (1-3 mg/kg/day)
- Phototherapy with UV/ Infrared rays x 3-10 min/day
Management of portal hypertension and its consequences

- Variceal bleeding
  - Blood products
  - Sclerotherapy
  - Balloon tamponade
  - Propranolol

- Ascites
  - Sodium restriction
  - Diuretics (spironolactone, furosemide)
  - Albumin
  - Paracentesis
KASAI PROCEDURE

- Roux-en-Y portoenterostomy

- Bile flow re-established in 80-90% if performed < 8 weeks-old.
- Bile flow re-established in less than 20% if performed > 12 weeks-old
LIVER TRANSPLANTATION

Indications:
• Decompensated liver disease (ascites and/or encephalopathy).
• Failed portoenterostomy.
  ▪ 1-year survival rate - 85-90%
  ▪ 5-8 year survival rate - 75-80%
  ▪ 1/3 to 1/2 patients are of Biliary Atresia
• Cost: In excess of 100,000 $
LONG TERM OUTCOME

• Biliary Atresia:
  ▪ Mean survival in untreated pts: 19 months
  ▪ 3-year survival: <10%

• Neonatal Hepatitis:
  ▪ >60% of pts with idiopathic NH recover completely without any specific therapy.
  ▪ >10% die acutely of bleeding manifestations or fulminant hepatic failure.
  ▪ 30% progress to liver cirrhosis and death.
- NeoReviews Vol.14 No.2 February 2013
- Canadian Family Physician • Le Médecin de famille canadien Vol 55: december • décembre 2009
THANKS FOR LISTENING

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