Patient 1 – Slide B

- Twin A: **27 4/7 wk** gestation; 1090 gm
- Maternal gestational DM, ITP - Rx IVIG
- Ventilatory support for 3 months
- Multiple episodes of sepsis
- **TPN** from Day 2 to 16, w trophic feeds; enteral intake adequate thereafter
• Bc 2.8 day 5, 1.7 at one month, 3.8 at 3 mo, with AST 84, ALT 59, AlkP 47, GGT 556

• Serial abd Ultrasound: hyperechoic liver, contracted GB; no duct dilatation in liver

• HIDA at 3mo: poor uptake, no excretion

• Stool color not mentioned in chart until now

• Liver biopsy: DOL 145
Patient 2 – Slide A

- Twin B – 31 3/7 gestation, 828 gm

- Hypoglycemia – no lactic acidosis but urinary organic acids suggested abnormal gluconeogenesis

- RDS >>> BPD; peripheral pulmonic stenosis

- Microcephaly – no CNS symptoms or signs

- Metaphyseal dysplasia

- Multiple infections

- Abd Ultrasound: ascites, contracted thick GB; no organ abnormalities
• TPN exclusively until Day 21; then feeding began

• On transfer at 90 days, anemia, thrombocytopenia; PT and PTT prolonged

• Bc 1.5, AST 82, ALT 101, AlkP 829, GGT 66

• HIDA: poor uptake but with excretion

• Liver biopsy – day 105
Biopsy Diagnosis of Biliary Atresia

- Bile duct proliferation with bile plugs and acute cholangitis
- Ductular proliferation at interface of expanded tracts, with bile plugs, PMN;s
- Portal edema and fibrosis, with mixed WBC infiltrate

- *Variable parenchymal cholestasis, giant cells, EMH --- non-specific*

Alternative Diagnoses in a First Biopsy

• 1. If early, maybe no duct proliferation
• 2. Obstruction from choledochal cyst, perforated duct, myofibroblastic tumor, other mass lesion
• 3. Obstruction due to “sludge” in association with parenteral nutrition, lack of oral intake
• 4. Cystic fibrosis
• 5. Alagille syndrome
• 6. Congenital Cytomegalovirus infection
• 7. Alpha 1-Antitrypsin deficiency
• 8. North American Indian cirrhosis (CIRH1A mutation)
• 9. PFIC 3 (high GGT) – MDR 3, ABCB4.
Patient 1
after biopsy
Liver Plate - Hilum
“collateral veins” = proximal Hepatic duct
Common hepatic duct remnant
Common bile duct – distal end
gall bladder

Cystic duct
Subsequent Course

• Patient 1 - post-Kasai

• Bc fell steadily from 6.5 to 1.0 on day 16 and remains Zero at 3 mo.

• However, GGT has climbed from 457 to 1197 in the same interval

• Infant had multiple infections – meningitis, possible cholangitis
Questions Raised

• 1. Differential diagnosis of conjugated bilirubinemia in **prematures**

• 2. Pathogenesis of **Acquired** Atresia

• 3. Prognosis for Patient 1

• 4. How long after TPN is stopped does jaundice persist, and why?

• 5. What is disease in patient 2?
Pathogenesis of Biliary Atresia

• 1. Is there a fetal-embryonal form and does it correspond to the minority “Syndromic” disease? (Developmental malformation theory)

• 2. Is there a molecular genetic basis?

• 3. Is it Inflammatory, or Immunologic, maybe with an Infectious origin?

• 4. Could it be Vascular?
References


- Davenport M. A challenge on the use of the words Embryonic and Perinatal in the context of biliary atresia. *Hepatol* 2005; 41:403 (with response from Bezerra and Sokol, 404)

- Gaudio E et al. Administration of r-VEGF-A prevents hepatic artery ligation induced bile duct damage in bile duct ligated rats. *Am J Physiol Gastrointest Liver Physiol* 2006; 291: G307


Prognosis

• 1. Is earlier porto-enterostomy beneficial?
• 2. Is PE after 60 days doomed to fail?
• 3. Does bile flow post- Kasai or Bc predict long-term outcome?
• 4. What other features influence rate of progression?
• 5. Are there interventions available short of transplantation?
References


“TPN”- related biliary disease

1. Severity and rate of progression worst with extreme prematurity

2. All portal tract features can be seen by 10 days (duct proliferation, bile plugs, PMN)

3. Hilar ducts may be inflamed by two weeks

4. Biliary cirrhosis (portal bridging) may be present by one month

5. Bc elevations may persist for weeks after oral intake begins

6. In term infants with Short gut, intestinal transplant can reverse hepatic dysfunction, maybe even degree of scarring
References


• Chen CY et al. UCDA therapy in very-low birth weight infants with TPN-associated cholestasis. *J Pediatr* 2004; 145: 317


Further Diagnostic study of Patient 2

- Normal karyotype
- Normal plasma amino acids
- No urinary succinyl acetone
- Normal NMR spectroscopy of basal ganglia
- Normal Transferrin isoelectric focusing,
- Niemann-Pick A, B, C excluded.
Muscle Biopsy – 4 months

- **Morphology**: marked fiber size and shape variation; excess glycogen and lipid; Z band streaming
- **ETC activity reduced** in all complexes but not to diagnostic levels
- **No Mutation** in *POLG1, DGK, MPV 17, TK2* (1st 3 are associated with mtDNA depletion syndrome and Hepatic failure)
Outcome for Patient 2

- Died 2 months after biopsy with ischemic necrosis of small bowel
- Biliary Cirrhosis
- Neuronal migration disorder with cerebral heterotopias, microdysgenesis

- Etiology undetermined .....but, identical (monochorionic) twin is unaffected!
References – patient 2

• Ducluzeau, P.-H.; Depletion of mitochondrial DNA associated with infantile cholestasis and progressive liver fibrosis. J. Hepat. 30: 149-155, 1999

• Ferrari, G.; Infantile hepatocerebral syndromes associated with mutations in the mitochondrial DNA polymerase-gamma A. Brain 128: 723-731, 2005
