TEACHING FILE

GRAND ROUNDS

Ira Shah

GALACTOSEMIA

Case: A 3½ months old boy born of non-consanguineous marriage presented with abdominal distension for 8 days, jaundice and ecchymoses over trunk for 1 day. There was no clay coloured stools or fever. He was a full term delivered child with birth weight of 3 kg and no antenatal or post natal complications. He was immunized till date and was on breast feeds. He had achieved social smile and partial head holding. On examination, height was 67 cms, weight was 5.6 kg, vital parameters were normal. He had jaundice, hepatosplenomegaly, ascitis and ecchymotic patch over trunk. Other systems were normal. There were no cataracts. Investigations showed hemoglobin of 10.7 gm/dl, WBC of 7100/cumm, platelets of 1,64,000/cumm, bilirubin of 12.3 mg/dl (direct bilirubin of 5.3 mg/dl), SGOT of 121 IU/L, SGPT of 36 IU/L, alkaline phosphatase of 1785 IU/L, GGTP of 186 IU/L, total proteins of 5.8 gm/dl, albumin of 3.0 gm/dl, prothrombin time and partial thromboplastin time of more than 2 mins. Venous blood gas showed pH of 7.468 and bicarbonate of 9.4 mmol/L. Urine reducing substance was positive and urine organic acids showed increased glycine, serine, threonine, galactose, galactitol, galactonate. HIDA showed excretion of tracer in the intestines and ultrasound abdomen was normal. Galactose-1 – phosphate uridyl transferase levels were 2.8 units/gm Hb (Normal range = 10-45 units/gm Hb), which were again repeated and found to be 2.9 units/gm Hb. Patient was treated with galactose free diet and breast feeds were stopped. In view of ascitic fluid showing 500 cells/cumm (2 percent polymorphs, 98 percent lymphocytes) and proteins of 2.5 gm/dl, patient was treated with IV antibiotics for 10 days. On follow up at 6 months of age, patient weighted 7 kg, had normal milestones, bilirubin was 0.5 mg/dl, SGOT was 50 IU/L, SGPT was 35 IU/L. However the child had developed portal hypertension.

What is the long term outcome in patients with galactosemia?

Expert's opinion: Galactosemia is the most common carbohydrate metabolism disorder which is inherited in an autosomal recessive manner and can cause life-threatening illness during the newborn period. There is inability to metabolize the sugar galactose properly. Infants affected by galactosemia typically present with lethargy, vomiting, diarrhea, failure to thrive, hepatomegaly with hepatic dysfunction and jaundice. There may be bleeding from coagulopathy. Cataracts may sometimes be seen as early as the first few days of life. These patients are prone to E.coli sepsis. Ascites may also be seen in early infancy. The only treatment for classic galactosemia is eliminating lactose and galactose from the diet. This is usually accomplished by switching the baby from drinking breast milk or a milk-based formula to drinking a low galactose formula, such as soy or elemental formula. Cataracts usually self-resolve following dietary galactose restriction. Rarely surgery may be required to remove the cataracts. Even with an early diagnosis and a restricted diet, however, some individuals with galactosemia experience long-term complications such as speech difficulties, learning disabilities, neurological impairment (e.g. tremors, etc.), and ovarian failure. (1).

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RIFAMPICIN INDUCED HEPATITIS

Case: A 2½ years old boy had fever for 6-7 days for which Mantoux test was done which was 10 x 15 mm. Chest X-Ray was suggestive of primary complex. He was started on 3 drugs anti TB treatment (ATT) consisting of isoniazid (5 mg/kg/day) (H), rifampicin (R) (10 mg/kg/day) and ethambutol (E) (15mg/kg/day) by his local physician. However after 6 weeks the child had asymptomatic elevated SGPT and HR were stopped and child was shifted to ethambutol (E) and ofloxacin (Ofx). He was subsequently referred for further management in May 2008. His serial SGPT and ATT are depicted in Table 1. On reintroduction of rifampicin again he had elevated liver enzymes following which he completed ATT with HE and treatment was stopped in September 2008.

	March 08	May 08	June 08	July 08	July 08	Aug 08
SGPT	-	690	19	40	157	39
Isoniazid	5 mg/kg	Stopped	5 mg/kg	5 mg/kg	Stopped	5 mg/kg
Rifampicin	10 mg/kg	Stopped	Not given	5 mg/kg	Stopped	Not given
Ofloxacin	-	Started	Continued	Continued	Continued	Stopped
Ethambutol	15 mg/kg	Continued	Continued	Continued	Continued	Continued

How does ATT cause hepatotoxicity?

Expert's opinion: The single biggest problem in the treatment of tuberculosis (TB) is drug induced liver dysfunction, which has a mortality of upto 13 percent. Pyrazinamide (Z), isoniazid (H) and rifampicin (R) are hepatotoxic drugs in decreasing toxicity. (1)

Isoniazid causes hepatitis due to the formation of

hydrazines. They are formed by the action of P450 on acetyl hydrazine, a product of isoniazid metabolism in the liver. The hydrazines get covalently bound to liver proteins thus damaging the cells. Higher plasma levels of isoniazid do not increase the risk of hepatitis. (2)
Rifampicin induces P450 enzymes and therefore increases the risk of hepatotoxicity when given with isoniazid. Hepatitis due to rifampicin alone occurs in 1 percent or less of patients. It occasionally causes dose-dependent interference with bilirubin uptake, resulting in subclinical, unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. This may be transient and occur early in treatment or in some individuals with pre-existing liver disease. Hepatocellular injury appears to be rare. (2) Thus hepatitis as a presentation of rifampicin toxicity is rare and usually presents as jaundice.
PZA may induce both dose-dependent and idiosyncratic hepatotoxicity. PZA may induce hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis in a limited number of cases. It is hydrolyzed by a microsomal deaminase to the active metabolite, pyrazinoic acid, which is then hydroxylated by xanthine oxidase to 5-hydroxypyrazoinoic acid. These are eliminated renally. (2)

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BILIARY ATRESIA WITH CONGENITAL ANOMALIES

Case: A 1½ month old girl born of non consanguineous marriage presented with jaundice and clay colored stools since birth. On examination, she had cleft lip and palate with jaundice and hepatomegaly. Investigations are depicted in Table 1. Child underwent portoenterostomy after 1 week. On table, it was noted that child had atretic gall bladder with malrotation with Meckel's diverticulum and megaureter. A karyotype was sent but subsequently on discharge, patient was lost to follow up.

	Patient 1
Billirubin (mg/dl)	15.6
Direct (mg/dl)	9.4
SGOT (IU/L)	344
SGPT (IU/L)	218
Total proteins (gm/dl)	6.1
Albumin (gm/dl)	3.2
USG Abdomen	Hepatomegally, No gall bladder seen
Echocardiography	Mild right pulmonary artery stenosis
HIDA	Good extraction, no excretion of tracer
TORCH	Toxoplasma, CMV, Rubella IgG positive

What are the anatomical malformations associated with biliary atresia?

Expert Opinion : Biliary atresia is characterized by obliteration or discontinuity of the extra hepatic biliary system, resulting in obstruction to bile flow. There are 3 types of biliary atresia:

Type 1: Atresia restricted to common bile duct

Type 2: Atresia of the common hepatic duct

Type 3: Atresia of the right and left hepatic duct

Patients with biliary atresia generally pass acholic stools with onset at about 2 weeks of life. They are average birth weight. They have firm hepatomegaly. (1) There is a female predominance. They may have associated polysplenia syndrome, heterotaxy, and reverse rotation of intestine, in isolation or in various combinations and intra-abdominal vascular anomalies. (2) In addition, malrotation, Meckel's diverticulum and jejunal atresia have also been reported with biliary atresia. (3) Biliary atreisa in association with other congenital structural anomalies may have a poor prognosis. These patients have poor bile secretion after hepatic portoenterostomy. (4)

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From: Medical Sciences Department, Pediatric Oncall, Mumbai.

Address for Correspondence Dr Ira Shah, 1/B Saguna, 271, B St Francis Road, Vile Parle (W), Mumbai 400056.