A 15-month-old male child presented with history of yellowish discoloration of the body and yellow-colored urine of 1-month duration. He had history of passing pale stool and abdominal distension for the last 20 days, fever for the last 2 days, and altered sensorium for 1 day. There was no history of GI bleed, cough, dyspnea, urinary incontinence, or blood transfusion. Since the age of nine months, the child failed to gain weight; he received some medication for this, but the details are not known.

The child was born to a non-consanguineous marriage. The antenatal history was uneventful. The child was delivered at full-term by normal vaginal delivery. The immediate post-partum period was normal. He was top-fed with milk boiled in copper vessel, which was also used for boiling milk for the family. There was global delay in the developmental history of the child and he could sit up without support only at 12 months of age and able to speak only monosyllables. There was no history of similar illness in the family.

On examination, he weighed 7500 grams, which was only 68% of the expected weight-for-age. His height was 74 cm (92% of expected). Head circumference was 41 cm (<2 standard deviation). Heart rate was 108 per minute, respiratory rate 46 per minute. He was pale, moderately icteric, and had pedal edema. All peripheral pulses were palpable. Capillary filling time was 2 seconds. There was no lymphadenopathy or clubbing.

He had distended abdomen. Liver was palpable 4 cm below the xiphisternum (span 8 cm), firm, with sharp leafy margin. He also had a palpable gall bladder. Spleen was palpable 4 cm below the left costal margin. There was shifting dullness. The cardiovascular, respiratory and central nervous systems were normal.

The clinical impression was chronic liver disease with decompensation, ascites and grade 1 hepatic encephalopathy.

Investigations showed anemia (hemoglobin 4.0-8.4 g/dL, suggestive of iron-deficiency anemia with occasional schistocytes), leukocytosis (23,000-54,400 per cumb, with neutrophilic predominance), normal platelet count, and elevated ESR (40-62 in 1st hour). Coagulogram was de-ranged, with elevated APTT and INR 4.9.

Blood sugar 100 to 150 mg/dL. Blood culture sterile. Venous blood gas: pH 7.37; pO2, 45 mmHg; pCO2, 43 mmHg; HCO3, 25 mmHg; base deficiency -0.6; SPO2, 80%. Ascitic fluid examination: low protein and sugar; no WBC; sterile culture.

Chest X-ray showed multiple bilateral parenchymal fluffy shadows; the heart appeared to be enlarged. Abdomen showed hepatomegaly.

Discussion

The differential diagnosis that could be considered are as follows:

**Indian childhood cirrhosis**

Unpublished data of 80 patients admitted in our Pediatric Gastroenterology unit (1.6% of the total number of indoor patients) from January 1995 to December 2004 showed the following: i) age range from 8 months to 3 years with male dominance (5.2:1); ii) insidious onset of disease in 72.5% and acute presentation in 27.5%; iii) all children were characteristically very irritable; iv) history of exposure to copper vessel was documented in 96%; v) at presentation, decompensated liver disease was seen in 70% and 6.3% had palpable gall bladder; vi) ascites was present in 56%, 27% had spontaneous bacterial peritonitis; and vii) esophageal varices were present on endoscopy in 40% of patients. Seventeen died in hospital; 14 patients are on d-penicillamine therapy till date. Similar features were reported in earlier studies.1-4 Children who had jaundice, ascites and palpable gall bladder at presentation had shorter survival.

Rapidly progressive disease, palpable gall bladder, and evidence of intravascular hemolysis favor a diagnosis of Indian childhood cirrhosis in this child. Developmental delay has not been described in such children.

**Glycogen storage disorder Type IV**

The age of presentation, progressive liver disease, portal hypertension and developmental delay could also suggest a diagnosis of type IV glycogen storage disorder. But cholestatic jaundice and intravascular hemolysis would be odd features. These children gradually develop neuromuscular weakness with severe hypotonia, muscle wasting and neurodegenerative disorder. Death is usually in the neonatal period.
Absence of these characteristic features makes this diagnosis unlikely.

**Veno-occlusive disease**

These patients would have history of exposure to herbal medication, toxin or drugs. The condition may also be seen following bone-marrow transplantation. Onset of this disease is usually sudden and associated with abdominal pain and ascites. This child did not have such history. Besides, presence of developmental delay, gradual onset of the disease with intravascular hemolysis, and cholestatic jaundice would not favor the diagnosis. Up to 20% of patients would die in the acute phase, 30% develop cirrhosis, portal hypertension and ascites, and 50% recover in 4 to 6 weeks’ time.

**Autoimmune hepatitis type 2**

The features supporting such a diagnosis in this child would be i) age, ii) presence of cholestatic jaundice, iii) hypergammaglobulinemia, iv) rapid downhill course, and v) intravascular hemolysis. Dark urine and pale stool could be seen in more than 70% of patients. Unexplained pain in the right upper quadrant is seen in 48% of cases, 30% of whom would have generalized myalgia, diarrhea and anorexia. The condition is seen more frequently in female children. There is no known association with developmental anomaly or growth retardation.

**Congenital hepatic fibrosis – cholangitic form**

Onset of this disease is in childhood. These patients presents with firm enlarged liver with portal hypertension. There could be associated cholestatic jaundice. Occasionally there is cholangitis with fever. All these clinical features were observed in this child. However, developmental delay, encephalopathy, intravascular hemolysis and coagulopathy are not usually seen in congenital hepatic fibrosis.

**Budd-Chiari syndrome**

These patients could present with acute or chronic disease. In the acute disease, patients complain of severe abdominal pain associated with vomiting. There could be mild jaundice, marked hepatomegaly, and massive ascites. In chronic cases, there is massive ascites, with tender and enlarged liver. These patients could bleed from esophageal or fundal varices and dilated veins over the anterioal abdominal wall. The points favoring this diagnosis in this child include presence of firm and enlarged liver with rapid clinical deterioration. But developmental delay, failure to thrive, and intravascular hemolysis make this possibility unlikely.

**Final clinical diagnosis**

Indian childhood cirrhosis with portal hypertension, coagulopathy, encephalopathy, intravascular hemolysis and intracranial bleed.

**Pathology protocol**

A partial autopsy was performed. The child was noted to be icteric. Peritoneal cavity yielded 600 mL of straw-colored fluid, and 80 mL of similar fluid was present in the pericardial cavity.

**Liver** weighed 325 grams (normal weight for age ~300 g). Capsular aspect was smooth and bile stained. Liver felt firm and was difficult to cut through. The cut surfaces were deeply bile stained. At places, liver parenchyma appeared nodular. Biliary tree and hepatic veins were normal. Portal system showed marked dilatation. Microscopically, there was diffuse effacement of the architecture. At places, hepatocytes showed ill-formed micronodules. Portal tracts were expanded with variable degree of bile duct proliferation and mixed inflammation (Fig 1). Inflammatory cells including neutrophils surrounded hepatocytic necrotic foci (satellitosis) (Fig 2). Hepatocytes showed marked cytoplasmic eosinophilia and clumping resembling Mallory hyaline (Fig 2). They also showed extensive intracytoplasmic and intracanalicular cholestasis (Fig 1). Marked and diffuse pericellular fibrosis was present around individual and small groups of hepatocytes. Shikata orcein stain demonstrated coarse cola-colored granules of copper-binding proteins within the hepatocytes (Fig 3). On Masson’s trichrome stained sections, the pericellular fibrosis showed green collagen fibers, and the Mallory hyaline appeared as deep red cytoplasmic tangles and coarse granules (Fig 4). Immunohistochemistry for hepatitis B surface and core antigens was negative.

![Fig 1: Microphotograph showing part of portal tract with bile duct proliferation and inflammatory cell infiltration and one large intraductal bile plug. Hepatocytes have fuzzy cellular outline, cytoplasmic granularity and clumping with intralobular inflammation (H&E, 150X)](image-url)
Spleen was weighed 40 grams (normal weight ~24 g). The capsule and parenchyma had no gross abnormality. Microscopically, there was depletion of white pulp and expansion of red pulp with capillarization of the sinusoids.

Esophagus and stomach appeared normal on gross examination. Representative sections showed dilated thin-walled blood vessels in the submucosa. Gastric mucosa had many small blood vessels in the lamina propria.

Lungs together weighed 183 grams, which is overweight. Pleural surface was dull, with multiple hemorrhagic areas of few millimeters size becoming confluent at places. Microscopy revealed intra-alveolar fresh hemorrhages with pulmonary edema.

The other organs were normal.

Final autopsy diagnosis
1. Indian childhood cirrhosis
2. Portal hypertension
3. Pulmonary edema and fresh hemorrhages

Discussion
There has been mark reduction in the incidence of this disease except in northern India. We continue to see the disease at our institute. This disparity could be due to a true geographic or regional variation, probably with a genetically predisposed ethnic group here. The practice of boiling milk in copper-containing utensils (a prime suspect as etiology) continues in northern India. We may also postulate the presence of some unknown or infective agent or contaminant in the cow’s milk or in the environment. The more frequent use of biopsy in children when indicated increases detection, and autopsy and discussion of cases at our center increases awareness of the continued existence of the condition and the ability to recognize atypical histological features.

References