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Direct Hyperbilirubinemia of Infancy

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ABSTRACT Direct hyperbilirubinemia of infancy is a commonly encountered disease in pediatric practice. The disease can be due to various causes including giant cell hepatitis, galactosemia, hereditary fructose intolerance, cystic fibrosis, infection (viral, bacterial), hereditary tyrosinemia, intra-hepatic biliary atresia and extrahepatic biliary atresia. In this article, the current knowledge on the subject is reviewed, the various causes are discussed, and a systematic approach using the relevant investigations including nuclear scanning and percutaneous liver biopsy, is formulated.

KEY WORDS: conjugated hyperbilirubinemia, Jaundice

Direct hyperbilirubinemia (i.e. direct bilirubin ≥ 1.5 mg/100 ml) constitutes a common difficult problem in pediatric practice, which can be due to the following causes :

1. Giant Cell Hepatitis (GCH)

Also called idiopathic neonatal hepatitis. It constitutes 35-40% of all cases of direct hyperbilirubinemia of infancy (DHOI). It usually occurs in males more frequently than in females, with a male/female ratio of 2:1. Some cases are transmitted as an autosomal recessive disease. GCH has a higher incidence among premature infants. Jaundice appears in the first week of life in 80% of the GCH cases, while it may be delayed up to the third month of life in the remaining cases. Other findings include dark urine, mild anemia, vomiting and poor feeding. There is intermittent loss of pigment in the stool. Hepatomegaly is the rule and splenomegaly occurs in 50% of the cases[1]. Laboratory findings include (a) raised direct bilirubin, transaminase and alkaline phosphatase, (b) normal albumin and gamma-globulin, (c) prothrombin time might be prolonged[2], (d) liver biopsy reveals giant cells containing bile in the centrilobular zones[3].

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Such patients require no therapy, and 75% recover by the end of their first year of life, while the remaining patients progress to cirrhosis[4,5].

2. *Galactosemia*

Galactosemia is an autosomal recessive disease caused by deficiency of galactose-1-p-uridyl transferase[6]. Vomiting, diarrhea, failure to thrive and DHI can occur. Patients may also develop hepatomegaly and ascites. Laboratory investigations include: (a) galactose in urine, (b) enzyme assay in RBCs[7], (c) liver biopsy, revealing pseudoacinar formation of hepatocytes with scar tissue formation.

Exclusion of galactose from the diet of the newborn is dramatically effective; signs of hepatomegaly disappear, even if advanced, scarring and ascites clear within a few days. Cataract formation is arrested or reversed[8].

3. *Hereditary Fructose Intolerance (HFI)*

Hereditary fructose intolerance is an autosomal recessive disease due to deficiency of fructose-1p-aldolase or fructose 1,6 diphosphatase. Infants develop vomiting, diarrhea, hypoglycemia, seizures and cholestatic jaundice upon introduction of sucrose and fructose into the diet. Hepatomegaly, ascites, liver cirrhosis and liver failure may also be present. Laboratory findings include: (a) proteinuria, (b) fructosuria, (c) hypoglycemia, (d) liver biopsy showing steatosis, edema, parenchymal pseudoacinar formation, cholestasis and extensive periportal fibrosis[9].

4. *Neonatal Hepatitis (with cortisol deficiency)*

This disease affects infants with congenital adrenal hyperplasia. It is diagnosed by the finding of low serum cortisol[10].

5. *Cystic Fibrosis*

Cystic fibrosis is an autosomal recessive disease, with an incidence of 1/2000. It involves the hepato-biliary tract in 30% of patients with focal biliary cirrhosis[5]. It presents during the neonatal period with DHI and hepatomegaly. These patients might eventually progress to portal hypertension and GI hemorrhage. Standard sweat test confirms the definite diagnosis.

6. *Hereditary Tyrosinemia*

This is an autosomal recessive disease due to the deficiency of the enzyme para-hydro-phenylpyruvic acid. It occurs in two forms, acute and chronic. It this disease, tyrosine and methionamine are elevated in the serum. The disease is treated by a diet low in phenylalanine and tyrosine[11].

7. *Infections*

These includes:

(a) Hepatitis B virus

Whereby infants develop Hepatitis B surface antigens at 2-3 months of age and continue to be positive for years after. Liver biopsy reveals transaminase deficiency with mild inflammatory changes in the portal zones in a small number of infants[12].

(b) Cytomegalo-inclusion virus

For which the diagnosis can be made by urinary cultures and demonstration of rising titres of specific IgG and IgM antibodies[13].

(c) Herpes simplex, Coxsackie B virus, Echovirus 14/19

These are usually fatal, if involving the liver and liver biopsy reveals massive necrosis[14].

(d) Rubella

Hepatic histology reveals periportal fibrosis, cholestasis, focal necrosis which subside[15].

(e) Congenital syphilis

This is a rare cause of DHI; liver biopsy shows interlobular fibrosis with pericentral mononuclear infiltrates[16].

(f) Congenital toxoplasmosis

This affects the liver mildly. Liver biopsy reveals non-specific periportal inflammation and the presence of histiocytes filled with toxoplasma[17].

8. Other Hepatocellular Causes

Such as α-1-antitrypsin deficiency, Wolman disease, glycogen storage disease, total parenteral nutrition, ...etc.

9. Intrahepatic Biliary Atresia (Paucity of interlobular ducts)

This is characterized by a diminished number of interlobular bile ducts and, in some patients, by a diminished number of portal zones[18]. In addition, this particular category of intrahepatic cholestasis may be associated with physical and visceral abnormalities, which allow a separation into two distinct subgroups:

(a) Syndromic type (Watson Alagille Syndrome)

In this disease, patients present with characteristic facial features; the forehead is prominent, just as the nasal bridge. The eyes are deep-set and hypertelorism is commonly found. The chin is small and slightly pointed, at least in early life, and may project forward. Physical examination reveals an enlarged, firm liver. Splenomegaly is absent in most cases. Cardiac murmurs can frequently be found and are consistent with central or peripheral pulmonary stenosis, ASD, coarctation, or tetralogy of Fallot. The fingers may be short and the thumbs are broad. Incomplete fusion of the vertebral bodies or anterior arch may be present. There may be renal abnormalities and neurologic features, *e.g.* areflexia, ataxia, and ophthalmoloplegia. Laboratory findings include: (1) mild elevation of serum bilirubin (2-8 mg/100 ml), which is direct in more than half of the cases, (2) alkaline phosphatase, and gamma-glutaryl transferase are greatly elevated, so is the cholesterol level, (3) serum bile acids are always elevated, (4) slightly elevated transaminase with normal coagulation profile, (5) liver biopsy shows steatosis, mild giant cell transformation and pseudoglandular arrangement, portal zones are fewer in number than normal[19].

(b) Non-syndromic Intrahepatic biliary atresia

In this disease, infants show the usual features of cholestasis, the latter may be sufficiently severe to cause confusion with possible extrahepatic causes, when the results of chemical and biochemical studies are considered. However, liver biopsy is

discriminating and shows features consistent with intrahepatic cholestasis, *e.g.* lobular disarray, giant cell transformation and portal inflammation. Portal interlobular bile ducts may be sparse, collapsed or difficult to identify due to surrounding edema and the inflammatory reaction[20]. Pruritis, xanthomas, thickened skin on hands and feet, short stature and developmental delay are typical consequences. The long-term prognosis is not favorable, even with the use of choleretics, vitamins and nutritional support. Biliary cirrhosis and liver failure usually occur before adolescence[21].

10. Extrahepatic Biliary Atresia

This disease occurs in 1/8,000-1/14,000 live births. The incidence increases in orientals with a female/male ratio of 2:1. Extrahepatic biliary atresia can be immediately suspected if a work-up reveals the presence of cardiovascular anomalies with malrotation of the bowel or abdominal hilerotoxia, levocardia, ...etc. These findings suggest the polysplenic syndrome, the only abnormality most consistently associated with biliary atresia[22,23].

Usually, such infants are delivered at full term and jaundice appears 2-3 weeks after delivery. Dark urine can alter the color of the diaper, a problem which can be reported by the mother. Not infrequently, the stools are somewhat pale, yellow, tan or buff-colored, presumably because the shed bilirubin-laden intestinal mucosa cells are present in the stool[23]. However, once they become acholic, little variation in color is observed subsequently. Unless the pediatrician delays the diagnosis, the infant seldom looks very ill, however some degree of failure to thrive can be detected. Jaundice may present more green rather than yellow. The patient might develop finger clubbing or xanthoma. The liver is typically enlarged and generally quite firm or hard. The spleen is seldom palpable in the early stage, since portal hypertension takes time to develop in this disease. Later signs of Vitamin D deficiency appear. Histopathologically, the liver biopsy will show periportal fibrosis and ductile proliferation[24].

Clinical and Laboratory Approach

1. Clinical Approach

With regards to jaundice, the age of its onset is of great importance. Jaundice in galactosemia appears in the early neonatal period. On the other hand, jaundice in hereditary fructose intolerance appears in approximately the fourth month of life with the introduction of food containing sucrose. A history of jaundice in the mother prior to or during pregnancy suggests the possibility of transmission of hepatitis B infection to the infant.

The family history is especially important in liver disease presenting in early infancy. The liver and biliary tract are affected by heritable disorders and congenital malformations which become manifest within days or weeks after birth and may lead to chronic or fatal liver disease, unless recognized and treated promptly.

On examination, one should look for hepatomegaly, which in infants is defined as a palpable liver which is more then 2-3 cm below the costal margin. We should also

look for macrocephaly (intrauterine infections, Watson Alagille Syndrome), abnormal facial features (Watson Alagille Syndrome), cataract (galactosemia, rubella), abnormal auscultatory findings in the chest (cystic fibrosis), as well as the growth parameters.

2. Investigations

(a) Serum bilirubin, direct and indirect.

(b) Liver function tests: alkaline phosphatase is raised more than three times normal in intra-hepatic biliary atresia.

(c) Ida scanning: radio-nuclide scanning with ^{99m}Tc pipida offers one of the best tools to test for the patency of the biliary passages. Before the scan is performed, the infant should receive phenobarbitone (5 mg/kg/day) for one week, then ^{99m}Tc pipida is introduced. The presence of pipida in the intestine will exclude extrahepatic biliary atresia.

(d) Ultrasonography is helpful in detecting dilated bile ducts.

(e) CT scan of the liver is of limited value in the diagnosis of DHOI.

(f) Liver biopsy is the most valuable diagnostic tool in pediatric hepatology. The safety record of percutaneous liver biopsy (PBL) is excellent, without a single mortality and few complications reported among thousands of children with ages ranging from one week to fifteen years, who underwent biopsies with the Mengini needle[25].

Systematic Approach

The causes for direct hyperbilirubinemia can be broadly classified into two types (Fig. 1).

Type II	Type I
Intrahepatic hepatocellular disease	Extrahepatic biliary atresia

FIG. 1. How to Investigate D.H.O.I.*

* Modified : **Thaler MM** *JAMA* 1977; **237:** 60.

The First Step

As illustrated in Fig. 2a, we initially look for bile in the stool. In classical extrahepatic biliary atresia, there is absolute discontinuation between the hepatobiliary tract and the intestine, therefore we do not find bile in the stool. On the other hand, in intrahepatic biliary atresia, although the intrahepatic biliary tract is atretic, the extrahepatic hepatobiliary tract is normal and patent and a small amount of bilirubin can dribble into the intestine[26].

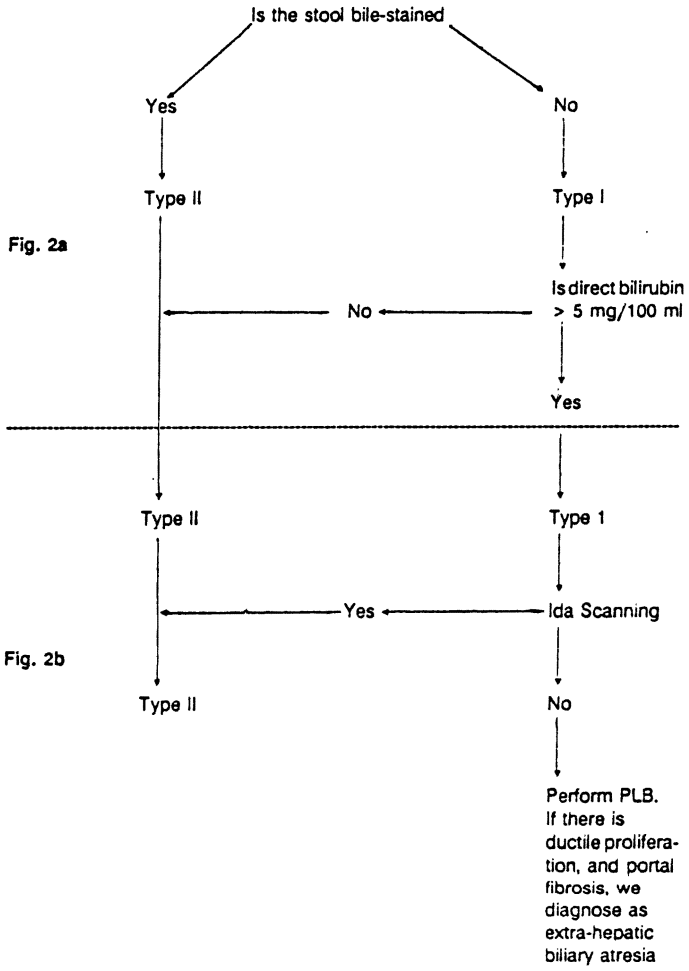

FIG. 2. The First and Second Step in the Investigation of D.H.O.I.

The Second Step

As illustrated in Fig. 2b, the next step is to perform Ida-scanning on patients suspected of having type I, if the direct bilirubin is more than 5 mg/100 ml. The presence of Ida in the intestine proves the patency of the extra-hepatic biliary tract[26].

The Third Step

As shown in Fig. 3, the cases mentioned as Type II are dealt with. For intrahepatic atresia, one performs percutaneous liver biopsy in stage (A) if alkaline phosphatase is more than three times normal, to detect the atretic ducts. In cases of hepatocellular disease (b), we can use different tools of investigations, *e.g.* α-1-antitrypsin assay (for α-1-antitrypsin definition), sweat test (cystic fibrosis), and metabolic profile for galactosemia and HFI[26].

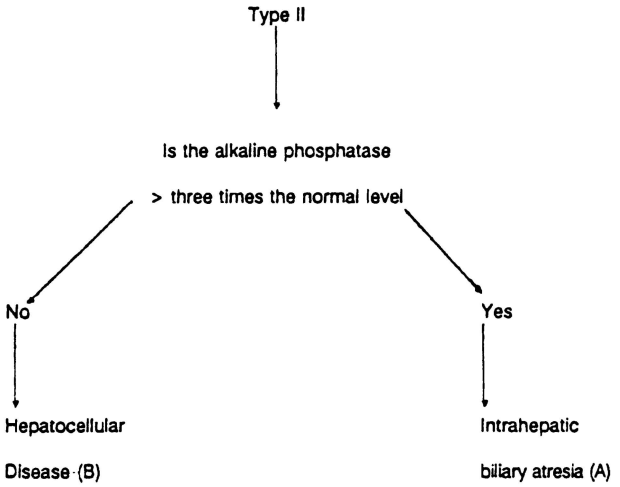

FIG. 3. The Third Step in the Investigation of D.H.O.I.

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ارتفاع البليروبين المباشر عند الأطفال

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المستخلص . يعتبر ارتفاع نسبة البليروبين المباشر في الأطفال في السنة الأولى مشكلة كثيرة الحدوث وصعبة الحل في كثير من الأحيان . ويحدث ارتفاع نسبة البليروبين المباشر نتيجة أسباب عديدة منها :

(١) الالتهاب الكبدي العملاقي ويمثل ٢٥-٤٠٪ من مجموع حالات ارتفاع نسبة البليروبين المباشر ، ويحدث الالتهاب في الذكور أكثر من الإناث بنسبة ٢ : ١ ، ويظهر اليرقان على الوليد في الأسبوع الأول في ٨٠٪ من الحالات .

(٢) الجالاكتوزمية ، وهو مرض يتميز بتضخم في الكبد واستسقاء في البطن . في هذا المرض يظهر الجالاكتوز في البول ويتم علاج هذا المرض بإبعاد الجالاكتوز من غذاء الطفل .

(٣) التايروزينيمية ، وتعالج عن طريق إبعاد الألانين الفنيلي والتايروسين من غذاء الطفل .

(٤) التليف الكيسي ، وفيه يظهر اليرقان في الأسابيع الأربعة الأولى من الولادة ويؤدي في بعض الحالات في النهاية إلى ارتفاع الضغط في الوريد البابي الكبدي .

(٥) الالتهابات الفيروسية والبكتيرية .

(٦) الرتق المراري الداخلي وينقسم إلى قسمين :

أ - الرتق المراري الداخلي التناذري أو تناذر واطسن العاجل .

ب - الرتق المراري الداخلي غير التناذري .

(٧) الرتق المراري الخارجي .

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