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Conjugated Hyperbilirubinaemia in Early Infancy

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Summary

Johnson AOK. Conjugated Hyperbilirubinaemia in Early Infancy. *Nigerian Journal of Paediatrics* **2001; 28: 29.** Conjugated hyperbilirubinaemia exists when the conjugated serum bilirubin level is more than 2 mg/dl or more than 20 per cent of the total serum bilirubin. It is always pathological in early infancy. The causes are many and diverse and most result in cholestasis. Initial diagnostic tests should include tests of liver function, blood and viral cultures, abdominal sonogram, hepatobiliary radionuclide test or duodenal aspiration test to detect the presence of bile in the gut, metabolic screen, and liver biopsy. When carried out early in the course of the disease, these tests will often differentiate between idiopathic neonatal hepatitis and congenital biliary atresia, the two most common causes of conjugated hyperbilirubinaemia in early infancy. While neonatal hepatitis generally requires only supportive therapy, biliary atresia and other mechanical obstructions of the hepatobiliary tree require surgery. Unrelieved chronic cholestasis results in fat malabsorption and growth failure, as well as biliary cirrhosis and ultimate liver failure.

Introduction

JAUNDICE in early infancy may be due to erythrocyte haemolysis and this results in elevation of indirect–acting or unconjugated serum bilirubin. This may be physiological or pathological. Conjugated hyperbilirubinaemia is defined as the presence of direct–acting (conjugated) serum bilirubin fraction of more than 2 mg/dl or more than 20 per cent of the total serum bilirubin. It is due most commonly, to obstruction to the outflow of conjugated bilirubin in the hepatobiliary system, and causes retention not only of bilirubin, but also of other substances, such as bile salts and cholesterol, which all depend on bile flow for their excretion. Conjugated hyperbilirubinaemia in early infancy is always pathological, and requires prompt evaluation to avoid the grave pathophysiological consequences of prolonged cholestasis such as growth compromise due to fat malabsorption, biliary cirrhosis and its complications of portal hypertension, and liver failure.

Causes of Conjugated Hyperbilirubinaemia

Causes of conjugated hyperbilirubinaemia in early infancy are many and varied (Table I). Hepatobiliary excretory function including bile acid transport is immature in the newborn. This immaturity predisposes to infectious, toxic, and metabolic insults in early infancy.[1] The causes of conjugated hyperbilirubinaemia may be intrahepatic or extrahepatic. Rotor's and Dubin-Johnson syndromes are due to deficient secretion of conjugated bilirubin from the hepatocyte. These syndromes cause chronic elevation of both conjugated and unconjugated serum bilirubin fractions, with the conjugated fraction usually more than half. Liver function tests and bile acid levels are normal, and thus, there is no cholestasis. Rotor's syndrome is familial with an autosomal recessive mode of inheritance,[2] while Dubin-Johnson syndrome is a genetic disorder due to a defective canalicular multispecific organic anion transporter (cMOAT). cMOAT is encoded by a single gene located on chromosome 10q24.[3] cMOAT is essential for the excretion of non-bile salt organic anions at the apical canalicular membrane of the hepatocyte.[4] Either syndrome may present in early childhood with jaundice which, in Rotor's syndrome, may be intermittent and is the only clinical manifestation. Patients with Dubin-Johnson syndrome may have, in addition to jaundice, abdominal discomfort and hepatomegaly. A brownish black pigment located in the hepatocyte lysosome giving a characteristic colouration to the liver is the hallmark of Dubin-Johnson syndrome. The liver is otherwise normal in both syndromes.

The other causes of conjugated hyperbilirubinaemia result in obstruction to bile flow and therefore are associated with cholestasis. Mowat estimated that 1 in 500 newborns would manifest cholestasis.[5] It presents with jaundice, pale stools, and dark urine. Biochemical tests suggest varying degrees of hepatocellular inflammation and dysfunction, as well as hepatobiliary obstruction. Several reports indicate that idiopathic neonatal hepatitis and biliary atresia are the two most common causes of conjugated hyperbilirubinaemia followed by α_1-antitrypsin deficiency, familial intrahepatic cholestasis, and viral hepatitis (Table II). In our series of 102 infants with conjugated hyperbilirubinaemia, bacterial sepsis was a cause in 12 per cent of the cases.[6] Recent reports suggest that inborn errors of bile acid synthesis are emerging as important cause(s) of neonatal cholestasis.[7] Anecdotal evidence suggests that total parenteral nutrition

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Table I

*Disorders Associated with Conjugated Hyperbilirubinaemia in Early Infancy**

I Intrahepatic Disorders:

A. Idiopathic neonatal hepatitis
B. Toxic
  1 TPN associated
  2 Drug induced
C. Vascular: Shock / Hypoperfusion
D. Cholestasis associated with infection
  1 Bacterial sepsis / endotoxaemia
  2 Toxoplasmosis
  3 Rubella
  4 CMV
  5 Herpes virus
  6 Syphilis
  7 Listeriosis
  8 Hepatitis B, C, other non-A non-B viruses
  9 Other viruses: Coxsackie
    ECHO
    Parvovirus B 19
    Reovirus Type 3
E. Metabolic disorders
  1 Disorders of carbohydrate metabolism: e.g., Galactosaemia
  2 Disorders of amino acid metabolism: e.g., Tyrosinaemia
  3 Disorders of lipid metabolism: e.g., Gaucher's disease
  4 Disorders of bile acid metabolism:
    a Primary: e.g., 3 β-OH steroid dehydrogenase / isomerase deficiency
    b Secondary: e.g., Zellweger syndrome
  5 Mitochondrial hepatopathies
  6 Defect / mechanism uncharacterized
    a α_1–antitrypsin deficiency
    b Cystic fibrosis
    c Neonatal iron storage disease
    d Infantile copper overload
    e Arginase deficiency
  7 Deficient hepatocyte function
    a Rotor's syndrome
    b Dubin-Johnson syndrome
F Anatomical
  1 Congenital hepatic fibrosis (Infantile polycystic disease of liver & kidneys)
  2 Cystic dilatation of intrahepatic ducts (Caroli's disease)
G Endocrinological disorders
  1 Idiopathic hypopituitarism
  2 Hypothyroidism
H Chromosomal disorders
  1 Down syndrome
  2 Trisomy 18
I Defect in bile/canalicular transport
  1 Persistent intrahepatic cholestasis
    a Arteriohepatic dysplasia (Alagille syndrome)
    b Nonsyndromic paucity of intrahepatic ducts
    c Byler disease
  2 Recurrent intrahepatic cholestasis
    a Benign recurrent intrahepatic cholestasis
    b Hereditary cholestasis with lymphoedema

II Extrahepatic Disorders:

Biliary atresia
Choledochal cyst
Bile duct stenosis / stricture
Choledochopancreatico ductal junction anomaly
Spontaneous perforation of bile duct
Extrinsic compression by stone, tumor

* Adapted from *Semin Liver Dis* 1987;7:61-6

(TPN) is a very common cause of cholestasis in early childhhood. However, it is iatrogenic and usually resolves when TPN is discontinued. It is therefore excluded in most published series of causes of cholestasis in early infancy.

Evaluation

It is important that the infant with conjugated hyperbilirubinemia be recognized and evaluation expedited to identify disorders such as sepsis that will respond to ap-

Table II

*Relative Frequency of the Clinical Forms of Conjugated Hyperbilirubinaemia in Infancy**

Causes	*Cumulative Per cent*
Idiopathic neonatal hepatitis	35-40
Biliary atresia	25-30
α_1–antitrypsin deficiency	7-10
Intrahepatic cholestasis syndromes	5-6
Hepatitis	
CMV	3-5
Rubella, Herpes	1
Inborn errors of bile acid biosynthesis	2-5
Bacterial sepsis	2
Endocrine	1
Galactosaemia	1

* Adapted from *Semin Liver Dis* 1987;7:61-6.

propriate antibiotic treatment or galactosaemia that will require dietary manipulation, and those that will require surgery before cirrhosis occurs. Accordingly, the goals of the evaluation of jaundice in early infancy are to:

(i) Determine the type of jaundice, and determine if there is associated cholestasis. This involves a detailed history to document when jaundice was first noted, colour of the stool, child's alertness, and associated fever, among others. Also important are maternal health prior to and during pregnancy, and in the immediate postnatal period, as well as the duration of gestation, child's birth weight and postnatal health. Physical examination, in addition to noting icterus, should document the presence or absence of pallor and organomegaly. The stool should be visualized, and the colour noted. Laboratory tests should include determination of total serum bilirubin and the direct fraction; evidence of hepatocyte disruption: SGOT (AST), and SGPT (ALT); evidence of biliary obstruction: serum alkaline phosphatase, gamma glutamyl transpeptidase (GGT), 5′ nucleotidase; and hepatic synthetic function: serum albumin, prothrombin time, blood glucose, and ammonia. Serum GGT is elevated in most cholestatic disorders except progressive familial intrahepatic cholestasis and disorders of bile acid synthesis.

(ii) Exclude treatable and other specific disorders by carrying out bacterial cultures of blood and urine, VDRL and viral serologies, α_1–antitrypsin phenotype which is more significant and diagnostic than the serum quantity, as newborns may have low levels even with normal phenotype; serum T_4 and TSH; sweat chloride or DNA mutation analysis in populations at risk for cystic fibrosis, screening for metabolic disorders which includes determination of urine reducing substances, serum bile acids, amino acids, and ferritin.

(iii) Differentiate extrahepatic biliary tract obstruction and biliary atresia from intrahepatic disorders. Abdominal ultrasonography may demonstrate cystic dilation in choledochal cyst, and absent or hypoplastic gall bladder in a fasting state in biliary atresia. Hepatobiliary radionuclide study using technecium-labelled iminodiacetic acid after a 5-7 day course of a choleretic like phenobarbital will demonstrate delay in hepatic dye uptake but ultimate excretion into the gut usually within 24 hours in neonatal hepatitis, while in biliary atresia, hepatic uptake is prompt, but there is no excretion into the gut. Similar information may be obtained by the duodenal aspiration test, which is relatively simple and inexpensive, and has been shown to have high diagnostic accuracy in the differential di agnoses of cholestasis in early infancy.[8]

Liver biopsy when done early is considered the most reliable in differentiating biliary atresia from neonatal hepatitis, and may be diagnostic in other causes of intrahepatic cholestatic disorders. When the biopsy is done within the first two months of life, liver histology in biliary atresia commonly shows bile duct proliferation, portal fibrosis, intraportal bile thrombi, and periductular inflammation. In hepatitis, the liver histology is more likely to show lobular disarray with hepatocyte swelling, multinucleated giant cells due to coalescing of adjacent hepatocytes, and focal necrosis. There is infiltration of the portal area by inflammatory cells, and evidence of extramedullary haematopoiesis.

Pathogenesis of Biliary Atresia and Idiopathic Neonatal Hepatitis

The exact pathogenesis of biliary atresia and idiopathic neonatal hepatitis remains obscure. Landing postulated the concept of obstructive cholangiopathy in 1971.[9] He opined that both conditions are due to an insult to the foetal hepatobiliary system, and that the resulting clinical manifestation depends on the timing, location, and nature of the insult, which could be infectious, toxic, or metabolic. Aberrant embryogenesis resulting in ductal plate malformation is considered another plausible basis for both conditions.[10]

Two categories of idiopathic neonatal hepatitis, sporadic and familial, have been identified, based on epidemiological data.[11] Idiopathic neonatal hepatitis is more likely to be associated with low birth weight and relatively reduced weight gain in early infancy. Splenomegaly may be noted at presentation. The incidence of biliary atresia ranges from 1 in 8,000 to 1 in 25,000 live births, and the incidence may be higher in non-Caucasian compared to Caucasian children.[12] Clinicopathological findings suggest that there are also two distinct varieties of biliary atresia: an embryonic or foetal type, and a perinatal type.[13] While jaundice may not occur until after the first week of life in the perinatal type, the embryonic type is characterized by earlier onset of jaundice, and it may be associated with other congenital malformations. The stool is

Table III

*Clinical Features of Conjugated Hyperbilirubinaemia in Early Infancy**

Feature	*Idiopathic Hepatitis*	*Biliary Atresia*
Type	Sporadic or Familial	Foetal or Perinatal
Low birth weight	> 75 %	May be in foetal type
Sex incidence	M>F	F≥M
Jaundice in 1st week of life	~ 50 %	~ 75 %
Acholic stool	30 - 50%	> 75 %
Failure to thrive	~ 50 %	No
PCV < 30 %	> 30%	~ 10 %
Splenomegaly	> 60%	Rare
Hepatomegaly	< 33 %	> 66 %
Associated anomalies	Rare	15-20 % in fetal type

* Age < 2 months

(Compiled from Refs. 6, 13, &14)

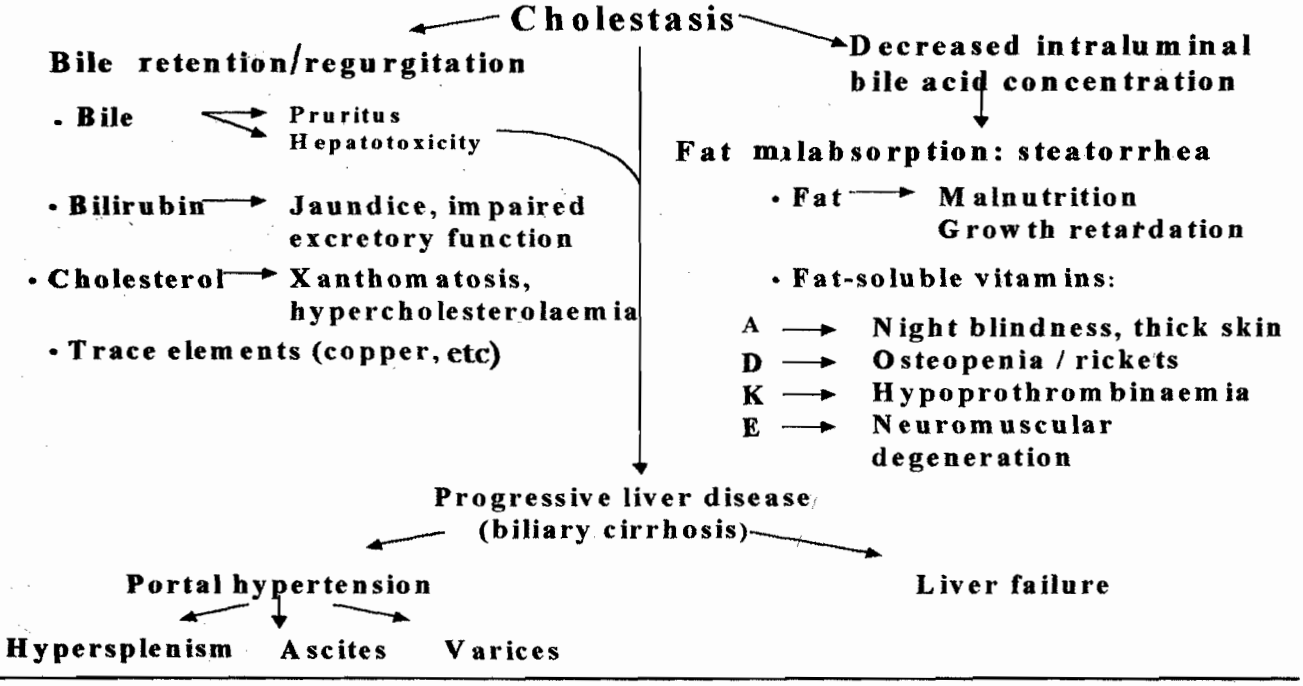

Fig. Complications of prolonged cholestasis

more likely to be strikingly pale in biliary atresia. Hepatomegaly is often noted when the infant with biliary atresia presents; splenomegaly occurs later and is evidence of portal hypertension secondary to biliary cirrhosis. Table III shows the differentiating features between idiopathic neonatal hepatitis and biliary atresia.[6,14]

Management

The need for prompt evaluation in conjugated hyperbilirubinaemia cannot be overemphasized. Sepsis will require prompt parenteral therapy with appropriate antibiotics. It is essential that metabolic conditions such as galactosaemia be diagnosed early and lactose excluded from the diet of such infants to prevent the complications of such disorders. Idiopathic neonatal hepatitis requires supportive treatment, which includes nutritional and general medical management of the complications of prolonged cholestasis (Figure). Biliary tract obstruction also requires prompt surgical intervention to facilitate resolution of cholestasis. Localized lesions such as choledochal cyst and focal stenosis are amenable to resection with prompt relief of the obstruction.

Intraoperative cholangiogram will define the extent of obliteration in atresia. Correctable biliary atresias are extrahepatic lesions with patency of the proximal portion of the bile duct up to the porta hepatis and these are also amenable to resection and anastomosis as appropriate. Noncorrectable biliary atresia involves total obliteration of the extrahepatic bile ducts up to the porta hepatis and the lesion invariably involves atresia of the intrahepatic ducts as well. Noncorrectable atresia constitutes 70-85 per cent of biliary atresias.[6,15] Surgical correction is attempted in all cases of biliary atresia who present preferably prior to the onset of biliary cirrhosis. The surgical procedure employed in noncorrectable biliary atresia is hepatoportoenterostomy with Roux-en-Y anastomosis first described by Kasai.[16] This procedure involves resection of the atretic extrahepatic ducts, and apposition of the proximal jejunum to the porta hepatis in an attempt to promote bile drainage directly into the small intestine. Success in establishing bile drainage is related to the age of the patient at operation, histology of ductal remnants at the porta hepatis, and the experience of the surgical team.[17] Kasai reported approximately 80 per cent success rate in infants who had the procedure prior to two months of age, but less than 20 per cent when the infants were older than three months.[16,18] Although this age dependent outcome appears to be the prevailing consensus, there have been reports of successful outcomes of the Kasai procedure or its modification performed in infants as old as 120 days.[19,20] Also, older children of African ethnicity undergoing the Kasai procedure appear to fair better than Caucasian children of comparable age, and the Caucasian race has been reported as a predictor of poor surgical outcome for the Kasai procedure.[15,19] Steroid administration in immunosuppressive dosage may improve the clinical outcome after the Kasai procedure.[21] The long term benefit from the Kasai procedure varies as there is gradual progression of the intrahepatic disease to end-stage liver disease in the majority of patients necessitating liver transplant for continuing survival. Biliary atresia is the most common indication for liver transplant in the paediatric population.[22]

As there is no specific therapy for cholestasis *per se*, management is directed at improving nutritional status, and ensuring the patient's comfort. Decreased luminal bile acids results in deficient lipolysis and malabsorption of dietary fat, which are long chain triglycerides. As medium chain triglycerides (MCT) can be absorbed in the absence of bile acids, MCT-containing formula such as pregestimil or portagen are given to improve caloric intake. Absorption of fat-soluble vitamins are also compromised, and supplementation at a dose of two or three times the recommended daily allowance of these vitamins is often necessary to avoid manifestations of hypovitaminosis A, D, E, and K. Pruritus may cause significant morbidity. Its exact aetiology in cholestasis is uncertain but it may be related to elevated skin level of bile acids.[23] Therapy with phenobarbital or cholestyramine increases bile acid flow, and reduces itching.[24] Other anti-pruritic agents that have been tried include ursodeoxycholic acid and rifampin.[25,26] These therapies may also reduce xanthomas which are cutaneous depositions of cholesterol. Partial external biliary diversion has been used to treat intractable cholestasis and pruritus unresponsive to these medications.[27]

Ascites due to portal hypertension and hypoalbuminaemia is managed with spironolactone, an aldosterone antagonist, and judicious use of intravenous albumin and abdominal paracentesis. Variceal bleeding, also a complication of portal hypertension, requires intensive care initially with transfusion of blood or blood substitutes as indicated. When the patient is haemodynamically stable, endoscopic sclerotherapy of oesophageal varices may be necessary if bleeding persists. This is preferred to surgical transection of vessels especially if liver transplant is envisaged.

Outcome

Outcome in conjugated hyperbilirubinaemia is related to the presence or absence of cholestasis. As was noted above, both Rotor's and Dubin-Johnson syndromes are not associated with cholestasis. They are essentially benign conditions with no significant morbidity and no mortality. Disorders associated with prolonged cholestasis result in significant morbidity and are potentially lethal. The eventual outcome depends on the specific aetiology and the promptness of the diagnosis and treatment. Idiopathic neonatal hepatitis often resolves with no sequela. However, in our series of 102 infants with conjugated hyperbilirubinaemia, two (6 per cent) of the 33 cases with neonatal hepatitis died,[6] and other studies have reported significantly higher mortality.[28-31] There have been reports that sporadic idiopathic neonatal hepatitis has a better outcome than the familial type, perhaps because the latter is often associated with underlying metabolic problems.[7]

Untreated, the outcome in biliary atresia is death usually by the age of two years.[32] The Kasai procedure hardly ever results in a permanent cure and the overall five and 10-year survival rates are about 48 per cent and 30 per cent, respectively.[15,33] The Kasai procedure remains the first option for the surgical management of non-correctable biliary atresia. Even when less than adequate bile drainage results, the procedure and the subsequent nutritional management allow time for the patient's growth, which improves the overall chance for a successful liver transplant. The details and outcome of liver transplant in the paediatric population are be-

yond the scope of this review, and the interested reader is referred to appropriate texts.[27,34]

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