

## Cholestatic jaundice in a sample of Iraqi Infants (A hospital based study)

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**Summary:**

**Background:** Cholestatic Jaundice is a dilemma facing not only the primary care provider but also the specialist pediatricians in our country.

**Subjects & methods:** Analysis of 50 cases of cholestatic jaundice aged 3 weeks- 18 months were carried out over 18 months in the Gastroenterology & Hepatology unit in the Children Welfare Teaching Hospital, Medical City, and Baghdad. Clinical, biochemical, radiological and histopathological results were recorded.

**Results:** Fifty patients with Cholestatic Jaundice, 28 males & 22 females, were evaluated. The main causes of Cholestatic Jaundice were Biliary Atresia in 22 cases (44%) (the mean age of presentation was 4.1 months), and Neonatal Hepatitis Syndrome of different etiology in 17 cases (34%) (The mean age of presentation was 5.9 months). Galactosemia was the most common cause of metabolic liver disease and CMV was the commonest of the intrauterine viral infections. Two cases of choledocal cyst (4%) and no definite cause was found in 9 cases (18%)

**Conclusion:** Biliary atresia was the most common cause of cholestasis in this study of extra-hepatic type. Different stages of cirrhosis were found in almost all cases of biliary Atresia because of delayed presentation. Clay color stool, hepatomegaly, high alkaline phosphatase & high cholesterol level favor atresia cases. Ultrasonography & liver biopsy prove to be very valuable tools in the differentiation between Biliary Atresia & Neonatal Hepatitis Syndrome.

**Key Words:** Cholestatic Jaundice, Infants, Biliary Atresia.

*Fac Med Baghdad  
2011; Vol. 53, No.1  
Received May 2010  
Accepted Nov. 2010*

**Introduction:**

Infants with jaundice beyond 2-3 weeks after birth should be evaluated & conjugated hyperbilirubinaemia should be differentiated from unconjugated types, which are usually benign (1). An abnormal direct bilirubin is defined as a value greater than 17mmol/L (1 mg /dl), if the total bilirubin is < than 5 mg/dl or a value of direct bilirubin that represents more than 20% of the total bilirubin if the total bilirubin is greater than 5 mg/dl (2)(3).

Cholestasis includes retention of conjugated bile, bile salts and other components of bile and it is a signal that disease exists. The mechanism in which diseases produce cholestasis can be classified as either hepatocellular or obstructive cause. (4).

Cholestasis is estimated around 1 in 2500 (5). The most common causes of Cholestasis in infancy are Biliary Atresia (BA) (Extra & Intrahepatic) and Neonatal Hepatitis Syndrome (NHS), a term which is given now to non specific hepatic inflammation, which develops secondary to many different etiologies including Intra uterine infection, Endocrine disorders and Inborn error

of metabolism (6,7,8). Early detection is essential to facilitate timely intervention and minimize adverse outcome in several conditions including Biliary Atresia (BA), Hypothyroidism, and Galactosemia (3).

The aim of this study was to find out the etiological causes of cholestatic jaundice in a sample of Iraqi infants and to find clues from the clinical, biochemical, radiological and histopathological findings to plan for early management as there was no similar study done in Iraq before.

**Patients & methods:**

This prospective study was done on 50 infants aged 3 weeks -18 months admitted with Cholestatic Jaundice to the GIT & Hepatology unit in Children Welfare Teaching Hospital / Medical City/ Baghdad over a period of 18 months. Patients were referred from all over the country for evaluation. Premature babies and storage diseases were excluded from the study.

The infants were included when the cholestasis was persisting beyond two weeks in the neonatal period or cholestasis lasting for four weeks or more in older infants (9). Complete history and physical examination with thorough investigations done to all patients in the group. Specific investigations were added when needed as TORCHS antibodies, MRCP, bone marrow aspirate, thyroid function test and alpha-1-antitrypsin level.

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As long as we had no metabolic screening test and no enzymatic assays in Iraq, we depended on the clinical presentations and the finding of abnormal reducing sugars in urine to diagnose Galactosemia and Fructosemia and high alpha feto protein level in the blood to diagnose Tyrosenemia.

Every patient was subjected to an ultrasound examination looking for one of these findings to diagnose Biliary Atresia:

1. Small size Gall bladder (< 2.5mm) even after fasting for 4 hours and loss of contractility after feeding (10,11).

2. Finding a triangular cord sign of a high reflectivity corresponding to fibrotic ductal remnants at the porta-hepatis (12, 13).

Percutaneous liver biopsies were done using Menghini technique for 30 patients only, when the ultrasound was in doubt and to estimate the degree of fibrosis before submitting child to surgery. Extensive ductular proliferation with elongated and angulated ductules that occasionally contain bile plugs with portal tract edema & fibrosis helps the diagnosis of Extra-hepatic biliary atresia(6)(14), while relative paucity of the portal zone bile ducts supports the diagnosis of Intra-hepatic biliary atresia (6).

#### Results:

Fifty infants with cholestatic jaundice (28 males & 22 females) were studied. All patients presented with jaundice and dark color urine. Table (1) shows that Biliary Atresia was the commonest cause of cholestatic jaundice in this study 22 cases (44%) with the mean age of presentation of 4.1 months and Neonatal hepatitis syndrome in 17 cases (34%) with the mean age of presentation of 5.9 months.

Table no. (2) Indicates that the main cause of BA was extra-hepatic type in 17(34%) and there were 5(10%) syndromatic intra-hepatic biliary paucity. Three of them had the typical facies of Allagile syndrome (2 with ASD & one with PDA and kidney abnormalities) with a history of death in an older sibling in one of the families. Two Down's syndrome also had intrahepatic biliary paucity diagnosed by liver biopsy.

All cases of extra-hepatic biliary atresia presented with clay color stool and hepatomegaly. Intermittent coloring of the stool were found in the intra-hepatic atresia and in the choledocal cysts cases.

ULtrasonography was helpful in diagnosing Extra-hepatic BA in 18(81.8%) cases compared to liver biopsy results (88%).

Sepsis was the contraindication to liver biopsy in 6 cases, and no consents were given for the others. Almost all cases suggestive of BA had different stages of cirrhosis. Surgery was done to only 3 cases where the liver architecture were still preserved, three months later one died of sepsis and the other two were surviving & in good health.

Two cases with choledocal cysts were operated upon and were well after 6 months. Table (3) shows the

different causes of NHS, Galactosemia was the commonest cause of metabolic liver diseases in 6 cases out of 11 (35.3%), family history was positive in ½ of the cases. All cases presented with failure to thrive, two with bleeding tendency & sepsis. Two Fructosemia cases in this series both presented with hepatosplenomegaly & one had positive family history of 5 deaths with the same problem. Both Tyrosenemia cases presented with fulminant hepatic failure in the late neonatal period (One of those families had 2 previous neonatal deaths).

Bleeding varices was the presentation of 16 months old girl who had a tinge of jaundice since birth, proved by investigation to be severe alpha-one antitrypsin deficiency. Three patients were CMV IgM +ve, one presented with petechiae and hepatosplenomegaly, and there were two additional cases of BA who had also CMV IgM +ve antibodies (counted with the BA cases).

One baby presented with sepsis had HSV IgM +ve with positive history of vaginal herpetic lesion in the mother. The baby was very ill with coffee-ground vomiting. One case only had Toxoplasma IgM+ve.

Hypothyroidism was diagnosed by +ve thyroid function test in 4 months old with typical features presented with severe chest infection and sepsis. No definite causes were found in 9 cases from all the investigations done and labeled as idiopathic neonatal hepatitis, six were alive and thriving well after 6months follow up, one admitted with sepsis & 2 lost to follow up.

The biochemical profile in table (4) showed that serum cholesterol & alkaline phosphatase levels were increased in BA cases rather than in NHS and total serum bilirubin & transaminases levels seem to have no impact on the differential diagnosis. Six patients died in this study (12%), 2 with fulminant hepatic failure with the diagnosis of Tyrosenemia, four with sepsis (one with Fructosemia & one with herpes infection, one 3 months after surgery and one after 6 months with Idiopathic neonatal hepatitis).

#### Discussion:

Cholestasis in young infants has various etiologies. Early diagnosis is important as cirrhotic changes occur early & correctable conditions become untreatable if the diagnosis is delayed (15). Male predominance fit some studies (16) (17) but did not coincide with other (15).

Mean age of presentation in all cases of BA in this study was (4.1 months) whereas in another study only (25%) of their infants with BA presented beyond four months of age (18).

The late presentation of all children in this study regardless of the cause lead to poor prognosis especially the BA cases where surgery could save that child if done at the right time as 60-70% of patients with BA will develop cirrhosis and require liver transplantation in childhood and late referral will

affect the overall survival rate after transplantation(3). Inadequate health education, inaccessible medical care and late referral from the primary health physician with the fact of the unavailability of liver transplantation in our country made the problem even worse.

The most frequent cause of cholestasis in this study was Biliary Atresia 22 cases (44%).Which disagrees with a study done by Deghady et al in Alexandria, who found Biliary Atresia as the second common cause in their series (24%) and NHS comes first (41.43%) (4), they depended on Gamma Glutamyl Transpeptidase levels for the differentiation of both main causes (which is not available in Iraq) and they found it the only biochemical test of discriminative value. This also disagrees with studies done by Dick et al (19) where he found BA cases to be (20.4%), but Yachha et al (19.4%) (20) including the choledocal cysts and in John et al study it was (34%). (21)

Extra-hepatic type in this sample was present in 15 cases which constitute (30%) of all the cholestatic causes as it was in Danks et al study (32.2%).(22)

Biliary Atresia cases used to be high in an older study (3) and idiopathic hepatitis used to be the main cause of neonatal hepatitis in the past [Danks et al (22) and Dick et al (19)] but recently the sophisticated technology, advanced serological tests with the immunohistochemical studies and enzymatic assays lead to the description of new metabolic causes of cholestasis and reverse the ratio .As some of the intrahepatic biliary atresia may be caused by intrauterine insults as viruses or metabolic process started in utero.(6) These facilities are unavailable in Iraq yet.

The frequency of non syndromatic bile duct paucity was (4%) in this study and (2.8%) in another study (4). Alagille's syndrome was not found in their series but it was 6% in this study and even higher in other studies (22, 23) and they explain this on a genetic background. Clay color stool was presented in BA rather than NHS cases as in other study (24) and hepatomegaly was also found in all cases of BA as in other study (18).

Choledocal cyst frequency was low in this study (4%) as it was in all other studies between (2.9%), (3%) and (4%) respectively. (4, 25, 20)

The role of liver biopsy in this study was valuable and depressing at the same time because of the late referral and the established cirrhosis in most of the BA cases. Liver biopsy before 8 weeks of age sometimes confusing (26), as changes characteristic of BA may appear after 9 weeks of age. Bile duct paucity & normal bile duct to portal space ratio do not preclude the subsequent development of BA, so sequential liver biopsies should be done until clinical improvement occurs or until BA can be excluded from the differential diagnosis .(27,28)

Magnetic resonant cholangiopancreiography (MRCP) is being increasingly used to assess the biliary tract. It was done in 3 suspected cases of BA; one result was

suggestive of BA by the absence of gall bladder & non visualization of CBD. It needs more studies to prove reliability of this investigation (29).As MRCP required deep sedation or general anesthesia, the Cholestasis Guideline Committee concludes that this test can not routinely be recommended based on the currently available data (2).

Consanguinity is very high in our community so inherited diseases are frequently seen. Galactosemia was found as the main cause of Neonatal Hepatitis Syndrome in (35.29%) of the metabolic causes which was almost the same as in the Indian study (35%) (20) but none was found in Deghady study (4). Small number of cases of Tyrosenemia was reported in study of Alexandrian (4) (1.43%) and (4%) in an Indian study (20) and also (4%) in the present study. Both patients in this group had fulminant hepatic failure and died in the neonatal period.

Two patients had Fructosemia (4%) which is another autosomal recessive disorder and is common in relatives. It usually appears after introduction of sucrose and fructose in the weaning food (6).In our community, it is an old practice to give any newborn baby water and table sugar (sucrose) in a false believes of getting rid of jaundice after delivery. It was also reported in small number in the literature (20).

Severe Alpha-one antitrypsin deficiency was found in one patient only (2%). It was the first case to present with bleeding varices at such a small age. Alpha one antitrypsin deficiency was also seen in different studies with different frequencies ranging from (17.4 %) (25), (4 %) (20) to (1.43 %) (4).It may also follow a genetic background as it usually decides the variable incidence of metabolic diseases.

CMV infection was the commonest cause of intrauterine infections in this sample and also reported as the main cause in other studies. (21, 4) Two other patients had CMV +ve IgM antibodies and had Biliary Atresia at the same time.

In some children, positive CMV infection may coexist with cholestasis of different etiology, so elimination of possible atresia of extrahepatic bile duct is absolutely necessary even if CMV was positive .(30)

One case of Herpes infection reported in this study (2%) died 2 days after admission with severe jaundice and repeated convulsions. One study reported three cases of neonatal herpes simplex infection presented with fulminant hepatic failure. (31) It was also reported in 4.29% in another study. (4)

Toxoplasmosis infection was found in one case only (2%) as in other two studies (20) (4). The biochemical profile in table (4) gives a clue to the biliary atresia cases from the rise of serum cholesterol level and alkaline phosphatase which fit other studied. (32, 4)

In 9 patients (18%) no definite cause could be found, their biochemical profiles were not conclusive and the liver biopsies gave mixed picture of ductal proliferation, cholestatic features and inflammatory cell infiltration.

In conclusion, this study reveals that Biliary Atresia with all its types is the most common in this series. Cirrhosis was found in almost all cases because of delayed presentation of those cases.

Clay color stool, hepatomegaly, high alkaline phosphatase and high cholesterol levels found mostly in Biliary Atresia cases.

It was concluded from this study that Biliary Atresia (Extra hepatic type) was the most common cause of cholestasis in early and late infancy. Different stages of cirrhosis were found in almost all cases of biliary Atresia because of delayed presentation. Clay color stool, hepatomegaly, high alkaline phosphatase & high cholesterol level favor atresia cases. Ultrasonography & liver biopsy prove to be very valuable tools in the differentiation between Biliary Atresia & Neonatal Hepatitis Syndrome

**Table no. (1) The causes of cholestatic jaundice in the study group.**

Causes of Cholestatic Jaundice	Numbers	Percent %
Biliary Atresia(BA)	22	44
Neonatal hepatitis syndrome (NHS)	17	34
Idiopathic Neonatal hepatitis Syndrome	9	18
Choledocal cyst	2	4
<b>Total</b>	<b>50</b>	<b>100</b>

**Table no. (2) The main causes of Biliary Atresia in the study group**

Types of Biliary Atresia (BA)	Numbers	Percent %
Extrahepatic BA	15	30
Syndromatic intrahepatic Biliary paucity	5	10
Non- syndromatic intrahepatic Biliary paucity	2	4
<b>Total</b>	<b>22</b>	<b>44</b>

**Table no. (3) The different causes of Neonatal Hepatitis syndrome in the study group.**

Causes of Neonatal Hepatitis Syndrome	Numbers	Percent %
1- Metabolic:		
a-Galactosemia	6	12
b-Fructosemia	2	4
c-Tyrosenemia	2	4
d-Alpha 1 antitrypsin deficiency	1	2
2- Intra uterine infection:		
a-CMV	3	6
b-HSV	1	2
c-Toxoplasmosis.	1	2
3- Endocrine:		
Hypothyroidism	1	2
<b>Total</b>	<b>17</b>	<b>34</b>

**Table no. (4) The biochemical profile of the study group**

Biochemical tests	BA (n.)24 Mean (range)	NHS (n.)17 Mean (range)	INHS (n.)9 Mean (range)
TSB(mg/dl)	12.6(3.7-25)	10 (3-18)	6.3(3.2-8.3)
ALT(u/l)	80.8(34-176)	75.8(35-150)	49.8(17-94)
ALP(u/l)	943.3(350-1660)	688.4(500-1200)	935.6(600-1480)
S.cholesterol (mg/dl)	283.2(115-480)	174.5(112-230)	201.8(111-290)

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