Infantile Cholestasis in the Central-Eastern Province Saudi Arabia

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Summary

In the King Khalid University Hospital (Central Province) and King Fahad Hospital of the University (Eastern Province) Saudi Arabia, we identified 64 infants with cholestasis. The causes of cholestasis were idiopathic neonatal hepatitis in 29; extrahepatic biliary atresia in 17; neonatal hepatitis secondary to *Rubella* and Cytomegalovirus in six and four infants, respectively; paucity of intrahepatic bile ducts in six and galactosaemia in two. The diagnosis was confirmed by liver biopsy and or operative cholangiography, in all infants.

Introduction

Cholestasis is stoppage or suppression of the flow of bile which causes conjugated hyperbilirubinaemia. It is not common in infants but its presence carries serious implications in the majority of cases.[1]

The obstruction is either intrahepatic or extrahepatic. It could be total or partial, but in some cases it is due to malformation of the biliary system, while in others it could be due to inflammation of hepatocytes which results in obstruction of biliary canaliculi due to oedema.[2] The clinical presentation is prolonged jaundice.

The aim of this communication is to highlight the major causes of cholestasis, their clinical presentation and the results of laboratory investigations in two different centres in the Kingdom of Saudi Arabia.

Patients and Methods

The data were obtained from case files of infants admitted with cholestatis in two major University hospitals in the Kingdom of Saudi Arabia viz. King Khalid University Hospitals in Riyadh (Central Province) and King Fahad Hospital of the University (Eastern Province).

The data collected include age at which jaundice was noted in the infants, as well as birth weight, height, head circumference and gestational age. Family history of jaundice, hepatomegaly and liver disorders, as well as haematological diseases was inquired into. Prenatal history including fever, skin rash and joint pain during pregnancy was recorded; duration of cholestasis, stool and urine colour, presence of pruritis, abdominal distension, hepatosplenomegaly, and facial dysmorphology were looked for. Other data collected include results of laboratory investigations like liver function test. Prothsomein time (PT), partial thromboplastin time (PTT), urine for reducing substances, metabolic screen in urine, TORCH screen, hepatitis B surface antigen, hepatitis C, Epstein bars virus, HIV and blood and urine culture results, results of sweat chloride, TSH, and alpha one antitrypsin. Results of abdominal ultrasound and HIDA scan after 5 days of phenobarbitone were also added. Other results included are liver biopsy histology and operative cholangiography.

The final diagnosis was based on the analysis of findings in the history, physical examination, and investigations. The diagnosis of extrahepatic biliary atresia was always confirmed by laparatomy and intra-operative cholangiography showing absence of extra-hepatic bile ducts and atretic gall bladder.

Intrahepatic cholestasis was diagnosed when patency of the extrahepatic bile duct was demonstrated by scintigraphy or laparatomy. These include, idiopathic neonatal hepatitis, paucity of intrahepatic bile ducts and others.

Biopsy findings of cholestasis, absence or decrease in number in intralobular bile ducts with unobstructed extrahepatic bile ducts was labelled as paucity of intrahepatic bile ducts. The finding of low red blood corpuscles galactose-1 phosphate uridyl transferase confirmed galactosaemia.

The data were reviewed and analysed on a micro-computer using the statpac gold statistical analysis package.

The chi-square and student *t*-test were used as appropriate to test the significance of association and differences of variables.

All tests were considered significant at the 5 per cent level. In 2×2 contingency with the cell frequencies, the Fisher's Exact Test was used.

Results

During the study period we identified 64 infants with cholestasis.

There is equal distribution among the two genders as in Table 1. Sixty and 56 per cent of the infants with extrahepatic and intrahepatic cholestasis respectively, are males. Most of the infants in the two groups are Saudis (Table 1).

The age of onset of cholestatic jaundice and at first admission varies widely among the infants in this study, but are similar in both extrahepatic and intrahepatic cholestasis as shown in Table 1.

Age at first admission were delayed in both group as in Table 1.

Birthweights were almost equal in proportion in both types of obstruction as in Table 1.

History of acholic stool was significantly associated with the type of cholestasis ($P = 0.008$; Table 1).

All patients with extrahepatic cholestasis had history of acholic stools as compared with 48 per cent who had intrahepatic cholestasis.

There was a preponderance of dark urine in patients with extrahepatic cholestasis. This was statistically significant ($P = 0.039$, Table 1).

The physical findings presented in the two disorders did not reveal any differential characteristics features (Table 2).

Hepatomegaly and splenomegaly are common in both disorders.

The mean value of haemoglobin, white cell count, platelets, total protein, and albumin are all within normal limits. The mean prothrombin time and partial thromboplastin time were slightly higher than normal, but did not reach the 5 per cent level of statistical significance. The liver enzymes, serum bilirubin, both direct and indirect were all raised (Table 3).

Igm antibodies were positive for both *Rubella* and Cytomegalo virus in six and four infants, respectively. RBC-galactose 1 phosphate uridyl transferase was low in two infants.

Liver biopsy confirmed the diagnosis of neonatal hepatitis ,in 39 infants and paucity of intrahepatile bile ducts in the same six infants, as well as biliary atresia in 17 infants. Serum alpha-one antitrypsin, sweat chloride, serum and urine amino acid, and TSH were normal in all infants.

The final diagnosis for 64 infants with cholestatis is shown in Table 4.

Discussion

Few studies on childhood cholestasis were carried out in Saudi Arabia.[3]

Some workers described cholestatic jaundice with

TABLE 1

Demographic characteristics of 64 infants with cholestasis: final diagnosis

Demographic characteristics medical/family history		Extrahepatic cholestasis	Intrahepatic cholestasis	P values
1. Sex:	Male	9/15 (60%)	25/45 (55.6%)	$x = 0$
	Female	6/15 (40%)	(20/45 (44.4%)	$P = 1$
2. Nationality:	Saudi	14/15 (93.3%)	38/46 (82.6%)	$P = 0.28$
	Non-Saudi	1/15 (6.7%)	8/46 (17.4%)	(Fishers test)
3. Age (days) of onset Mean + SD		9.6 + 10.6 ($n = 16$)	15 + 17.2 ($n = 41$)	$P = 0.08$
4. Age at first admission (months) Mean + SD		2.8 + 3 ($n = 12$)	2.6 + 2.0 ($n = 41$)	$P = 0.34$
5. Birth weight Mean + SD		3.0 + 0.5 ($n = 4/17$)	2.6 + 2.0 ($n = 27/47$)	$P = 0.08$
6. Acholic stool		12/12 (100%)	19/39 (48.7%)	$P = 0.008$
7. Colour of urine:	Dark	10/13 (76.9%)	20/40	$P = 0.039$
	Clear	2/13 (15.4%)	(50%)	(Fishers test)

TABLE 2

Physical findings at first admission of 64 infants with cholestasis: final diagnosis

Physical findings	Extrahepatic cholestasis	Intrahepatic cholestasis	P value
1. Hepatomegaly	14/17 (82.4%)	35/47 (74.5%)	$P = 0.38$
2. Splenomegaly	9/16 (56.3%)	21/47 (44.7%)	$P = 0.30$
3. Ascites	1/13 (7.7%)	3/47 (6.4%)	
4. Oedema	2/15 (13.3%)	1/47 (2.1%)	
5. Clubbing	1/14 (7.1%)	0	
6. Congenital abnormality	1/14 (7.1%)	3/47 (6.4%)	

TABLE 3
Initial laboratory data for 64 infants with cholestasis: final diagnosis

Laboratory investigation	Extrahepatic obstruction $x + SD$	Intrahepatic obstruction $x + SD$	P value
1. Total Bilirubin (μmol/l)	161 + 81.5 ($n = 17$)	113.1 + 127.7 ($n = 45$)	0.0498
2. Direct Bilirubin (μmol/l)	101.9 + 51.2 ($n = 16$)	67.5 + 85.5 ($n = 44$)	0.0418
3. AST (U/l)	302.7 + 229.9 ($n = 15$)	265.4 + 219.2 ($n = 40$)	0.297
4. ALT (U/l)	184.9 + 139.2 ($n = 17$)	218.6 + 197.2 ($n = 40$)	0.2619
5. Alkaline Phosphate (U/l)	480.7 + 428.7 ($n = 15$)	684.5 + 534.6 ($n = 42$)	0.079
6. G.G.T. (U/l)	227.5 + 167 ($n = 4$)	238.5 + 164 ($n = 15$)	0.3436

TABLE 4
Diagnosis of cholestasis

Diagnosis	Frequency
1. Extrahepatic biliary atresia	17
2. Intrahepatic cholestasis	
(a) Idiopathic neonatal hepatitis	29
(b) Neonatal hepatitis of known cause	
(i) *Rubella*	6
(ii) Cytomegalovirus	4
(c) Paucity of intrahepatic bile ducts	6
(d) Galactosaemia	2
Total	64

urinary tract infection and acute lymphoblastic leukemia associated with normal liver enzymes.[4] None of our infants had these two associations.

Cholestatis in infancy has been attributed to multiple causes like neonatal hepatitis, biliary atresia, and other rare diseases.[5]

A lot of viral and parasitic infections has been incriminated as a cause of neonatal cholestasis like cytomegalovirus, rubella, hepatitis B, herpes simplex, coxsackie and toxoplasmosis.[6] Igm for the first two viruses was positive in four and six of our infants, respectively. To further incriminate cytomegalovirus (CMV) as a cause of neonatal hepatitis positive PCR for CMV genome,[7] was performed.

Other virus which is rarely associated with cholestasis is human immunodeficiency virus which cause a clinical syndrome of cholestasis and hepatitis during early infancy.[8] HIV was negative in all our infants.

Drugs taken during pregnancy and lactation, e.g. carbamazepine has also been incriminated as a cause of cholestatic hepatitis.[9] None of our infants had history of medication during the intra-uterine life.

Halothane used in anaesthesia has also been found as a cause of cholestatic hepatitis in children.[10] None of our infants was exposed to halothane. It was emphasized that pediatricians should be aware of the importance to recognize rapidly a specific treatable, metabolic, infectious or malformative disease in order to institute an early, specific, and effective therapy.[11] Unfortunately, most of our infants with cholestasis were referred late.

Extrahepatic biliary atresia was found in 17 (27 per cent) of 64 children in our study compared with 22 (39 per cent) of 57 infants by Guelrud in Venezuela.[12]

The male/female ratio in our study was 1.3 which is similar to 0.93 ratio from Brazil.[13]

Most of the infants presented with pale stools and dark urine which usually occur in extrahepatic and intrahepatic cholestasis. Twelve (70 per cent) of those with extrahepatic cholestasis presented with acholic stool suggesting severe cholestatis. This is a significant finding in our study $P = 008$ Fishers exact test.

Ten (77 per cent) of our infants with extrahepatic cholestasis presented with the same history. This is also a significant finding in our study $P = 0.0.039$ the Fishers exact test.

Our study revealed that idiopathic neonatal hepatitis is commoner than neonatal hepatitis of determined causes in Saudi Arabia. This finding is similar to previous

finding reported in the past by Danks *et al.*[14] and Dick and Mowat.[15] Six (13 per cent) of our infants with intrahepatic cholestasis has paucity of intrahepatic bile ducts while 2 (4 per cent) had galactosaemia. This last finding was also reported by Dick and Mowat in 1985.[15] Other aetiological factors of intrahepatic cholestasis not seen in our children are total parenteral nutrition[16] and Byler's disease.[17]

The administration of fat soluble vitamins A, D, E, and K cannot be over emphasized in the supportive therapy of cholestatic infants. Fat soluble vitamins deficiencies is known to result in various complications that might be prevents.[18,19] All our infants were given fat soluble vitamins.

Intractable pruritis was seen in some of our infants for which they needed cholestyramine. Rifampicin has been shown to be effective in alleviating pruritis in five children with cholestasis compared with placebo-treated group.[20] Rifampicin was not administered to any of our infants.

Some of our infants were also given phenobarbitone to decrease the serum concentration of bilirubin. This is also in contrast to some views in the United States. Nemeth *et al.*[21] showed that liver function tests results generally did not improve in children with cholestatis given phenobarbitone; however, serum concentration of bilirubin decreased.

Other studies have shown that liver biopsy and histopathology could be a reliable diagnostic investigation after which one may proceed to more complex investigations.[22] Ultrasound and biliary scintigraphy were also performed to make proper diagnosis in our patients.

Reports from Japan state that Endoscopic Retrograde cholangiopancreatography is a relatively easy and safe technique when applied to infants and small children.[23] They also claim that it is a useful procedure when making morphologic diagnosis of organic disorders around the biliary and pancreatic ductal system, that was not done to any of our infants.

It has been documented that patient with biliary atresia (extrahepatic obstruction) should be referred for surgery for Kasai portoenterostomy on time before the age of 60 days at which prognosis of surgery is better and survival was significantly longer.[24] Seven of our infants had successful Kasai operation.

In summary, infantile cholestasis is not rare in the Kingdom of Saudi Arabia. Pediatricians should detect and investigate conjugated hyperbilirubinaemia in infancy, and we recommend early referral to higher centre with facilities to differentiate neonatal hepatitis from biliary atresia so that Kasai portoenteromy can be performed early to avoid long-term sequelae of late referral.

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