DISSERTATION ON

USEFULNESS OF CLINICAL FEATURES AND ULTRASONOGRAPHY IN THE DIAGNOSIS OF NEONATAL CHOLESTASIS SYNDROME

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CERTIFICATE

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INTRODUCTION

INTRODUCTION

Neonatal cholestasis is one of the commonest liver problem in neonates and infants. Various diseases of different etiology result in neonatal cholestasis. The etiology may be infectious, endocrine, genetic, metabolic, congenital, toxic or inflammatory.

The two major causes of neonatal cholestasis are biliary atresia and idiopathic neonatal hepatitis. Many cases previously described as idiopathic neonatal hepatitis have been found to have genetic basis and now they have been reclassified as metabolic diseases. Almost all these diseases manifest with jaundice, elevated liver enzymes, cholestasis and nutritional deficiency. While some diseases improve with supportive treatments, others progress to chronic liver disease and cirrhosis.

CAUSES

The major causes of neonatal cholestasis may be classified as follows;

1. **Infection**

   Toxoplasmosis

   Rubella

   Cytomegalovirus

Herpes simplex virus

Varicella-Zoster virus

HBV

Syphilis

HCV

Human immunodeficiency virus

Parvo virus B19

Syncitial giant cell virus

Listeria

Tuberculosis

Sepsis

UTI

2. Genetic

Trisomy 21

Trisomy 18

Cat-eye syndrome

3. Endocrine

Hypopituitrism

Hypothyroidism

4. Structural

Extra Hepatic Biliary Atresia (EHBA)

Choledochal cyst

Neonatal Sclerosing Cholangitis

Inspissated Bile

Spontaneous perforation of common bile duct

5. **Duct paucity syndrome**

Alagille syndrome

Non syndromic bile ductular hypoplasia

6. **Metabolic**

Alpha-1-Antitrypsin deficiency

Cystic fibrosis

Galactosemia

Tyrosinemia

Hereditary Fructosemia

GSD Type 4

Niemann - Pick type A & C

Primary disorders of bile acid synthesis

Byler disease

Wolman disease

Zellweger syndrome

7. **Immune**

Neonatal lupus erythematosus

Neonatal hepatitis with autoimmune hemolytic anemia

CLINICAL FEATURES

The symptoms and signs commonly seen in all these disorders

-Jaundice

-Pale stools and dark urine

-Hepatomegaly

-Splenomegaly

-Ascites in some cases

-Deficiency of fat soluble vitamins

-Failure to thrive

The following symptoms and signs are peculiar to certain diseases and they aid in their diagnosis

1. Small for gestation: Alagille syndrome
   Metabolic liver disease
   Intrauterine infection
2. Dysmorphic facies: Trisomy 18 & Trisomy 21
   Zellweger syndrome
   Alagille syndrome
3. Hypoglycemia: Hypopituitarism
   Metabolic liver disease
   Severe liver disease

4. Associated other system anomalies:

Polysplenia/Asplenia - EHBA

Neurodegeneration - Niemann-Pick disease

PDA, PS, Vertebral anomaly-Alagille syndrome

Snuffles, osteitits –Congenital Syphilis

INVESTIGATIONS

1. Serum bilirubin – elevated in all cases of neonatal cholestasis. When the direct fraction is more than 20% of total bilirubin, it indicates cholestasis.

2. Liver enzymes (AST, ALT) – elevated in almost all cases of neonatal cholestasis. Not particularly useful in the differential diagnosis of neonatal cholestasis. Markedly elevated levels (>800 u/l) indicate hepatocellular damage as the cause of cholestasis. However in some cases of acute biliary obstruction, aminotransferase are elevated similarly because of secondary hepatocellular damage.

3. GGT – elevated in most cases. But will be normal or low in cases of Byler's disease, and primary bile acid synthesis defect. GGT is more specific than alkaline phosphatase as a indicator of damage to

biliary radicals, as alkaline phosphatase is also secreted by bones in growing children.

4. Serum albumin – Usually normal, unless there is severe liver disease.

5. PT & PTT – prolonged in severe liver disease / vitamin K efficiency.

6. Abdominal ultrasound – non visualization of gallbladder and positive 'TRIANGULAR CORD' sign are features of EHBA. Recent studies have suggested the use of gallbladder ghost triad and hepatic arterial diameter in predicting biliary atresia. Choledochal cyst, inspissated bile, coexistent congenital malformation like polysplenia, asplenia, situs anomalies can be made out with ultrasound.

7. Radioisotope scan: Used to demonstrate hepatic uptake and biliary excretion into the gut. Useful to rule out EHBA

8. Liver Biopsy- The most informative of all investigations. It helps in assessing the severity of hepatocellular involvement and extent of fibrosis, identifying features of EHBA and differentiating it from hypoplasia of bile duct, identifying infiltrative / storage / infectious diseases.

Hepatocellular damage with formation of multinucleated giant cells is a non-specific finding. Bile duct proliferation is said to be prominent in bile duct obstruction, but it also occurs in children with neonatal hepatitis syndrome, particularly those with Alpha-1-Antitrypsin deficiency, Cystic fibrosis, and endocrine deficiency.

SPECIFIC INVESTIGATIONS

1. Antibody assay- Infections like TORCH, Parvovirus B19, HIV, HBV and HCV
2. Urine culture – CMV, UTI
3. Blood culture – Sepsis
4. TSH, T3, T4, cortisol - Hypopituitarism, Hypothyroidism
5. Karyotyping – Trisomy 18, 21
6. Serum A_1AT, PI Phenotype – Alpha-1-Antitrypsin deficiency
7. Sweat chloride – Cystic fibrosis
8. RBC Gal-1-phosphate uridyl transferase – Galactosemia
9. Serum tyrosine, AFP, urine succinylacetone - Tyrosinemia
10. BM aspirate, Liver, Rectal biopsy – Niemann-Pick disease
11. Urine bile acid study by FAB-MS–primary bile acid synthesis defect.

MANAGEMENT

1. Supportive treatment

    Nutritional support

    Fat soluble vitamins

    Management of cholestasis and pruritus

2. Specific treatment

Nutritional support

Infants with neonatal cholestasis have increased resting energy expenditure-about 30% higher than in normal infants of the same sex and age[1]. Thus the calorie intake should be 120-150% of estimated average requirement. Infants taking breast feeds adequately should have supplementation with easily digestible high calorie density formula. Growth monitoring should be done in all children and appropriate measures to correct nutritional deficit should be undertaken.

Fat soluble vitamin supplementation

Vitamin A - 5000-25000 units/day

Vitamin D - 800-5000 units/day

Vitamin E - 15-25 IU/Kg/day

Vitamin k - 2.5 mg twice/week

Management of cholestasis and Pruritus

1. Cholestyramine- 1-4 g daily
2. UDCA – 15-30 mg/kg/day
3. Phenobarbitone – 5-10 mg/kg/day
4. Rifampicin – 5-10 mg/kg/day

SPECIFIC TREATMENT

1.	Toxoplasmosis	-Spiramycin
2.	CMV hepatitis	-Gancyclovir
3.	HSV	- Acyclovir
4.	Syphilis	- Penicillin
5.	Sepsis / UTI	- Appropriate antibiotics
6.	Tuberculosis	- ATT
7.	Syncitial giant cell hepatitis	- Ribavirin
8.	Panhypopituiarism	- Corticosterone, thyroxine
9.	EHBA	- Kasai's portoenterostomy
10.	Choledochal cyst	- Surgical resection
11.	Spontaneous perforation of CBD	- Surgical repair
12.	Primary bile acid synthesis defect	- Bile acid supplementation
13.	Drug induced	- Stop causative drug

EXTRAHEPATIC BILIARY ATRESIA

HISTORY OF BILIARY ATRESIA

1891: Thompson from Edinburgh reported a series of infants dying of liver failure secondary to congenital biliary atresia.[2]

1935: Ladd from Boston, USA, first described successful operation for ‘correctable’ types of biliary atresia; wherein atretic segments was limited to the common bile duct and hepatic ducts with patency of proximal biliary tree.

1959: Morio Kasai, a Japanese surgeon, first described Portoenterostomy- with increasing number of children having their jaundice cleared and surviving for longer periods.[3,4]

INCIDENCE OF BILIARY ATRESIA

It is a rare disease with incidence of 1:10,000 live births. Slight female preponderance has been described.[5]

DEFINITION

Biliary atresia is an idiopathic, localized complete obliteration or discontinuity of hepatic or common bile duct - at any point from the porta hepatic to the duodenum.[6,7]

PATHOGENESIS

Biliary atresia is a cholangiopathic panductular disease. The histologicalappearances in biliary atresia[8] are characterized by

-bile duct plugging.

-bile ductular proliferation.

-portal edema.

-variable giant cell formation.

The intrahepatic ducts are also affected in all cases of biliary atresia. Three types of biliary atresia are classified on the basis of the level of atresia of hepatic tree.

Type 1- Atretic common bile duct.

Type 2- Atretic common hepatic duct.

Type 3- Atresia of all hepatic ducts

Type 3 is most common accounting for 85% of all cases. Types 1 and 2 are less common and they carry a better prognosis.

Two types of biliary atresia have been described.[9]

- Embryonic form: With associated anomalies, thought to be due to intrauterine insults / infections.

- Perinatal form: Thought be due to viral infection-probably reo or rota virus.

ETIOLOGY

Congenital hepatic embryopathy : Bile duct, spleen, portal vein, inferior vena cava –all structures develop by 25-40 days of gestation. In about 10% of cases of biliary atresia, the cholangiopathy is accompanied by malformation of spleen (polysplenia/asplenia) known as biliary atresia spleen malformation (BASM) [10].

Thus an ‘insult ’occurring in early phase of development may be a cause of these anomalies. One study showed an association between gestational diabetes mellitus and BASM.[10]

There is histological and immunohistochemical similarity between hepaobiliary system developing at 11-13 weeks of gestation and a well established case of biliary atresia. Thus it has been suggested that biliary atresia without syndromic features may represent an arrested development of biliary radicals.

A small number of biliary atresia cases had gestational ultrasound anomalies from 17 weeks. GGT is an enzyme of fetal liver origin found in amniotic fluid from second trimester onwards and it relates to in-utero

bile production and defecation. A large study of amniotic fluid sampling showed that children born with biliary atresia had minimal levels of amniotic fluid GGT at 18 weeks gestation[11].

Viral studies : Experimental studies in animals with hepatotrophic viruses like reo[12] and rota virus have shown that these viral agents can reproduce some of the histological features of biliary atresia – although not usually the typical clinical extrahepatic appearance and sequelae.

Seasonal variation and winter predilection for Biliary atresia have been described suggesting viral etiology.

Anatomical factors : Common pancreatico-biliary channel I seen in <5% of normal population, whereas it is seen in 60% of infants with biliary atresia and 80% of infants and children with choledochal cyst[13]. When the common bile duct was ligated in experimental animals, it produced some of the changes of biliary atresia[14].

Acquired biliary atresia: A rare condition, associated with abdominal surgeries/ healing spontaneous perforation of bile duct. Here intrahepatic ducts are dilated in ultrasound. They have relatively good prognosis.

CLINICAL FEATURES

Infants with biliary atresia are usually born as AGA babies. Initially the newborn feeds normally and thrives normally. However as the obstruction progresses the child manifests with features of chronic liver disease and biliary cirrhosis.

The initial symptoms will be jaundice- which can occur as a continuation, or after a gap of physiological jaundice, associated with high colored urine and persistent pale stools. Signs are usually minimal in the earlier stages. In the later stages child can have hepatosplenomegaly, ascites, and features of portal hypertension.

The child can manifest as a case of bleeding diatheses due to vit-k deficient coagulopathy. Coexistent congenital anomalies like situs versus, malrotation can be identified.

INVESTIGATIONS

Early diagnosis and treatment will improve outcome.

1. Biochemical changes : Serum conjugated hyperbilirubinemia after 14 days of life. Serum AST, ALT, GGT elevated. Serum total protein and albumin normal in initial period. Serum cholesterol reduced.

2. Ultrasound abdomen : Rules out other surgical biliary conditions like choledochal cysts and inspissated bile. Used to identify biliary atresia by the non visualization of Gall Bladder during fasting and by demonstrating 'TRIANGULAR CORD' sign. Associated anomalies like situs inversus/ preduodenal portal vein/ polysplenia can be demonstrated.

3. Radionuclide hepatobiliary imaging:

   Imaging with Imino Diacetic Acid (IDA) demonstrates absence of gut excretion of bile even after 24 hours. But there is a high incidence of false positive results.

4. Percutaneous Liver Biopsy:

5. Laparotomy with operative cholangiography:

   During cholangiography, if the entire biliary tree is visualized it rules out the possibility of EHBA. If the biliary tree is atretic, surgery is proceeded.

TREATMENT

There is no medical treatment. Kasai's portoenterostomy is the initial step in the management of EHBA. In this surgery the atretic biliary tree along with gallbladder is removed and Roux-en-Y portoenterostomy done. Immediate postoperative complications are minimal and include

bleeding and persistent leak from abdominal drain. Potential complications that may rise in the follow-up include

- Ascending bacterial cholangitis.
- Portal hypertension with progressive chronic liver disease.
- Nutritional deficiencies
- Rare complications like intrapulmonary shunting and very rarely malignant changes[15].

Children in whom the initial surgery does not produce adequate biliary drainage- as in 40% of cases- and those children who have progressive liver disease in spite of initial drainage are the candidates of liver transplantation[16]. EHBA is the most common indication of liver transplantation[17]. Redo Kasai is usually avoided in cases of potential liver transplantation.

OUTCOME

Left untreated these children usually die by 2 years or earlier. 70 - 80% of infants operated with Kasai's develop bile flow following surgery and 50% survive to 5 years of age.[18] Various studies have shown that 30-40% of the children survive up to 10 years with their native liver[15, 19, 20, 21]. Approximately 65% of children who undergo primary Kasai will ultimately require liver transplantation[22, 7].

REVIEW OF LITERATURE

REVIEW OF LITERATURE

1. Choi *et al* [23] in 1998 published a study from Keimyung University Dongsan Medical centre, Korea in which the authors reviewed the ultrasonographic examination and hepatobiliary scintigraphy in a series of 41 infants suspected of having EHBA or neonatal hepatitis. The triangular cord was identified in thirteen infants. In twelve of thirteen infants who had triangular cord sign found by ultrasonogram, the diagnosis of EHBA was confirmed at the time of Kasai procedure. The remaining one died at 15 months without having treatment. Twenty-seven of twenty-eight infants with absent triangular cord sign improved with the medical treatment for neonatal hepatitis on follow up. The other, diagnosed to have neonatal hepatitis by needle and wedge liver biopsy, eventually showed a triangular cord on follow up ultrasound examination performed 40 days after initial examination. On review of the hepatobiliary scintigraphy, all 13 infants with positive triangular cord sign had no intestinal excretion of isotope. 13 of the 28 infants without triangular cord also had no intestinal excretion of isotope in 24 hour follow up, but all of them were confirmed to have neonatal hepatitis by percutaneous biopsy and follow up. On the basis of these results the authors conclude that the triangular cord is

a very specific finding representing the fibrous cone at the porta hepatis and is a quick, simple, and a definitive tool in the noninvasive diagnosis of EHBA. If triangular cord sign is visualized, no further studies are required and exploratory laparotomy can be done. If triangular cord sign is not visualized hepatobiliary scintigraphy is recommended to demonstrate bile duct patency. Liver biopsy is required only if triangular cord sign is negative and there is no intestinal excretion of isotopes.

2. Choi *et al* [24] in 1999 published a study with a primary aim to evaluate the importance of the ultrasonographic triangular cord coupled with gall bladder images in the diagnostic prediction of EHBA from neonatal hepatitis. Seventy nine infants with cholestatic jaundice underwent ultrasound examination focusing in the triangular cord and gall bladder images. The triangular cord sign was defined as visualization of a triangular or band like periportal echogenicity (3 mm or greater in thickness), which represents a cone shaped fibrotic mass cranial to the portal vein in infants with EHBA. An abnormal gall bladder (nonvisualized or small) was thought to be more suggestive of EHBA than neonatal hepatitis. Among 25 infants with EHBA, 21 showed triangular cord sign, whereas 4 had no triangular cord. 53 of 54 infants with

neonatal hepatitis had no triangular cord, showing a diagnostic accuracy of 94% with a sensitivity of 84% and a specificity of 98%. When positive triangular cord sign was coupled with an abnormal gall bladder the positive predictive value was 100%, it decreased to 88% when a positive triangular cord was coupled with a normal gall bladder, it further decreased to 25% when negative triangular cord was coupled with an abnormal gall bladder. The authors concluded that the triangular cord sign appears to be a specific and definite ultrasonographic finding in the early diagnosis of EHBA. Positive triangular cord sign regardless of gall bladder images is highly suggestive of EHBA showing a positive predictive value of 95%

3. Choi *et al* [25] published a study in 1996 in which the authors investigated whether TC was useful in the non invasive diagnosis of Biliary Atresia in 18 infants who had persistent neonatal jaundice. The triangular cord was identified in nine, and all of them were confirmed to have biliary atresia by histopathological examination. The triangular cord sign was not observed in other nine patients, who had neonatal hepatitis. On the basis of these results the authors concluded that ‘TC is a very specific

ultrasonographic sign, representing the fibrous cone at the porta hepatis, and is a useful tool in the diagnosis of EHBA'

4. Choi *et al* [26] in 1997 published a study in which the authors evaluated prospectively the utility of ultrasonography, Tc-99m-DISIDA hepatobiliary scintigraphy and needle liver biopsy in differentiating EHBA from intrahepatic cholestasis in 73 consecutive infants who had cholestasis. Ultrasonogram was done in all infants with 7.0 MHz probe focusing on the fibrous tissue in the porta hepatis. Although 17 of 20 ultrasonographic examinations from infants who had EHBA denoted triangular cord, 43 ultrasonographic examinations from infants with either neonatal hepatitis or other causes of cholestasis denoted no triangular cord , showing a diagnostic accuracy of 95%, sensitivity of 85%, and specificity of 100%. Investigation with radionuclide imaging showed that 24 of 25 infants who had EHBA had no gut excretion, and 16 of 46 infants who had either neonatal hepatitis or other causes of neonatal cholestasis had gut excretion showing a diagnostic accuracy of 56%, sensitivity of 96% and specificity of 35%. Forty four liver needle biopsies were carried out in 20 infants who had EHBA and 24 infants who had neonatal hepatitis or other cause of cholestasis. Although 18 of 20 biopsy findings in infants

who had EHBA were correctly interpreted as having EHBA, 23 of 24 biopsy results in infants who had neonatal hepatitis or other causes of cholestasis were correctly diagnosed, showing a diagnostic accuracy of 93%, sensitivity of 90% and specificity of 96%. The study revealed that 'The ultrasonographic TC sign is a simple, time saving, highly reliable, and non invasive tool in the diagnosis of EHBA from other causes of cholestasis. Based on these findings the authors proposed a new strategy in the evaluation of infants with neonatal cholestasis. If the TC is visualized prompt exploratory laparotomy is mandatory without further investigations. If the TC is not visualized, hepatobiliary scintigraphy is the next step. Excretion of tracer into the small bowel actually rules out EHBA. Liver biopsy is reserved only for the infants with no excretion of tracer. The authors conclude that 'the triangular cord sign seems to be a simple, time saving, highly reliable, and non – invasive tool in the diagnosis of biliary atresia from other causes of cholestasis'.

5. Kendric *et al* [27]published a study in 2000 from Kandung Kerbau Women's and Children's hospital, Singapore which was done to evaluate the accuracy and utility of the TRIANGULAR CORD sign and the gallbladder length in diagnosing biliary atresia by

ultrasonography. Sixty five infants with cholestatic jaundice aged 2 – 12 weeks were examined with a 5 – 10 MHz frequency probe focusing on triangular cord, gall bladder, and ducts. Diagnosis of biliary atresia was confirmed at surgery and histology. Non – biliary atresia infants resolved medically. Twelve infants had EHBA, and ten demonstrated a definite triangular cord. The two false negatives had small or non visualized gall bladders. No false positives were recorded. Scintigraphy and liver biopsy charges were 2 and 6 times that of sonography, respectively. The authors concluded that 'the triangular cord sign and gallbladder length together were found to be very useful markers in the diagnosis of biliary atresia'.

6. Kanegawa *et al* [28] from Kobe children's hospital, Japan published a study in 2003. A retrospective review was performed to evaluate the importance of the "triangular cod" sign in comparison with gallbladder length and contraction for the diagnosis of biliary atresia in pediatric patients. Fifty – five fasting infants with cholestatic jaundice were examined with ultrasound focusing on the triangular cord sign and the size and contractility of gall bladder. The diagnosis of neonatal hepatitis was made if the symptoms resolved during follow – up. A triangular cord sign was

found in 27 of 29 infants with biliary atresia and in one of 26 infants with neonatal hepatitis or other causes of neonatal cholestasis. The diagnostic accuracy was 95%, sensitivity was 93% and specificity was 96%. The gall bladder was abnormal in 21 of 29 infants with biliary atresia, whereas it was abnormal in 8 of 26 infants with neonatal hepatitis or other causes of neonatal cholestasis. The diagnostic accuracy was 71%, sensitivity was 72% and specificity was 69%. Gall bladder contraction was not confirmed in 11 of 13 infants with biliary atresia and seven of 26 infants with neonatal hepatitis or other causes of neonatal cholestasis. The diagnostic accuracy was 77%, sensitivity was 85% and specificity was 73%. The authors concluded that 'the triangular cord sign was more useful sonographic finding for diagnosing biliary atresia than gallbladder length and contraction'.

7. Kotb *et al* [29] from department of Pediatrics and Radiology, Cairo university children's hospital, Cairo, Egypt published a study in 2001.This study prospectively studied 65 infants who presented with conjugated hyperbilirubinemia. All infants were subjected to ultrasonographic examination and the TC was assessed. The triangular cord was identified in 25 infants, and all of them had histologic features suggestive of biliary atresia. Among the 40

patients who did not have the triangular cord sign, 6 had paucity of the intrahepatic ducts, 3 had alpha – 1 - antitrypsin deficiency, and 31 had neonatal hepatitis. Seven patients with biliary atresia were followed by ultrasonographic examination for 6 months after the Kasai portoenterostomy. The triangular cord sign disappeared in all cases after the surgery, however, the triangular cord sign reappeared in 3 patients progressive cholestasis after the procedure It was found that the TC sign is a simple, time saving, and reliable diagnostic tool in the infants with cholestasis. The triangular cord sign may also prove to be helpful in following patients after portoenterostomy. The authors suggested a diagnostic strategy based on their findings. When the TC sign is visualized, the patient should undergo intraoperative cholangiogran to confirm the diagnosis of biliary atresia, reserving percutaneous liver biopsy for those patients in whom the TC sign could not be detected.

8. D.K.Gupta *et al* [30] from All India Institute of Medical Sciences, New Delhi, India published an article in 2001.The authors performed this retrospective study to evaluate the reliability of AIIMS clinical score (ACS) in differentiating neonatal hepatitis from extrahepatic biliary atresia. ACS is based on 5 clinical parameters – age, jaundice, color of urine, pale stools, and clinical

examination of liver. 120 children referred to pediatric surgery department over 10 years were included in the study. Each child was given a score and was provisionally diagnosed either as biliary atresia or neonatal hepatitis clinically. The diagnosis of biliary atresia was established with operative cholangiography. ACS was favoring the diagnosis of biliary atresia in 84 patients, with a true positive of 75 and a false positive of 9. ACS was favoring a diagnosis of neonatal hepatitis in 34 patients, with 24 true neonatal hepatitis cases and the remaining 7 turned out to be falsely concluded as neonatal hepatitis. Thus ACS showed a sensitivity of 91.5%, specificity of 76.3%, PPV of 89.2%, NPV of 80.5%, and an overall diagnostic accuracy of 86.6%

NEED FOR THE STUDY

NEED FOR THE STUDY

EHBA and idiopathic neonatal hepatitis are two major causes of neonatal cholestasis syndrome. Differentiating EHBA from neonatal hepatitis is of paramount importance in the management of infants with cholestasis. The reason being early diagnosis and early surgical management of EHBA (before 8th week of life) will have relatively good prognosis as compared to late treatment[3,18,].

Clinical symptoms that are used to diagnose EHBA include[30]

1. Persistent pale stools.
2. Jaundice – severe and non-fluctuating.
3. Age of clinical presentation – late onset with EHBA.
4. Dark yellow urine.
5. Firm liver with sharp edge.

Of all the symptoms, persistent pale stools has been found to be highly diagnostic of EHBA, though it is also seen in severe forms of neonatal cholestasis.

The weightage for differentiating EHBA from idiopathic neonatal hepatitis is placed on investigations. The investigations that can differentiate EHBA from NH are;

Ultrasonogram

Hepatobiliary radionuclide imaging

Peroperative cholangiogram

Liver biopsy

Ultrasonogram : USG can be vital in the noninvasive diagnosis of EHBA. Previously diagnosis was made on the basis of visualization or non visualization of gallbladder in a fasting infant[31]. .Recent studies starting in 90's have highlighted the importance of 'TRIANGULAR CORD' sign in the diagnosis of extrahepatic biliary atresia[23-30]. It is a cord like echogenic structure identified cranial to the portal vein – representing the atretic extrahepatic biliary apparatus. These studies have concluded that TRIANGULAR CORD sign is a simple, noninvasive, specific, cost-effective diagnostic modality in the diagnosis of EHBA. A recent study has shown the usefulness of the gall bladder ghost triad in the diagnosis of biliary atresia[32]. Hepatic artery diameter and the hepatic artery/portal vein diameter ratio measured by ultrasonogram has been

shown to be an adjunct for the ultrasonographic diagnosis of biliary atresia in a recent study[33].

Hepatobiliary radionuclide imaging : Hepatobiliary imaging using 99m-Tc Iminodiaceticacid can be used to determine the hepatic intake and biliary excretion. In idiopathic neonatal hepatitis, liver will show delay in uptake but normal excretion. In EHBA, the uptake will be normal, but excretion will be delayed or absent. Though radionuclide imaging has good sensitivity, it shows high rates of false-positivity[29]. Of late, radionuclide imaging using 99m – Tc methylbromo diaminoaceticacid (mebrofenin) has been shown to be of higher diagnostic accuracy[34].

Studies have shown improved specificity when radionuclide study was done after administering Phenobarbital for 5 days. A study has reported the improved specificity of radionuclide scan in diagnosing biliary atresia if ursodeoxycholic acid was given for 2-3 days before the procedure[35].

Peroperative cholangiography : Peroperative cholangiography is an invasive procedure. In this procedure after instilling the dye in the gallbladder the biliary tree is imaged. Non-visualization of extrahepatic biliary apparatus is taken as a presumptive evidence of EHBA.

Percutaneous liver biopsy : Percutaneous liver biopsy shows the typical features of biliary atresia. But the sensitivity, specificity, diagnostic accuracy of this mode of investigation is highly varied.

Diagnostic approach to EHBA in ICH, Chennai

The diagnosis of EHBA is established in a child when he / she has the following features

- If the child presents with persistent acholic stools.
- If 3 serial ultrasound studies with the child fasting overnight shows absent gall bladder.
- If bile is not visualized with endoscope in duodenum.
- If radionuclide imaging shows absent biliary excretion even after 24 hours.
- liver biopsy is generally not done in our institution because of the late presentation of the children, where the difference between neonatal hepatitis and EHBA is generally not made out in the biopsy specimen.

JUSTIFICATION OF THE STUDY

The detection of triangular cord by ultrasonogram is a simple investigation modality which has been shown to be specific, cost-effective, non invasive diagnostic modality in the diagnosis of EHBA. Also it is a investigation where there is no ionizing radiation exposure and the instrument is usually portable and bed side diagnosis can be made. Evaluation of this particular sign in association with abnormal gallbladder is a must in our population before widespread use. Hence the present study intends to find the diagnostic utility of 'triangular cord' sign with abnormal gall bladder. If found highly sensitive, specific, as other similar studies done elsewhere, ultrasonogram will be very useful in our resource constrained clinical setup, obviating the need for costly investigations like radionuclide imaging, liver biopsy.

AIM OF THE STUDY

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a. To assess the usefulness of clinical features – viz., level of jaundice, onset of jaundice, persistent pale stools, dark urine, consistency of liver taken together (AIIMS Clinical Score – ACS) in differentiating EHBA (Extra Hepatic Biliary Atresia) from neonatal hepatitis.

b. To evaluate the usefulness of ultrasonographically determined gall bladder size, and 'TRIANGULAR CORD' sign in differentiating EHBA from neonatal hepatitis in isolation or in combination with ACS mentioned above.

SUBJECTS AND METHODS

METHODOLOGY

STUDY DESIGN

Descriptive study

Evaluation of a diagnostic test.

STUDY PERIOD

November 2006 – July 2008

PLACE OF STUDY

Department of Gastroenterology, Institute of Child Health and Hospital for Children, Chennai.

STUDY POPULATION

Inclusion criteria

All infants with conjugated hyperbilirubinemia

Exclusion criteria

Children with other surgical causes like choledochal cyst, spontaneous rupture of CBD, Inspissated bile.

SAMPLE SIZE

A total of 30 consecutive infants with neonatal cholestasis who presented to the department of pediatric gastroenterology were included in study.

MANOEUVRE

The following parameters of all the children enrolled in the study were noted- age of onset of jaundice, level of jaundice, color of stools, color of urine, consistency of liver and AIIMS clinical score was given to each child.

Table 1. AIIMS clinical score: various parameters and the respective scores[30]

Sl.No	Parameters	Score
1	**AGE OF PATIENT**	
	<6 weeks	2
	> 6 weeks	1
2	**JAUNDICE**	
	Fluctuating, mild or moderate	2
	Severe (bilirubin > 8 mg%)	1
3	**STOOL**	
	Normal or light yellow	2
	Mostly clay colored	1
4	**URINE**	
	Normal or light yellow	2
	Mostly dark yellow	1
5	**LIVER**	
	Soft & smooth	4
	Firm with sharp edge	1

Interpretation

Score $\geq$ 10 : neonatal hepatitis

Score < 10 : EHBA

All the infants who were eligible for the study were subjected to Ultrasonogram with a 7.0 – 10 MHz probe. The procedure was done with the child fasting for at least 4 hours. Size of the gallbladder was made out. Presence or absence of 'TRIANGULAR CORD' was evaluated and size of the cord was measured. Triangular cord sign is a cord like echogenic structure seen cranial to the portal vein. Studies have revealed that this particular sign to be present exclusively in EHBA Biliary atresia was diagnosed ultrasonographically if;

1. Abnormal gall bladder-gallbladder not visualized, gallbladder visualized but no lumen, gallbladder with lumen but length <1.5cm.

2. TC sign >3 mm.

If either of the findings were absent, the child was diagnosed ultrasonographically to have neonatal hepatitis.

The final diagnosis (gold standard) in biliary atresia was based on peroperative findings, peroperative cholangiogram and liver biopsy.

The gold standard for the diagnosis of neonatal hepatitis was based on presence of intestinal excretion of radionuclide and/or reduction of symptoms on follow up

STATISTICAL ANALYSIS

Sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy of

- USG diagnosed abnormal gall bladder,
- USG diagnosed triangular cord sign,
- AIIMS clinical score,
- Triangular cord sign coupled with gall bladder,
- Triangular cord sign coupled with AIIMS clinical score,
- Triangular cord sign coupled with gall bladder and AIIMS clinical score.

against the gold standard (peroperative findings/ cholangiography/liver biopsy in EHBA and resolution of symptoms on follow up in neonatal hepatitis) among all babies presenting with features of neonatal cholestasis was arrived by constructing 2/2 tables.

RESULTS

RESULTS

Table 2

Age and sex distribution of all infants with neonatal cholestasis syndrome

Age	Total number of cases n (%)	Male n (%)	Female n (%)
<30 days	8 (27)	8 (27)	0 (0)
1 – 2 months	8 (27)	6 (20)	2 (7)
2 – 3 months	6 (20)	4 (13)	2 (7)
3 – 4 months	4 (13)	0 (0)	4 (13)
4 – 6 months	4 (13)	4 (13)	0 (0)
Total	30 (100)	22 (73)	8 (27)

A total of 30 infants were included in the study. None of them were excluded. The age of these infants ranged from 20 days to 5 months with a median of 3 months. Out of the 30 infants, 22 (73%) were male children and 8 (27%) were female children with male : female ratio of 22:8.

Table 3

Sex distribution of subjects with EHBA and neonatal hepatitis

Diagnosis	Male n(%)	Female n(%)	Total n(%)
Neonatal hepatitis	14(47)	4(13)	18(60)
Biliary atresia	8(27)	4(13)	12(40)
Total	22(73)	8(27)	30(100)

Among the total of 30 babies with neonatal cholestasis18 (60%) were diagnosed to have neonatal hepatitis and 12 (40%) were diagnosed to have biliary atresia. 14(47%) male and 4(13%) female infants had neonatal hepatitis. 8 (27%) female and 4 (13%) male infants had biliary atresia.

Table 4

Evaluation of AIIMS clinical score in neonatal cholestasis syndrome

AIIMS clinical score	EHBA n(%)	Others n(%)	Total n(%)
< 10	8(27)	10(33)	18(60)
≥ 10	4(13)	8(27)	12(40)
Total	12(40)	18(60)	30(100)

AIIMS clinical score was 10 or more in twelve infants (40%), was less than 10 in eighteen infants (60%). Of the 12 infants finally diagnosed as EHBA, 8 (27%) infants had a score of <10, thus giving a sensitivity of 67%. Of the 18 infants finally diagnosed to have neonatal cholestasis due to cause other than EHBA, 8 (27%)had a score of >10, thus giving a specificity of 44%. Among the 18 children who had a AIIMS score of less than 10, 8 (27%)were EHBA thus giving a positive predictive value of 44%. Among the children who had a AIIMS score of 10 or more, 8 (27%)were neonatal hepatitis thus giving a negative predictive value of 67%. The overall diagnostic accuracy of this AIIMS clinical score was 53%.

Table 5

Evaluation of triangular cord sign in neonatal cholestasis syndrome

Triangular cord sign	EHBA n(%)	Others n(%)	Total n(%)
Positive	10(33)	1(3)	11(37)
Negative	2(7)	17(57)	19(63)
Total	12(40)	18(60)	30(100)

Triangular cord sign in ultrasound was observed in 10(33%) out of 12 cases of EHBA giving rise to a sensitivity of 83%. The sign was not seen in 17(57%) of 18 cases of etiology other than EHBA giving a specificity of 94%. Among the total 11 children who had positive triangular cord sign, 10(33%) children were proved to be EHBA giving rise to positive predictive value of 91% and negative predictive value of 89% as 17(57%) out of 19 children who had negative triangular cord sign were found to have neonatal hepatitis. In 27(90%) children out of 30 children with neonatal cholestasis, the triangular cord sign correlated with the gold standard diagnosis leading to overall diagnostic accuracy of 93%.

Table - 6

Evaluation of gall bladder in neonatal cholestasis syndrome

Gall bladder	EHBA n(%)	Others n(%)	Total n(%)
Abnormal	10(33)	4(13)	14(47)
Normal	2(7)	14(47)	16(53)
Total	12(40)	18(60)	30(100)

An abnormal gall bladder was noticed in 10(33%) cases out of 12 cases of EHBA giving a sensitivity of 83%. A normal gall bladder was observed in 14(47%) of 18 cases with diagnosis other than EHBA, thus giving a specificity of 78%. Out of 14 cases with abnormal gall bladder, 10(33%) had EHBA giving a positive predictive value of 71%. 14(47%) out of 16 cases with etiology other than EHBA had a normal gall bladder giving a negative predictive value of 88%. In 24(80%) children out of 30 cases of neonatal cholestasis, the gall bladder correlated with the final diagnosis, thus giving a diagnostic accuracy of 80%.

Table 7

Evaluation of triangular cord sign and gall bladder in neonatal cholestasis syndome

Positive triangular cord sign and abnormal gall bladder	EHBA n(%)	Others n(%)	Total n(%)
Yes	9(30)	0(0)	9(30)
No	3(10)	18(60)	21(70)
Total	12(40)	18(60)	30(100)

Positive triangular cord sign and abnormal gall bladder was seen in 9 (30%) cases and all of them were EHBA. Other combinations of triangular cord sign and gall bladder was seen in 21 cases, out of them 3(10%) were diagnosed as EHBA and 18(60%) were diagnosed as neonatal hepatitis. Thus when positive triangular cord sign and abnormal gall bladder were clumped together, the sensitivity, specificity, positive predictive value, negative predictive value, and the diagnostic accuracy in diagnosing EHBA was75%, 100%, 100%, 86% and 90% respectively.

Table 8

Evaluation of triangular cord sign and AIIMS clinical score in neonatal cholestasis syndrome

Positive triangular cord sign and AIIMS score <10	EHBA n(%)	Others n(%)	Total n(%)
Yes	8(27)	0(0)	8(27)
No	4(13)	18(60)	22(73)
Total	12(40)	18(60)	30(100)

Positive triangular cord sign and AIIMS score <10 was seen in a total of 8(27%) cases and all of them were biliary atresia. Other combinations of triangular cord sign and AIIMS clinical score was seen in 22(73%) cases, out of which 4(13%) cases were EHBA and 18(60%) cases were neonatal hepatitis. Thus when positive triangular cord sign and AIIMS clinical score <10 was clumped together, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy in diagnosing EHBA was 67%, 100%, 100%, 82% and 87% respectively.

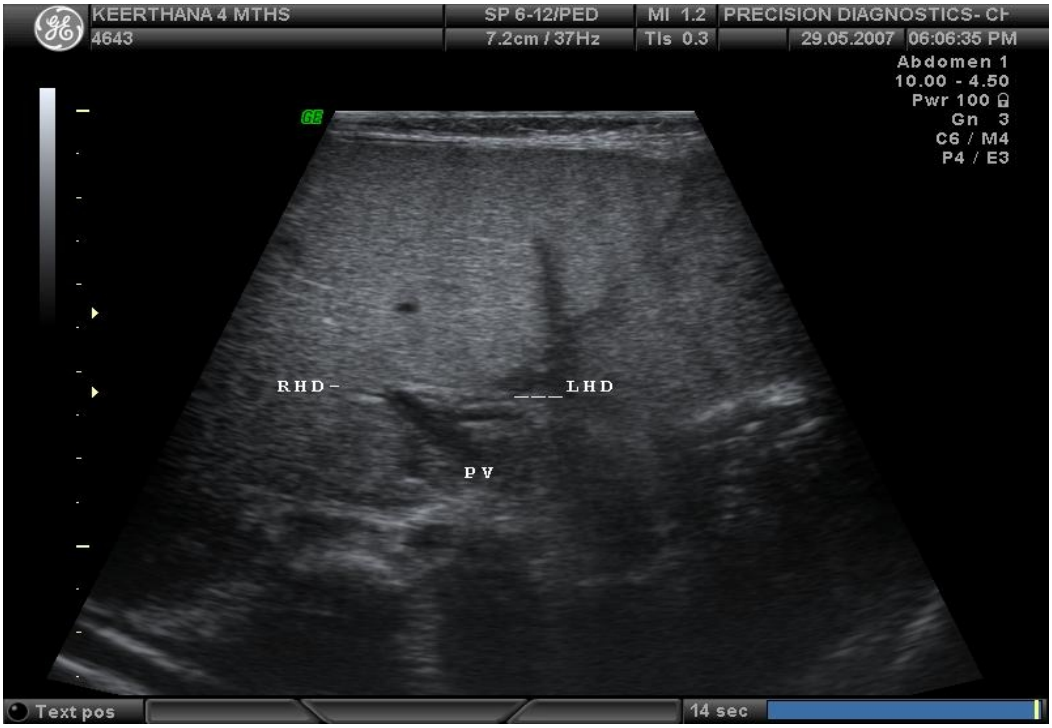
Table 9

Evaluation of triangular cord sign, gall bladder, AIIMS clinical score in neonatal cholestasis syndrome

Positive triangular cord sign, abnormal gall bladder and AIIMS clinical score <10.	EHBA n(%)	Others n(%)	Total n(%)
Yes	6(20)	0(0)	6(20)
No	6(20)	18(60)	24(80)
Total	12(40)	18(60)	30(100)

Positive triangular cord sign, abnormal gall bladder, and AIIMS score <10 was seen in a total of 6(20%) cases and all of them were EHBA. Other combinations of these findings was present in 24(80%) children, out of which 6(20%) were EHBA and 18(60%) were neonatal hepatitis.

Thus when positive triangular cord sign, abnormal gall bladder and AIIMS clinical score <10 was clumped together, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy in diagnosing EHBA was 50%, 100%, 100%, 75% and 80% respectively.



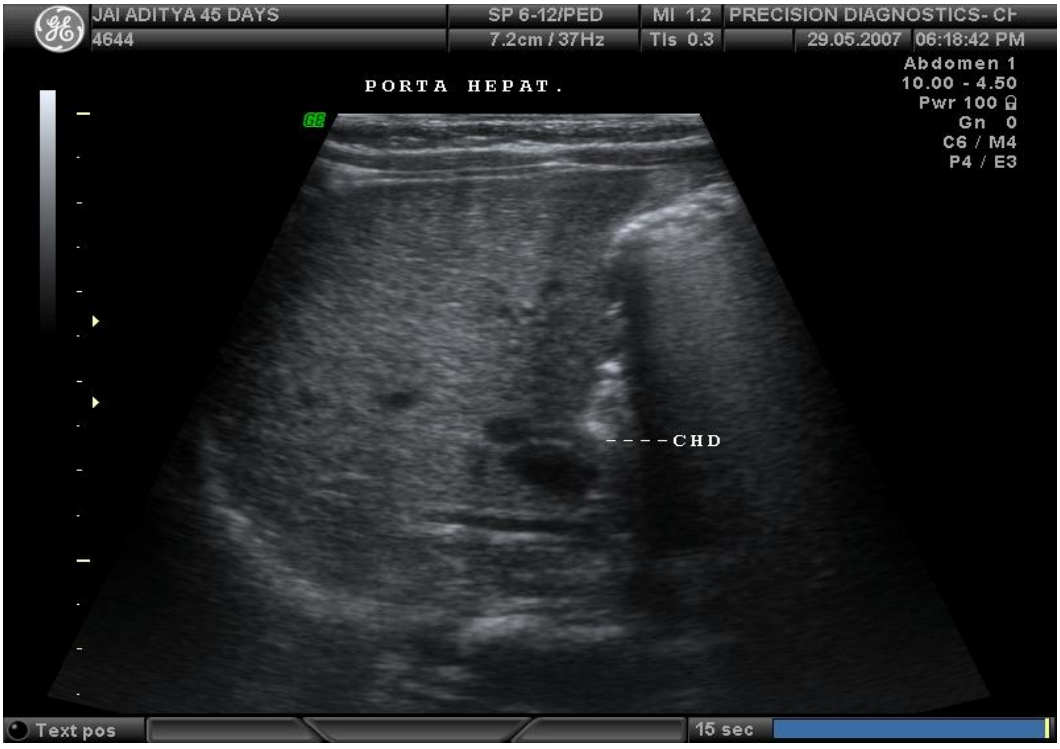
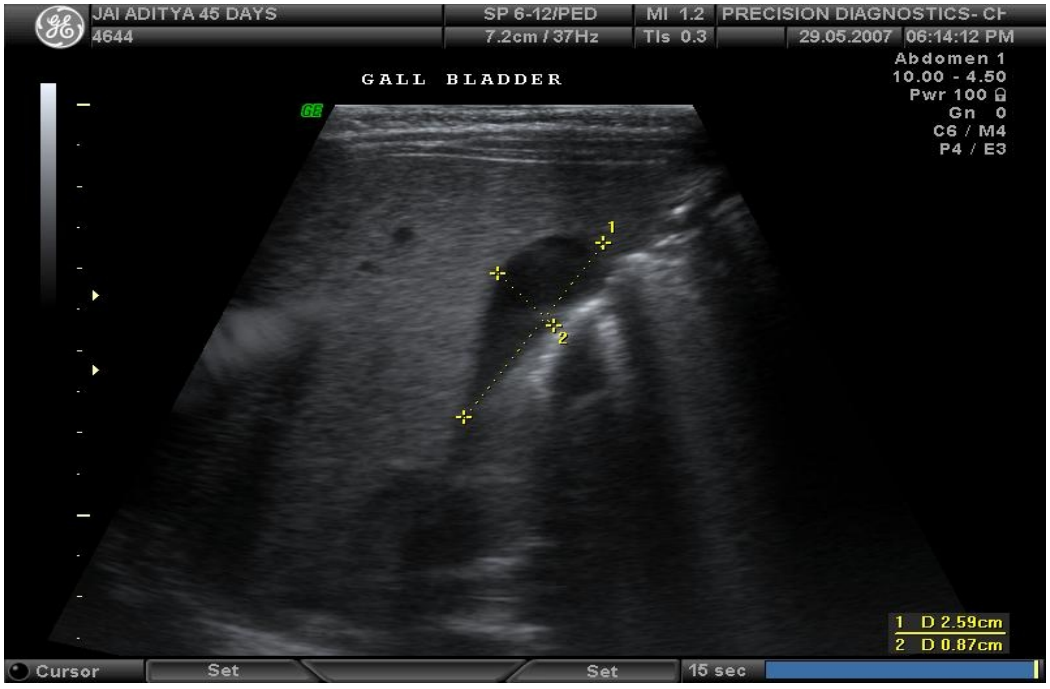


Figure 1. Ultrasonogram showing normal porta hepatis



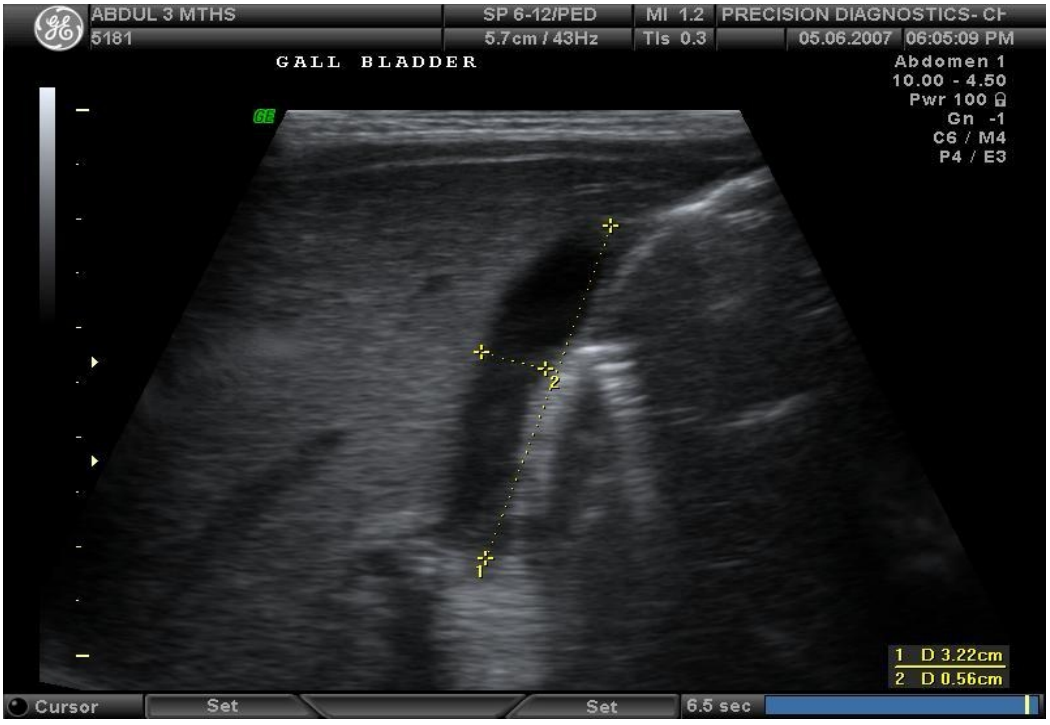


Figure 2. Ultrasonogram showing normal gall bladder

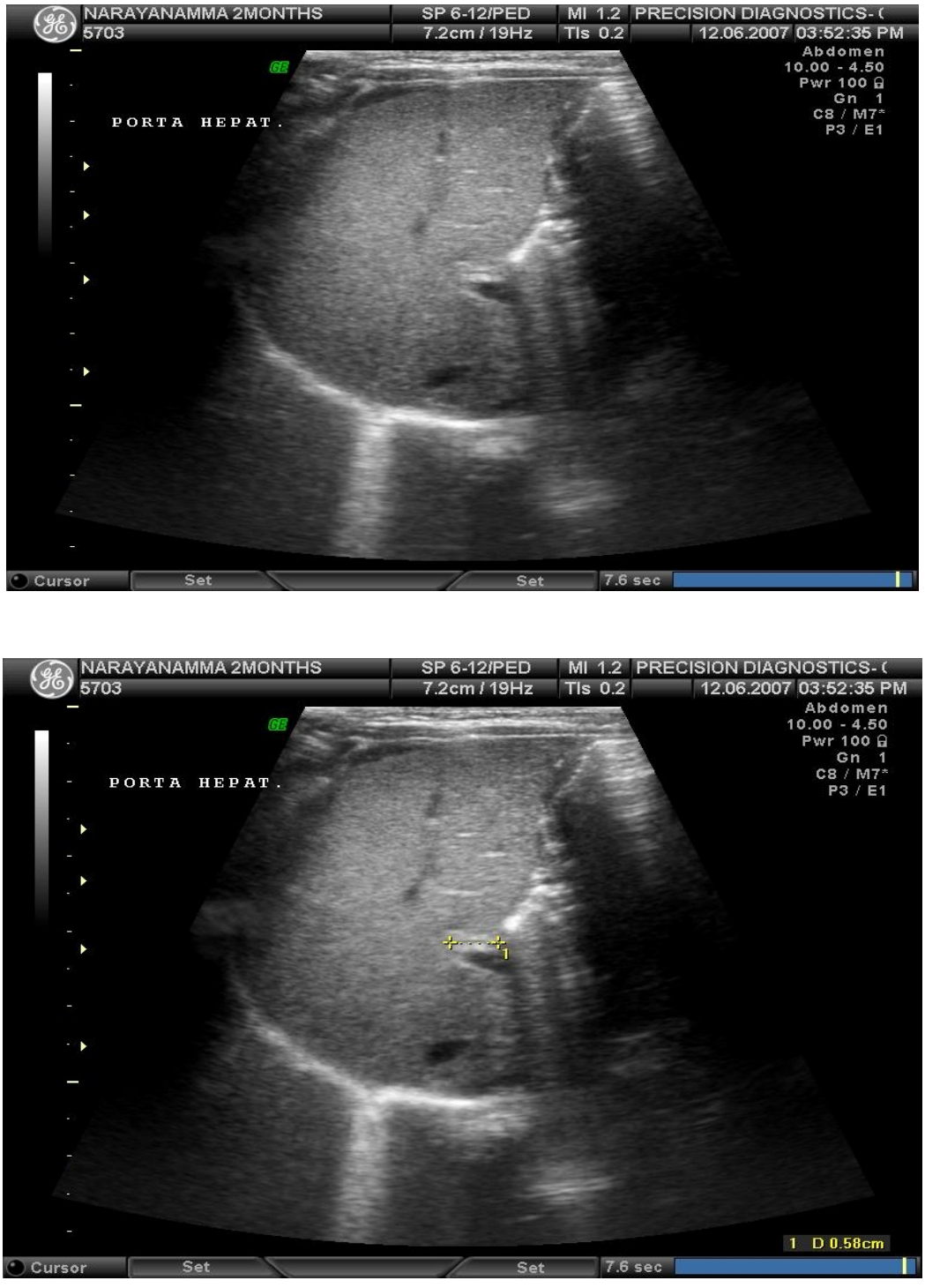
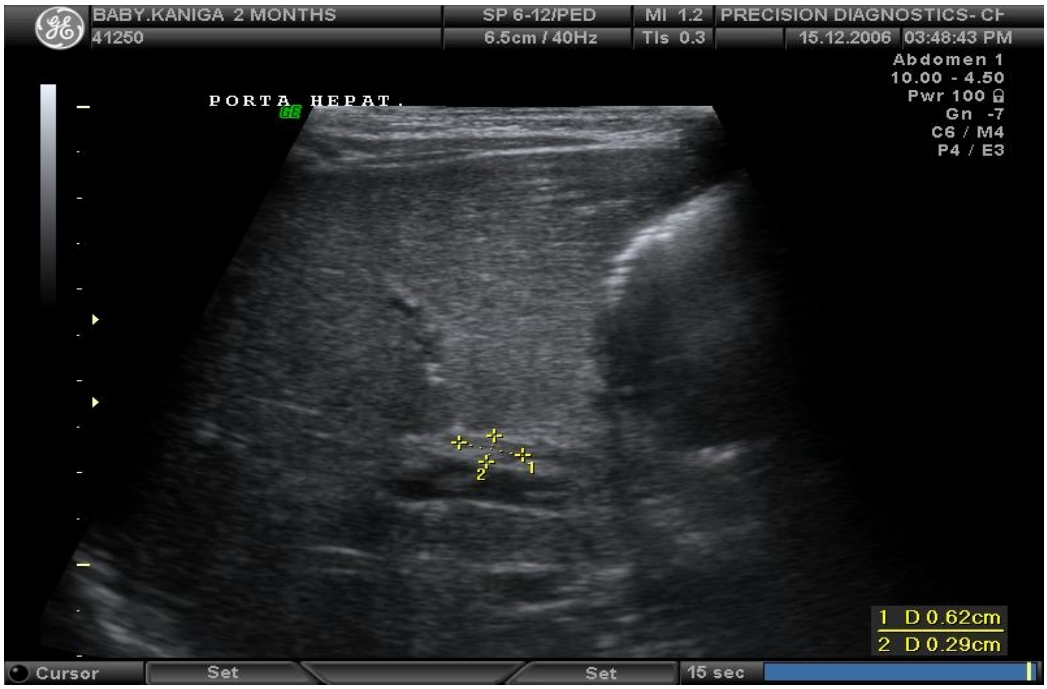


Figure 3.Ultrasonogram showing Triangular cord at porta hepatis



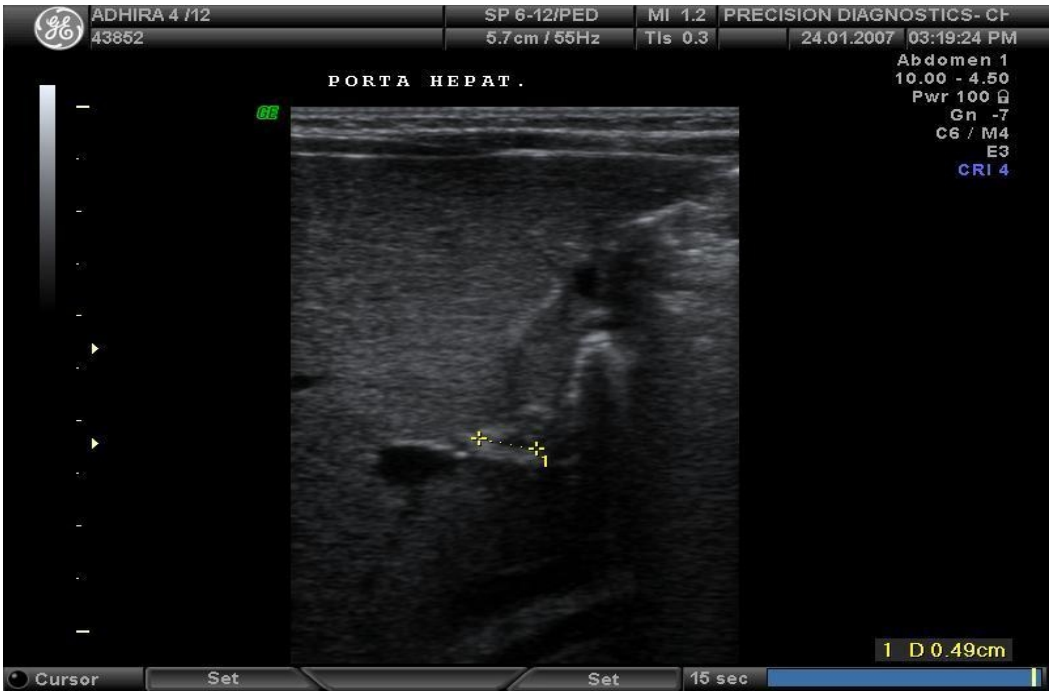
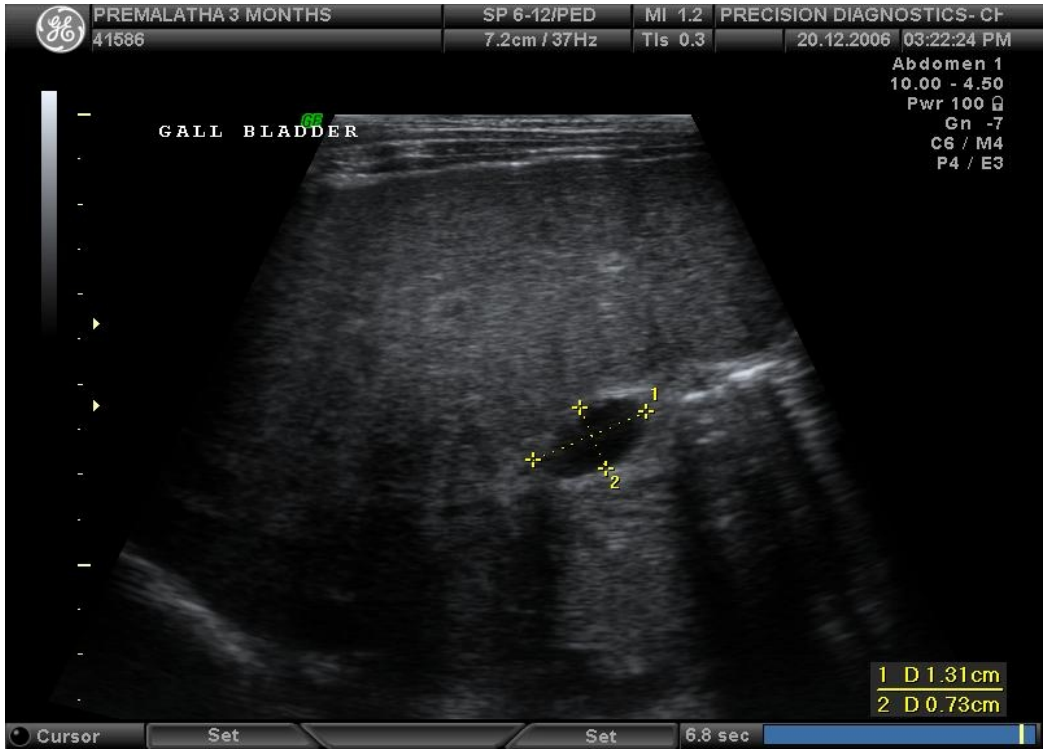


Figure 4.Ultrasonogram showing Triangular cord at porta hepatis



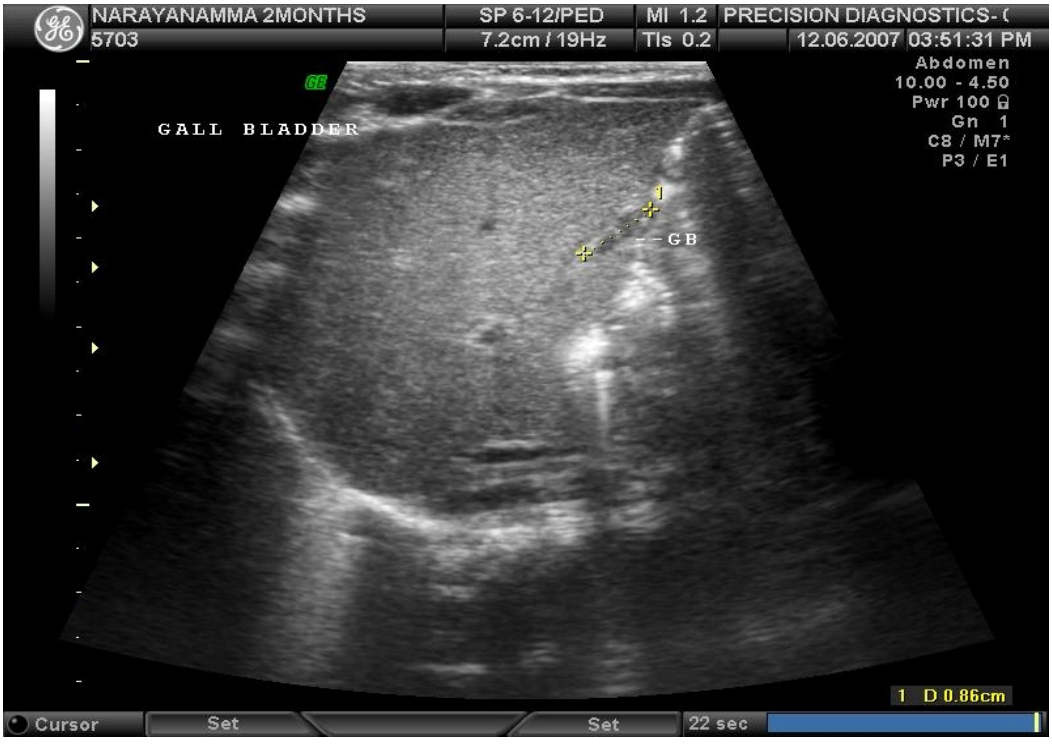


Figure 5. Ultrasonogram showing abnormal gall bladder

DISCUSSION

DISCUSSION

Neonatal hepatitis and extra hepatic biliary atresia(EHBA) are two major forms of neonatal cholestasis. Children with either disease present with similar symptoms like jaundice, dark urine, pale stools. Differentiating these two conditions is important and it must be done as early as possible. It is important because the management of neonatal hepatitis and EHBA are diagonally opposite – medical management for neonatal hepatitis, and surgical management for EHBA.

The need for earlier definitive diagnosis is that children with EHBA if operated early (< 8 weeks) will have good results as compared to late surgery[3,18]. Clinical features, ultrasound, radionuclide imaging, percutaneous liver biopsy can be used to diagnose biliary atresia from neonatal hepatitis

In the present study, a total of 30 subjects were included. None of them were excluded. Of these 30 infants, 22(73 %) were male and 8 (27 %) were female. Biliary atresia (12 subjects) and idiopathic neonatal hepatitis (18 subjects) made 40% and 60% of all diagnosis. The range of age of the subjects was 20 days to 5 months with the median of 3 months.

Table 10

Triangular cord sign - sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of various studies compared to the present one in diagnosing EHBA from neonatal hepatitis

Author and year of publication	Sensitivity (%)	Specificity (%)	Positive predictive value(%)	Negative predictive value(%)	Diagnostic accuracy(%)
Choi et al in 1998[23]	92	96	92	96	95
Choi et al in 1999[24]	84	98	100	92	93
Choi et al in 1996[25]	100	100	100	100	100
Choi et al in 1997[26]	85	100	100	93	95
Kendric et al in 2000[27]	83	100	100	97	97
Kanegawa et al in 2003[28]	93	96	96	92	95
Kotb et al in 2001[29]	100	100	100	100	100
Present study	83	94	91	89	93

In the present study, in which 30 infants were included, the sensitivity, specificity, positive predictive value, negative predictive value, and the diagnostic accuracy of triangular cord sign was 83%, 94%,

91%, 89%, 93% in diagnosing biliary atresia from neonatal hepatitis. Thus it can be seen that this particular sign has got a good specificity and positive predictive value. The results are similar to that obtained in similar studies done elsewhere. Almost all these studies done to evaluate triangular cord sign elsewhere showed a specificity more than 96%.

One study done by choi et al[24] in 1999 had a sample size close to the present study. In that study, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for triangular cord sign in diagnosing biliary atresia was 84%, 98%, 100%, 92%, 93% respectively.

The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the ultrasonographically detected abnormal gall bladder in differentiating biliary atresia from neonatal hepatitis was 83%, 78%, 71%, 88%, and 80% respectively. One study[28] has evaluated the usefulness of abnormal gall bladder and in that study, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of abnormal gall bladder in diagnosing EHBA from neonatal hepatitis was shown to be 71%, 69%, 72%, 69%, and 71% respectively.

The triangular cord and abnormal gall bladder are better than AIIMS clinical score in differentiating biliary atresia - which showed a sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 67%, 44%, 44%, 67% and 53% respectively. Only one study[30] from India has assessed the usefulness of AIIMS clinical score and in that study it was shown to have sensitivity, specificity, positive predictive value, negative predictive value and the overall diagnostic accuracy of 91.5%, 76.3%, 89.2%, 80.5%, and 86.6% respectively. The difference noted can be because of the wide difference in the sample size between these two studies. Also, the firm liver which is given a score of 4 in AIIMS clinical score, was present in both biliary atresia and neonatal hepatitis and thus a clinical diagnosis made with AIIMS clinical score was not always correct when compared with gold standard.

When triangular cord sign was coupled with the finding of abnormal gall bladder, specificity and the positive predictive value increased to 100% with reasonably good sensitivity, when compared to triangular cord sign and AIIMS clinical score combination or all the three parameters in combination. A study[24] which showed 100% positive predictive value for the triangular cord sign in combination with

abnormal gall bladder in diagnosing EHBA from neonatal hepatitis was reported by choi et al.

When triangular cord sign was coupled with AIIMS clinical score, again the specificity was 100%. However the sensitivity was less when compared to the sensitivity of the clubbed triangular cord and abnormal gall bladder. When triangular cord sign was clubbed with gall bladder and AIIMS clinical score, the sensitivity was the lowest, with the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy being 50%, 100%, 100%, 75% and 80% respectively. However no studies have been published, evaluating combination of clinical features and findings of ultrasonography in the diagnosis of neonatal cholestasis syndrome.

SUMMARY

SUMMARY

The present study has confirmed the high specificity and positive predictive value of triangular cord sign in the diagnosis of biliary atresia which was more than that of abnormal gall bladder and AIIMS clinical score considered separately. Further, when triangular cord sign was coupled with abnormal gall bladder and/or AIIMS clinical score the specificity was 100%. However clinical findings (AIIMS clinical score) alone had poor sensitivity and specificity in diagnosing biliary atresia. In view of our need for a diagnostic test which would identify EHBA accurately among cases of neonatal cholestasis syndrome, before going in for an appropriate invasive procedure, a diagnostic test with high specificity should be advocated; at the same time we should not miss cases. For this the diagnostic test should also have high sensitivity. In this study, ultrasonographic examination of porta hepatis and gall bladder looking for triangular cord and abnormal gall bladder appears to be a single test with high specificity and good sensitivity when compared to others parameters evaluated.

Table 11

Sensitivity, Specificity, Positive predictive value, Negative predictive value & diagnostic accuracy of various parameters considered in the present study

Diagnostic parameters	sensitivity	specificity	P.P.V	N.P.V	Diagnostic accuracy
AIIMS clinical score	67%	44%	44%	67%	53%
Triangular cord sign	83%	94%	91%	89%	93%
Gall bladder	83%	78%	71%	88%	80%
Triangular cord and gall bladder	75%	100%	100%	86%	90%
Triangular cord and AIIMS clinical score	67%	100%	100%	82%	87%
Triangular cord, gall bladder, AIIMS clinical score	50%	100%	100%	75%	80%

CONCLUSION

CONCLUSION

1. The combination of triangular cord sign with abnormal gall bladder-both detected ultrasonographically-can be promoted as a diagnostic test for the diagnosis of extrahepatic biliary atresia. The advantage of going for the ultrasonogram as a single diagnostic procedure to find these two signs makes the test promising.

2. Clinical features in the form of AIIMS clinical score alone cannot correctly identify biliary atresia from neonatal hepatitis.

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BIBLIOGRAPHY

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ANNEXURE I

DATA COLLECTION FORM

Name:

Age/sex:

IP number:

Admitting ward:

Date of admission:

Date of discharge:

Diagnosis on discharge:

CLINICAL FEATURES

Jaundice - duration

Persistent / fluctuant

Pale stools - yes / no

Dark urine -yes / no

Liver - smooth / firm

INVESTIGATIONS

Level of jaundice

Fasting ultrasonogram – triangular cord sign and gall bladder

Radionuclide imaging (if done)

Peroperative cholangiography

Liver biopsy

FOLLOW UP

ANNEXURE II

Institute of Child Health and Hospital for Children

MADRAS MEDICAL COLLEGE

HALLS ROAD, EGMORE, CHENNAI - 600 008.

Ph : 28191135 / Direct : 28194181 / Fax : 044 - 28194181.

Date.....

Ref.No.Dir/EC/ICH/06

Institute of Child Health and Govt.
Hospital for Children, Chennai 8.
Dated:

Certificate

The dissertation committee for 2006, Institute of Child health and Hospital for Children, Madras Medical College, Chennai comprising of the following members has granted permission to MD post-graduate Dr.S.Kasirajan to proceed with his / her study titled **"Ultrasound in neonatal cholestasis syndrome"** after carefully scrutinizing his / her study proposal with special reference to ethical standards, methodology and relevance. His / Her study proposal was approved on 17.10.2006

1. Dr. Saradha Suresh
2. Dr.N.Thilothammal
3. Dr.S.Sethuraman
4. Dr.K.Githa
5. Dr.C.V.Ravisekar
6. Dr.P.Ramachandran
7. Dr.C.Ravichandran

Dr.Saradha Suresh

To
Dr.S.Kasirajan,
MD post-graduate, ICH & HC