Personal Practice

Neonatal Cholestasis Syndrome in India—A Diagnostic and Therapeutic Challenge

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Neonatal cholestasis syndrome (NCS) has now replaced Indian Childhood Cirrhosis (ICC) as the leading cause of chronic liver disease in children in India(l). This change is because of a dramatic decline in the incidence of ICC in recent years and a modest increase in the numbers of NCS presenting to hospitals. The average annual incidence of ICC at our center in KEM Hospital, Pune, has reduced from more than 50 cases a year in 1980 to less than 5 per year in 1995. The corresponding figures for NCS are around 10 per year in 1980 to more than 20 per year in 1995(1).

NCS is the term, presently in use to describe obstructive jaundice (conjugated hyperbilirubinemia) beginning in the neonatal period though the clinical presentation may be later in infancy(2). The syndrome is heterogenous comprising chiefly of congenital biliary atresia and neonatal hepatitis which in fact, may be different manifestations of the same disease process often referred to as 'Infantile Cholangiopathy' (3).

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Cholangiopathy"(3). Many other specific infective, genetic and metabolic diseases also present with cholestasis in early infancy (4).

It is unfortunate that despite being so common, NCS has received scant attention in our country(5,6). What are the causes of NCS in India? Do our diverse epidemiological and socio-cultural factors modify the clinical presentation? Is the outcome similar to descriptions from developed countries? The aim of this review (which is based largely on our own studies in Pune) is to address these questions as also to invite observations from other centers in India.

Clinical Presentation

There appear to be two distinct clinical patterns of NCS: *(i)* NCS - Early Neonatal Pattern; and *(ii)* NCS - Post Neonatal (Infantile) Pattern.

1. NCS - Early Neonatal Pattern

The usual bane of neonatal nurseries is unconjugated (hemolytic) hyperbilirubinemia. But whereas, unconjugated jaundice is often physiological, conjugated (obstructive) hyperbilirubinemia is always pathological. The neonate is particularly vulnerable to cholestasis from a variety of perinatal insults (infectious, metabolic or toxic) due to impaired intra-ductular solubility of bile salts. Sometimes, in the sick neonate, there are more than one insults, and the presentation includes hepato-splenomegaly, bleeding manifestations and multiorgan dysfunction. *Table I* shows the diverse conditions associated with NCS seen in our nursery in the last six years. Early evaluation is important as some of these

TABLE I *Pattern of Neonatal Cholestasis Syndrome (NCS) and its Outcome in KEM Hospital, Pune (1990-1995).*

Early Neonatal Period			Post Neonatal (Infantile) Period		
Diagnosis	n	Survivors	Diagnosis	n	Survivors
Sepsis	5	3	Biliary atresia	42	4
Toxoplasma	2	1	Choledochal cyst	4	4
Hepatitis B	3	2	Biliary hypoplasia	5	2
Malaria	2	2	Nonsyndromic 4		
Congenital syphilis	2	1	Syndromic 1		
Cytomegalovirus	1	1	Neonatal Hepatitis	31	20
Metabolic	4	1	Congenital infections 6		
TPN*	4	3	1 ATD** 3		
Idiopathic	4	1	Idiopathic 22		
Total	28	15		82	30

* Parenteral nutrition
** 1 antitrypsin deficiency

these conditions such as sepsis and malaria are amenable to specific therapy. Parenteral Nutrition (TPN) associated NCS has recently reduced in our nursery by maintaining a high calorie/protein ratio and early oral feeding(7).

Awareness of the early neonatal form of NCS is particularly important for the increasing numbers of sick premature babies, now managed in Neonatal Intensive Care Units (NICU).

2. *NCS-Post Neonatal (Infantile) Pattern*

In most babies with NCS, jaundice is first noticed between 6 to 8 weeks of life though in many it has continued since 'physiological jaundice'. The urine is dark yellow or brown but may be lighter because of the high urinary volume in infants. Stools are light yellow-green to chalky white depending on the degree of cholestasis. Liver and spleen are usually enlarged. Many a times, however, these features are ignored and the baby is brought to the hospital, later, with complications such as bleeding, ascites, hypoglycemia or malabsorption.

More than 80% of babies with NCS belong to two major diagnostic categories, namely, *(i)* Biliary Atresia (BA) and *(ii)* Neonatal Hepatitis (NH)(8). The urgent clinical concern is the early definitive diagnosis of BA as the prognosis in BA is said to be favorable only if corrective surgery is performed before the age of 8 weeks(9-ll). Unfortunately none of the clinical features are really discriminatory(12). Even pigmented stools do not rule out BA, as in upto 30% of BA the stools are yellow, especially in the early weeks(4). A relatively thriving baby goes in favor of BA while regression of jaundice goes against it(13).

Whereas laparotomy and operative cholangiography is the final diagnostic test in BA, anesthesia and surgery can be detrimental to the outcome of NH(4). An elaborate, sometimes invasive and time consuming scheme of investigations is, therefore, necessary to pick out the right

cases for surgery *(Table II).*

Diagnostic Approach

An immediate consideration in NCS is the exclusion of treatable infections such as septicemia, urinary tract infection, syphilis, malaria, toxoplasmosis and tuberculosis all of which can cause cholestasis in the infant(2,4). It is also important to consider treatable metabolic causes of NCS, such as galactosemia and fructosemia. A thorough prenatal, perinatal and family history with careful clinical (and ophthalmic) evaluation often gives important clues in the diagnosis of rarer causes of NCS, such as alfa 1 antitrypsin deficiency (alfa 1. ATD) and syndromic hypoplasias. A practical protocol of investigations to differentiate BA from NH is summarized in *Table II.*

Biochemistry

Standard liver function tests are usually abnormal with modestly raised levels of SGPT, SGOT and serum alkaline phosphatase. Serum albumin does not fall till late. Prothrombin time is usually delayed. None of the biochemical tests, however are of discriminatory value and at best reflect the degree of liver damage. The initial enthusiasm over alfa glutamyl trans-peptidase, serum nucleotidase and serum lipoprotein X as useful screening tests for BA has not been corroborated by other centers(14-16).

TABLE II— *Scheme of Investigations in the Diagnosis of Neonatal Cholestasis Syndrome.*

Routine Hematology and Biochemistry
Screen for infections
Bacteriology VDRL,
TORCH, HBsAg
Screen for metabolic diseases
Abdominal ultrasonography
Tc 99m Mebrofenin Radionuclide scan
Liver biopsy
Operative cholangiography;

Ultrasonography (USG)

USG is most useful in the definitive diagnosis of a choledochal cyst, which then requires no further investigations. The recent development of high resolution ultrasound recordings have considerably improved the role of USG in the differentiation of BA from NH (accuracy 80%)(12). Visualization of a normal gall bladder while fasting (4 hours) which contracts normally on feeding virtually rules out BA *(Fig. 1)* (17,18). The reverse is not- always true and in NH the gall bladder may or may not be visualized and may or may not contract on feeding *(Table III).* Further, intrahepatic bile duct dilatation or cirrhosis of liver cannot be reported reliably on USG in the neonate. Though the results are often inconclusive, USG is an important baseline investigation as it is relatively cheap, non invasive and readily available in most hospitals.

Radionuclide Scanning

The use of Technetium 99m labeled derivatives of iminodiacetic acid (IDA) has simplified hepatobiliary imaging especially as compared to the earlier

TABLE III—USG *and Radionuclide Scan Features of Biliary Atresia and Neonatal Hepatitis (KEM Hospital, Pune, 1994-1995).*

	Biliary atresia (n=13)	Neonatal hepatitis (n=12)
Ultrasonography (USG)		
Gall bladder visualized	8	12
Post feed contraction	0	10
Tc 99m Mebrofenin Scan		
Tracer excretion in bowel	0	11
Hepatic index >2	0	11

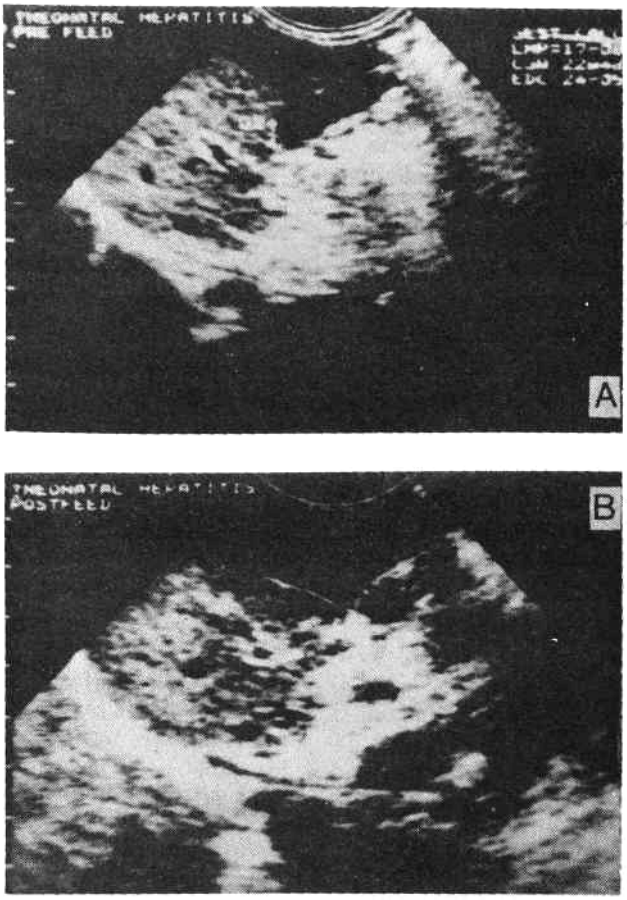
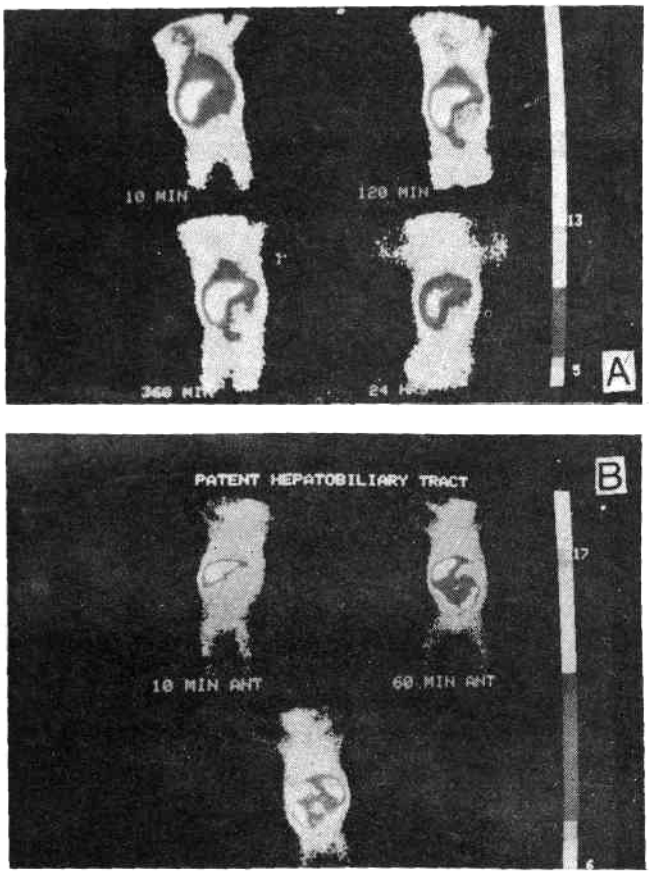


Fig.1 Ultrasonography showing normally contracting gall bladder in baby with Neonatal Hepatitis. A: Pre-feed sonogram B: Post-feed sonogram

^{131}I Rose Bengal fecal excretion test which involved meticulous collection of stools and urine for atleast 72 hours (19). We now use Mebrofenin which is the, latest IDA agent ahead of disopropyl (DISIDA) and trimethyl bromo (BRIDA). The advantages of Mebrofenin are low renal excretion, high hepatic uptake and rapid biliary excretion so that imaging can start within minutes of injection of the dye and delayed excretion studies are seldom required beyond 24 hours(20). Gamma emissions for the liver in relation to that for the heart and background are computed as Hepatic Index (HI). A high HI, *i.e.,* above 2 (signifying good hepatic uptake) and visualization of the tracer in intestinal tract within 4 hours virtually rules out BA *(Fig. 2)* (21,22). However, as in USG studies, the reverse is not always true and absence of excretion can occur in NH with severe cholestasis *(Table III).* Radionuclide scanning is now said to have a specificity of 82% and a sensitivity of 97% in the diagnosis of BA(22). Priming the baby with phenobarbitone (5 mg/kg for 3 days before the test) enhances hepatic uptake and excretion of the dye thereby improving the accuracy of the test(23).

Reliable scintigraphy is not yet available everywhere in our country and costs atleast Rs. 1,000/- per test, but because of its noninvasive nature should be carried out ahead of liver biopsy in the diagnostic evaluation of BA.



Liver Biopsy

Liver biopsy is still considered by many as the most important investigation in differentiating BA from NH with a reported accuracy of 83-97% (8,12,24). The predominant features in BA are involvement of portal tracts (widening of portal tracts, bile duct reduplication, portal fibrosis) whereas NH demonstrates hepatocellular disease (ballooning necrosis, giant cells, inflammation) *(Fig.* 3). There is of course a considerable overlap especially before age 4to 6 weeks, and definitive diagnosis requires a good sized biopsy (at least 5 portal tracts) and an experienced histologist *(Table IV).* Liver biopsy gives important clues to the etiology of NH, *e.g.,* PAS positive diastase resistant granules in alfa 1 ATD deficiency and inclusion bodies in cytomegalovirus disease. Biliary hypoplasia is essentially a histological diagnosis especially when non syndromic. Liver cirrhosis, an important prognostic feature, can be diagnosed only on a liver biopsy.

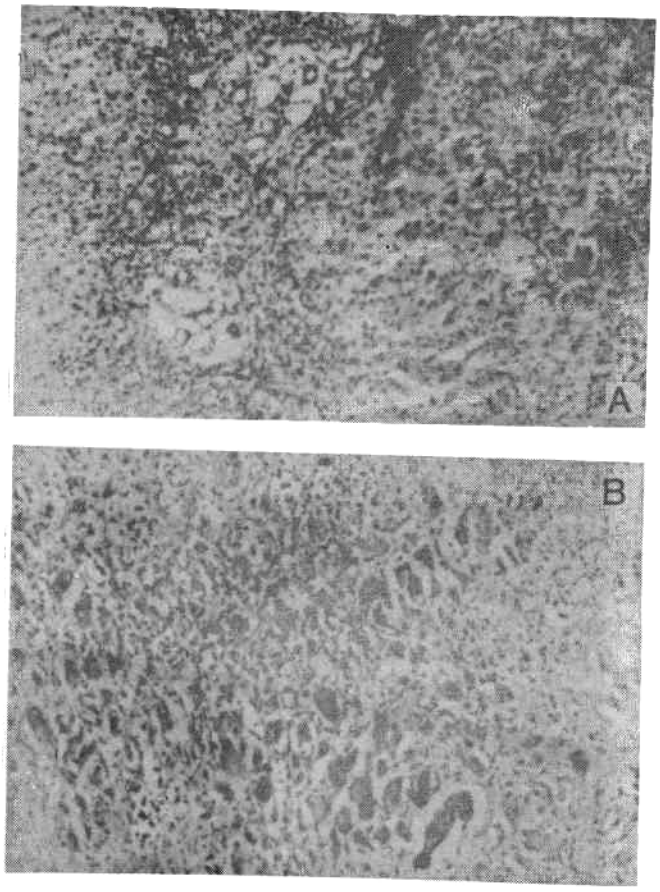


Fig. 3. Histological features (H & E ×100). A: Biliary atresia showing widened portal tracts with reduplication of bile ducts and prominent portal fibrosis. B: Neonatal hepatitis showing widespread inflammation and giant cell transformation.

As no single test is discriminatory, the scheme of investigations assumes importance. If the results of above tests are still inconclusive the final diagnosis of BA (and its operability) can be established only on operative cholangiography(2,4). If these tests reasonably rule out BA, further tests should only be directed to establish the etiology of NH. If screening tests such as VDRL and HBsAg are positive, further investigations are futile.

TABLE IV- *Histological Features in Biliary Atresia and Neonatal Hepatitis (KEM Hospital, Pune 1990-1995).*

Feature	Biliary Atresia (n=42)	Neonatal Hepatitis (n=31)
Portal fibrosis (%)	80	30
Bile duct reduplication (%)	86	11
Giant cell transformation (%)	13	58
Cirrhosis (%)	30	39

Management and Outcome

Biliary Atresia

The standard procedure in the correction of BA the world over, is a Kasai Hepatic portoenterostomy or one of its modifications (25-28). Our surgeons in Pune have devised an isoperistaltic gastric tube conduit in the anastomosis(29). The urgency for surgery in BA comes from recent reports mainly from Japan(10,30) and England(9) suggesting a survival of 80% or more if operated before the age of 6 to 8 weeks which falls to less than 30% if the operation is delayed beyond 12 weeks. However, only 7 of our 42 patients with BA were referred before the age of 8 weeks. Further, our results in Pune as in the rest of the country and many other parts of the world are disappointing even with early surgeries(5,31). The most frequent serious complications are: (*i)* cholangitis with associated septicemia, *(ii)* progressive liver damage, portal hypertension and cirrhosis, and *(iii)* malabsorption, anemia and growth failure.

In the last five years of our studies, 17 babies with BA had corrective surgery. Of these 17, only 2 are alive and well for at least two years with fairly good bile drainage. Four died within days of surgery while 9 others died between 2 months and 2 years after surgery of complications mentioned above. The remaining 2 are still alive, but ill with progressive liver disease. Of course without operation there is no hope and none of the babies with BA who refused operation (or were thought unfit) have survived beyond 6 months of presentation. The treatment for failed Kasai procedure is now liver transplantation.

BA is currently the tommonest indication for pediatric liver transplant with survival figures approximating 80% at 1 year, and 70% at 5 years in leading transplant centers(32,33). The technique is not yet available in our country.

Therefore, in the management of BA, of utmost importance is parental awareness of the risks, stress and finances involved. Even a successful 'corrective' operation with good initial bile drainage does not mean a 'cure', being often followed by progressive damage eventually necessitating a liver transplant(31).

Neonatal Hepatitis

On the other hand, the outcome in NH is much more optimistic(34,35). Upto 60% of babies with idiopathic NH recover completely after a variable period of cholestasis without any specific therapy. A few (upto 10%), die acutely of bleeding manifestations or fulminant hepatic failure and about 30% progress to liver cirrhosis and death due to chronic liver disease. Unfortunately there are no indicators to predict prognosis(8).

There is no specific therapy for genetic and metabolic diseases such as alfa 1 ATD, tyrosinema and biliary hypoplasia. Liver transplantation has considerably changed the outlook in these conditions too(33).

Supportive Medical Management

1. *Nutritional Support:* Supplementation of fat soluble vitamins A, D, E and especially K (to prevent hemorrhage) is necessary in cholestasis. Calorie and fat dense formulae, enriched with MCT (coconut oil) are often required to promote growth. At times, nasogastric tube feeding or intravenous

feeding have to be resorted to overcome anorexia.

2. *Cholestasis:* Phenobarbitone in a dose of 5 mg/kg is often used in cholestasis properties. Cholestyramine, a bile salt chelator has been helpful in reducing serum cholestorol, scrum bile acids and serum bilirubin in some patients but has many side effects, such as constipation, steatorrhea and Vitamin D binding(36). The agent of promise is ursodeoxycholic acid (UDCA) which is an endogenous hydrophylic (non-toxic) bile acid and probably works by competitive inhibition of other toxic bile acids(37). Long term treatment with UDCA after Kasai procedures have made the candidates more suitable for liver transplantation. One of the most distressing symptoms of cholestasis is pruritus. The medications tried for pruritus with limited success are skin lubricants, phototherapy, antihistamines especially terfenadine, steroids and rifampicin(2).

Liver Transplantation

At least one or two centers are making rapid strides towards setting up this important therapeutic modality in India. As of now, it is important to develop rapport with foreign centers where babies who can afford such treatment can be referred (cost in excess of $100,000) (2). The commonest indications as described above are failed Kasai procedure in BA, late presenting BA and metabolic diseases such as alpha 1 ATD and tyrosinemia. Current survival rates which approach 80% at one year are attractive but problems of long term immunosuppression, biliary tract complications and sepsis require constant monitoring. Supportive management is all important as results of liver transplant are related to overall nutrition of the baby(33).

Conclusion

Biliary atresia and neonatal hepatitis are common causes of pediatric liver disease in India. Differentiation between the two is difficult and requires an elaborate scheme of investigations. Surgical correction of biliary atresia is 'curative' only in a few; in the other liver damage is progressive, necessitating a liver transplant which is not yet available in India. Prognosis for idiopathic neonatal hepatitis though comparatively better is unpredictable. The possibility of environmental factors modifying the presentation and prognosis of these disorders in developing countries needs to be explored.

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NOTES AND NEWS

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This event is being organized by the LAP, Delhi Branch on October 13, 1996 at Lady Hardinge Medical College. The programme consists of **Dr. P.N. Taneja Oration** by Dr. Shanti Ghosh, a Panel discussion on Interpretation of Laboratory Investigations, Symposia on Pain in Children, and Management of Challenging Infections including Resistant Malaria, Resistant Tuberculosis, Meningitis, Fungal Infections, *Pneumocystis carinii* Pneumonia, Recurrent UTI, *etc.* The Registration fees is Rs. 150/- till 30.9.1996 and Rs. 200/- thereafter (Please add Rs. 20/- for outstation cheques). D. D. cheque to be drawn in favor of IAPA, ew Delhi, and mailed to Dr. Rajesh Mehta, Secretary, IAP Delhi, SP-15 Maurya Enclave, Delhi 110 034 [Tel. 7221447 (R) 665060/398 (O)] or Dr. P.K. Pruthi, R-503, New Rajinder Nagar, New Delhi 110 060 [Tel. 5745960 (R), 5721800 (O)].