Introduction

Neonatal cholestasis syndrome (NCS) comprises of heterogenous group of hepatobiliary disorders responsible for cholestasis during neonatal life. The cholestasis due to some disorders can extend beyond neonatal period hence, this is appropriate to call this syndrome as cholestasis of infancy. Most of the disorders have linkage with insults during antenatal, natal and postnatal period indicating intrauterine or postnatal events. Main causes of NCS are, infection, metabolic disorders and extrahepatic biliary obstructions those cover large number of conditions (1).

The present scenario about the spectrum of illnesses is changing fast. Premature babies are now being looked after in neonatal specialised care units, the causes of cholestasis due to sepsis, total parenteral nutrition (TPN), drugs etc, are emerging as another large group (2). But this remains a challenge to evaluate and manage NCS because of fast change in the diagnostic and therapeutic approach world over. It becomes mandatory to define the cause of NCS that needs battery of tests to carry out.

This is also important to do various tests simultaneously to differentiate between neonatal hepatitis (NH) and extrahepatic biliary atresia (EHBA) to avoid delay in Definition and Classification

Jaundice is a very common symptom encountered during neonatal life. Approach to jaundice during neonatal period and infancy is given in figure 1. This is also called hyperbilirubinemia when defined by raised serum bilirubin > 2mg/dl. Based upon the composition of serum bilirubin, this is divided into unconjugated and conjugated hyperbilirubinemia. Unconjugated hyperbilirubinemia is very common during first few weeks of life and the unconjugated bilirubin constitutes 80% of total serum bilirubin level. This is characterised by icterus, normal coloured urine and yellow normal coloured stools. Most of the times it is attributed to physiological jaundice or breast milk jaundice.

Whereas conjugated hyperbilirubinemia is defined when the conjugated fraction of bilirubin is more than 20% of the total serum bilirubin or when conjugated bilirubin is more than 1.5 mg/dl in neonatal period and is labelled as cholestasis. This is also associated with retention of bile salts in the blood. Cholestasis is also defined as pathological stage or reduced bile formation or flow and clinical criteria to define are; passage of high coloured urine that stains the diaper yellow and pale/white/acholic or intermittent pale yellow or yellow stools.

Cholestasis is characterised by itching that may not be
recognised during early life, but irritability is a common feature. After 6 months of life itching is quite apparent. These clinical pointers are very important to differentiate between cholestasis and unconjugated hyperbilirubinemia. Histopathological definition of cholestasis is the appearance of bile within the elements of the liver, responsible for secondary cell injury.

Various terms have been used in literature to describe cholestasis as neonatal cholestasis (NC), neonatal cholestasis syndrome (NCS), cholestasis of infancy, neonatal hepatitis (NH) and EHBA. Problem is that all the pathological conditions causing cholestasis do not start in neonatal period but may appear after one month of life or may last long and extend up to 6 months of life or even during second 6 months of life. So this may be appropriate to call this as cholestasis of infancy rather than NCS but this has been retained in the text.

**Figure-I. JAUNDICE DURING INFANCY**

<table>
<thead>
<tr>
<th>Jaundice</th>
<th>Hyperbilirubinemia</th>
<th>S. Bilirubin &gt; 2mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated</td>
<td>S. Bilirubin &gt; 20%</td>
<td>Urine high coloured</td>
</tr>
<tr>
<td>Unconjugated</td>
<td>S. Bilirubin &gt; 80%</td>
<td>Urine colour normal</td>
</tr>
</tbody>
</table>

Cholestasis

| Intrahepatic | Clay or normal coloured stools |
| Extrahepatic | Clay coloured stools or intermittent |

It is important to divide cholestasis into 2 groups which are well defined now and are intrahepatic cholestasis and extrahepatic cholestasis based upon the nature and site of pathological lesions. Intrahepatic cholestasis covers two important groups hepatocellular cholestasis: neonatal hepatitis and paucity of intrahepatic bile ducts (PIBD). For better understanding, cholestasis can also be classified into neonatal hepatitis and obstructive cholangiopathy or obstructive cholestasis. Obstruction could be at level of extrahepatic biliary tree and/or intrahepatic biliary tree also called as paucity of intrahepatic bile ducts (1,3,4).

**Factors predisposing of cholestasis during neonatal period**

New born infants are more prone to develop cholestasis because of immaturity of excretory function, inborn errors manifesting in early life and inherent susceptibility to various viral, septic and toxic insults. The immature liver cells are associated with peculiar kind of pathological response to different kind of noxious agents during neonatal life and infancy.

The excretory function is further compromised by the ineffective enterohepatic circulation of bile. There is gradual maturation of hepatocytes in respect to handling of bilirubin, excretion of bile, synthetic functions and enzymes system during infancy. The maturation of these functions may be equivalent to adulthood by age of 4-6 months. Some biochemical markers of cholestasis like alkaline phosphatase and glutamyl transpeptidase are raised during early life. Serum unconjugated bilirubin, bile concentration are normally in higher concentration in blood again suggesting that there are clearance problems in neonatal liver. Due to these reasons the neonatal hepatobiliary system is affected by various infective, metabolic and obstructive causes faster as compared to older children and adults (1,5).

**Etiology**

Various causes of cholestasis are given in table 1 (5). The spectrum of cholestasis of infancy seen in our centre is like this: neonatal hepatitis 62%, extra-hepatic biliary atresia (EHBA) 30%, choledochal cyst 6% and paucity of intrahepatic ducts 2%. Etiology of neonatal
hepatitis is as idiopathic neonatal hepatitis in 54%, bacterial infections 18.5%, intrauterine infection 8.5%, metabolic disorders 8.5% and miscellaneous 10% reported from our centre.

Table I. Causes of Cholestasis in Infancy

Anatomic Abnormalities

A. Extrahepatic
- Biliary atresia
- Bile duct stenosis
- Spontaneous perforation of bile duct
- CBD Stone
- Primary sclerosing cholangitis (PSC)

B. Intrahepatic

I. Idiopathic neonatal hepatitis

II. Intrahepatic cholestasis: persistent
(a) Nonsyndromic paucity of intrahepatic ducts (apparent absence of bile ductules)
(b) Arteriohepatic dysplasia (Alagille syndrome)
(c) Byler disease (severe intrahepatic cholestasis with progressive hepatocellular disease).
(d) Trihydroxycoprostanic acidemia (cholestasis with progressive hepatocellular disease).
(e) Zellweger syndrome (cerebrohepatorenal syndrome)

III. Intrahepatic cholestasis: recurrent (syndromic)
(a) Familial benign recurrent cholestasis
(b) Hereditary cholestasis with lymphedema
(c) Alpha-1 antitrypsin deficiency
(d) Miscellaneous
   - Cystic fibrosis
   - Idiopathic hypopituitarism
   - Hypothyroidism
   - Neonatal iron storage disease/haemochromatosis

- Indian childhood cirrhosis
- Multiple acyl-CoA dehydrogenation deficiency (glutaric acid type II)

IV. Hepatitis

(A) Infections
- Bacterial infection
- Hepatitis B virus
- Herpesvirus
- Coxsackie virus
- Toxoplasmosis
- Tuberculosis
- Malaria

(B) Metabolic disorders

a. Disorders of amino acid metabolism
- Tyrosinemia
- Hypermethioninemia

b. Disorders of lipid metabolism
- Cholestasis associated with parenteral nutrition
- Niemann Pick Disease type C.
- Infantile Gaucher disease

V. Genetic / chromosomal

- Trisomy F
- Down syndrome
- Donahue syndrome (leprechaunism)

VI. Miscellaneous

- Histocytosis X
- Congenital hepatic fibrosis
- Shock
- Caroli’s disease
- Intestinal obstruction

Pathophysiology and Consequences of Prolonged Cholestasis

The effects of cholestasis are devastating secondarily due to retention of bile and results into widespread problems with the advancing life of the cholestasis infants and children. Figure II gives the consequences of prolonged cholestasis (1).
Figure II - Consequences of Chronic Cholestasis

The retention of bile salts and conjugated hyperbilirubinemia are the hallmarks of NCS. In hepatocellular cholestasis (Neonatal hepatitis) the conjugated bilirubin effluxes directly from the hepatocytes by diffusion or vesicular exocytosis, whereas in case of obstructive cholestasis the bile and conjugated bilirubin from canalicular and ductular spaces effluxes back through weakened tight junctions and goes into the blood. It is loosely bound to albumin, hence gets excreted into urine. The excess of excretion of conjugated bilirubin and bile salts are responsible for dark coloured urine that stain the diaper in cholestatic children. At the same time less of bile production and less of excretion into the biliary tree resulting negligible bile into the intestine. The enterohepatic circulation is also effected considerably.

In cholestatic infants, it has been seen that they have increased unconjugated bilirubin also. This is possibly due to associated hemolysis or due to the hepatocellular injury leading to compromised conjugation. Recently, delta bilirubin or bili-protein has been fractionated. The presence of large quantity of this bilirubin denotes prolonged cholestasis. The estimation of this in the cord blood or in the newborn may suggest the intrauterine insult.

Retention of bile salts is responsible for pruritus possibly that is a serious symptom of cholestasis. It is very difficult to manage. Initially this may not be prominent but after the age of 6 months cholestatic baby starts scratching. This may become unremitting feature later on. Retention of bile salts also results into injury to various biological membranes of the body. In liver, production of secondary bile acid like lithocholic acid hastens
hepatocytic membrane injury and enhances hepatic fibrosis. Red blood cells may get hemolysed resulting hemolytic anemia. In respiratory tract, injury to mucus membrane leads to asthma like picture. Nasal bleeds are also very common.

Hyperlipidemia is characteristic of cholestasis. Metabolic degradation and excretion of cholesterol are affected. It hampers the function of hepatocytic and canalicular membranes and cholestasis increases. Deposition of cholesterol in the skin leads to formation of xanthomas on the body.

Major clinical effects of cholestasis are poor growth of the infants. This is due to malabsorption, poor nutrient utilisation, hormonal disturbances and secondary tissue injury. Malabsorption is due to lack of bile into the small bowel resulting inefficient absorption of fats and fat soluble vitamins. There is loss of significant calories in the stools in the children. Simultaneously there is loss of calcium due to Ca++soap formation with fats which are lost in the stools. In presence of vitamin D deficiency, this leads to development of rickets later on. In chronic cholestasis, during late infancy and early childhood, features of vitamin E deficiency in form of neuropathy and hemolysis develop. If untreated, can lead to crippling neuromuscular weakness and patient becomes bed ridden. Vitamin D deficiency results into rickets and osteopenia. Vitamin A deficiency leads to blindness and hyperkeratotic skin. Vitamin K deficiency is responsible for coagulopathy and bleeding and may have linkage with reduced brain development (1,3,4,5).

Approach to Cholestasis to differentiate Neonatal Hepatitis and EHBA.

In NCS, it is mandatory to differentiate between neonatal hepatitis and EHBA. Neonatal hepatitis warrants medical treatment whereas obstructive cholestasis largely EHBA needs only surgical treatment and is effective if done within 60 days of life. There should not be any kind of delay to find the underlying cause responsible for cholestasis.

Clinically, one should be able to pick up cases where there is high index of suspicion of EHBA. If the baby is passing pale or acholic stools from very beginning or starts after few weeks of life one should act very fast to make the diagnosis of EHBA. There is no point in wasting time. In EHBA, fibrosis sets in as early as 4 weeks of life. EHBA babies are usually term born and have good weight. 20% of these babies may have associated congenital malformations. Liver function tests at times may not help to differentiate. In case of obstructive cholestasis, alkaline phosphatase and Gamma GT may be very high in comparison to neonatal hepatitis. Liver enzymes like ALT and AST are nearly normal in EHBA but are always raised in NH. One should keep in mind that in case of severe cholestasis there is overlapping picture. In EHBA, prolonged PTI usually responds to vitamin K administration.

The approach to cholestasis to differentiate between obstructive cholestasis and hepatocellular cholestasis is given in algorithm 1.
ALGORITHM-I TO DIFFERENTIATE INTRAHEPATIC AND EXTRAHEPATIC CHOLESTASIS

Ultrasound

Choledochal cyst

No choledochal cyst

Gallstones

( TPN, drugs, hemolytic cause)

Surgery

No CBD stone

CBD obstruction

Conservative

ERCP

HEPATOBILIARY SCINTIGRAPHY

No intestinal excretion

Intestinal excretion

(rules out EHBA)

ERCP

Intrahepatic cholestasis

Neonatal hepatitis

MRCP

LIVER BIOPSY

Equivocal finding

EHBA

Neonatal hepatitis

PIBD

Observe

Observe

Age < 6 wks

Age > 6 wks

BRIDA scan

ERCP

Visualization of PD/NO CBD

Repeat bx (10-14 D)

Biliary tree defined EHBA ruled out

Neonatal Hepatitis

LAPAROTOMY AND IOC

EHBA confirmed

Mechanical obstruction

sludge, stone cleared

KASAI'S procedure

Biliary tree patent

Wedge Biopsy

Close and observe

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Ultrasound

Ultrasound done by an experienced person is a good modality to see the status of liver parenchyma, dilated intrahepatic or extrahepatic biliary tree and presence of gallbladder. Conditions like choledochal cyst, bile plug syndrome, common bile duct (CBD) stone and Caroli’s disease can be picked up with great accuracy. The presence or absence of gallbladder in light of normal intrahepatic radicles and non-visualisation of CBD does not rule out EHBA. Earlier, the presence of gallbladder was considered to be in favour of NH but in severe cholestasis GB may not be seen. Absence of gall bladder has been correlated with EHBA with low sensitivity and specificity (60-70%). But there is significant overlap. Even in severe cholestasis gallbladder may not be defined because of less production of bile and it may be hypoplastic. Inspite of problems with US examination, it is mandatory to rule out other obstructive lesions as mentioned earlier. Moreover, this is a non-invasive test (6).

Scintigraphy

HIDA scan is now becoming as investigation going out of fashion like it happened earlier with Rose Bangale excretion test. In severe cholestasis due to NH there may not be excretion of dye even after adequate priming with phenobarbitone for 5 days. In case where excretion of dye is seen, this favours the diagnosis of NH but does not rule out severe cholestasis due to NH and EHBA. However, EHBA is ruled out if dye is seen in duodenum. In absence of excretion of dye, it creates confusion whether one is dealing with EHBA or severe hepatocellular cholestasis. The sensitivity is very high to pick up severe cholestasis whereas specificity to pick up EHBA is very low i.e. 60-70%. In some centres this investigation is not done routinely since there is wastage of 6-7 days period.

Magnetic Resonance Cholangiopancreatography (MRCP)

This is newer modality but again has similar problems as we have seen in case of US. False positivity rate is very high but certainly where it defines gallbladder and CBD, it rules out EHBA.

Liver Biopsy

This is mandatory to do liver biopsy and histopathology report can be available within 2-3 days. But for interpretation, there is need of expert pathologist who is familiar with developing neonatal liver and then reaction of various toxic factors like infections, metabolic and obstructive insults. General pathologist can not do the justice. In best hand, histopathology can differentiate NH and EHBA up to the tune of 95%. But in 5% cases there can be overlap problems to label.

EHBA is characterised by presence of proliferation of interlobular ducts, plugged with bile casts and portal tracts show fibrosis. This liver parenchyma may be normal and may show intrahepatic or canalicular cholestasis. But in advanced cases after 2 months of life, there may be full fledged changes of secondary cirrhosis. If the biopsy is done early between 4-6 weeks of life, the changes classical of EHBA may be less prominent, hence repeat biopsy after 10-14 days is warranted to be sure about diagnosis of EHBA.

In neonatal hepatitis there is marked parenchymal injury suggesting focal necrosis, ballooning degeneration, gaint cell transformation, inflammatory infiltrate, pseudoacinar formation and portal tract may show mild portal triaditis. There is no fibrosis until the disease is chronic.

Diagnosis of PIBD can be made on histology if the ratio of presence of bile ducts to portal tracts is less than 0.4-0.6. But liver biopsy should contain minimum 5
portals to make the diagnosis of PIBD in a biopsy specimen.

If the results of biopsy are equivocal (5%) and age is less than 6 weeks, BRIDA scan and or repeat liver biopsy after 10-14 days should be done. Even if the diagnosis is not established by liver biopsy and the age is more than 6 weeks ERCP is indicated.

**Endoscopic Retrograde Cholangiopancreatography (ERCP)**

Problem with ERCP is technical failure and non-availability of small diameter ERCP scopes in most of centres.

**Percutaneous Transhepatic Cholangiography (PTC)**

This is done by injecting dye in dilated intrahepatic biliary radicles (IHBR) and then visualisation of extrahepatic biliary tree in antegrade manner. This is not routinely done since the IHBR are not dilated in EHBA.

**Laparoscopy**

Laparoscopic visualisation of hepatobiliary area has not been popularised in children but some experts are attempting it.

**Duodenal Intubation**

Aspiration of duodenal fluids for 24 hours to see for bile is procedure in Japanese centres whereas it has been accepted by others. This can be done during scintigraphy to define the radioactivity in stomach and duodenal fluids.

**Intraoperative cholangiography (IOC) or Peroperative cholangiography (POC).**

Explorative laparotomy is indicated in very small percentage of cases where diagnosis is not established with above modalities. In presence of gall bladder IOC showing dye in duodenum and after clamping the CBD showing dye in intrahepatic radicles rules out EHBA. There is advantage of taking wedge biopsy of liver. Incase there is EHBA, Kasai's postenterostomy can be done simultaneously (6,7,8). The results of investigations to pick up EHBA in a prospective study done by Lai et al. (7) are given in Table II.

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Diagnostic accuracy (Lai et al, 1994)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* LFT Alkaline phosphatase, Gamma GT, OT/PT</td>
<td>60-80%</td>
</tr>
<tr>
<td>Presistent clay coloured stools</td>
<td></td>
</tr>
<tr>
<td>Doudenal juice</td>
<td>90-92%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>78-80%</td>
</tr>
<tr>
<td>Hepatic scan (HIDA)</td>
<td>80-91%</td>
</tr>
<tr>
<td>Liver Biopsy</td>
<td>92-97%</td>
</tr>
<tr>
<td>ERCP</td>
<td>90%</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td>94-97%</td>
</tr>
<tr>
<td>IOC</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Approach to Neonatal Hepatitis**

Neonatal hepatitis is most important cause of NCS (60-70%). It is mandatory to record detail history regarding antenatal, natal and postnatal events, family history, exposure to various drugs, maturity of the baby, neonatal sepsis, intrauterine infections, various metabolic and genetic disorders. Though clinical examination is warranted. The clue to the etiological diagnosis should come from good clinical evaluation of the case. This should guide the clinician to decide which way to investigate. Infections in our set up are very important cause of neonatal hepatitis. These include bacterial, viral, protozoal and spirochaetal infections (algorithm II). If there is direct clue to some metabolic or a genetic disorder, the investigations should be done accordingly. If the infections have been ruled out reasonably, the next choice is to do metabolic work up. High index of
suspicion to think of these disorders should be based upon certain clinical pointers like family history of previous sib, death due to similar disorder, repeated hypoglycemia, seizures, vomiting, failure to thrive, cataract etc. Preliminary metabolic work up includes urine for reducing substances viz. galactose or fructose, serum alpha-1 anti-trypsin level, thyroid function tests, serum aminoacids, urine aminoacid screening, eye examination, urinary succinyl acetone, serum ferritin etc. Based upon the suspected diagnosis the specific enzyme estimation/genetic work up should be done.

Inspite of elaborate work, in 30-40% cases of neonatal hepatitis, the etiology can not be defined. This group is labelled as idiopathic neonatal hepatitis or gaint cell hepatitis. Liver histology shows marked giant cell reaction. Liver biopsy also gives clue towards metabolic disorders at times (3,5,9).

**Treatment**

**Neonatal Hepatitis**

Infections constitute major causative agents for neonatal hepatitis in developing countries. Bacterial infections must be treated very effectively. Urinary tract infection remains hidden infection in neonatal period and it should be diagnosed and treated energetically. Viral infections persay don’t require any specific therapy in this age group but protozoal infections like malaria and toxoplasmosis and congenital syphilis as mentioned in the algorithm II should be treated effectively.

**ALGORITHM-II APPROACH TO NEONATAL HEPATITIS**

```
INFECTION

Bacterial
  Infection found
    Treat with antibiotics
      Cholestasis resolves
      Cholestasis continues
      Consider change of antibiotics
        Cholestasis resolves
        Cholestasis continues

Viral
  Infection likely
    Viral
      *CMV
      *Rubella
      *Herpes
      *Hepatitis B
      *AIDS
        Positive
          if any
            Observe/treat accordingly
              Cholestasis resolves
              Cholestasis continues

Protozoal
  Positive
    *Toxoplasmosis
    *Malaria
    *Listeriosis
      Cholestasis resolves
      Cholestasis continues

Congenital Syphilis
  Negative
    Treat accordingly
      Cholestasis resolves
      Cholestasis continues

Congenital Syphilis
  Positive
    if any
      Observe/treat accordingly
        Cholestasis resolves
        Cholestasis continues

Consider metabolic work up
```

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Treatment of various metabolic disorders should be started at the earliest. The offending agent should be withdrawn promptly for example in case of galactosemia, milk should be stopped immediately to avoid effect on the developing brain. This is the commonest metabolic disorder encountered in our centre. In case of fructosemia, fructose containing food items must be withdrawn immediately. Treatment of various endocrinologic and metabolic disorders should be done accordingly. Genetic counselling and need of the antenatal diagnosis should be stressed in the affected families (10).

Obstructive Cholestasis

Extrahepatic Biliary Atresia (EHBA)

EHBA is a big challenge world-over, but it is more alarming problem in developing countries. This constitutes 30% of the NCS seen at our centre (11). The late presentation of the disease is responsible for development of cirrhosis. This is a stage when it becomes untreatable and death is inevitable within 2 years of life. The age of presentation of EHBA cases reporting at our centre is given in table III. Bile flow can be established in 80-90% cases after Kasai’s procedure (portoenterostomy) if done within 60 days of life (12). With the advancing age the bile flow decreases. If the surgery is done within 2-3 months, the bile flow can be established in 40-45% cases whereas if surgery is done after 3 months of age, the bile flow can be established in 10-20% of cases only.

Table III EHBA : Age of Presentation at (n-36) PGI

<table>
<thead>
<tr>
<th>Age in months</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>6 (16.6)</td>
</tr>
<tr>
<td>2-3</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>22 (61.2)</td>
</tr>
<tr>
<td>3-6</td>
<td>13 (36.1)</td>
</tr>
<tr>
<td>6-12</td>
<td>9 (25)</td>
</tr>
</tbody>
</table>

This shows that diagnosis of EHBA should be done at the earliest and surgery should be performed within 60 days of life. Best time is 4-6 weeks of life.

Inspite of advancement in surgical skills the outcome is not encouraging. Even after portoenterostomy, 1/3 cases deteriorate in perioperative period and first year of surgery and may require liver transplantation, 1/3 develop complications of liver disease during first decade of life and require liver transplantation whereas 1/3 survive beyond 10 years of life with abnormal liver functions.

One year survival reported is varying from 30-71%. The highest survival rate is reported by Japanese workers. One year survival in our country is 25-30%. This shows that surgery is not fool proof treatment and needs liver transplantation. Good prognostic factors of EHBA surgery are: surgery done under 60 days of life, minimal or no histology defect, good bile flow after surgery and absence of cholangitis in immediate post-operative or first year of life and availability of surgical expertise. In our set up, late presentation of the cases (Table III) and cholangitis are the main detrimental reasons for the bleak outcome of these cases.

Choledochal cyst during infancy is also very important cause of cholestasis (6%) and needs surgical treatment (11,13).

Liver Transplantation

Liver transplantation has revolutionised the outcome of EHBA worldover (14). The indications are: failed Kasai’s procedure, progressive liver disease inspite of successful Kasai’s procedure and late presentation of EHBA (unoperated). Ten years survival is 85-90% in various centres. In our country, this has not picked up because of lack of awareness, poverty, ignorance, over population and absence of cadaveric liver transplantation programme.
Medical Treatment of Cholestasis

Chronic cholestasis is responsible for various life threatening consequences which need prolonged therapy.

Pruritus

Pruritus is a most distressing symptom. It leads to miserable life in term of lack of sleep, emotional problems and children become mentally reckoned. Various treatment modalities in form of use of cholestyramine, phenobarbitone, rifampicin, terfenadine, UCDA and phototherapy have been tried with variable results. UDCA seems to be promising as it is one of choleric drug. Sometimes untreatable and unremitted pruritus becomes sole indication for liver transplantation (15).

Malnutrition

Malnutrition is very common and is due to obvious reasons mentioned in the Fig. IV. Breast feeding should be encouraged in these babies. If anorexia is a prominent feature nasogastric feeding is indicated. The diet should have 200 calories/kg and protein 1-2 g/kg body weight. The diet should be constituted by MCT, 2-3% calories from PUFA, carbohydrates (glucose polymers), minerals, trace elements and vitamins. MCT rich available diets are coconut oil, Simyl MCT, Pregestimil and Portagen. All vitamins should be given in double the daily requirement.

Vitamin A

Vitamin A should be given 2500-5000 IU/day. Monitor the vitamin level. If blood level is less than 30ug/dl increase the oral dose by 10 folds or 50,000IU IM monthly should be given.

Vitamin D

Daily 400-1200 IU of vitamin D are recommended. This can be given in form of 40,000 IU IM monthly. 25 hydroxycholecalciferol 5-7 μg/kg can be given daily. Monitor serum calcium, phosphate and alkaline phosphatase and X-ray wrist at 2 months interval.

Vitamin E

Vitamin E deficiency is now recognised very oftenly since the age of the children with cholestasis is increasing. The dose of vitamin E recommended is 15-200 mg daily. Serum monitoring is mandatory. If levels are on lower side, then higher dose should be given. Six monthly neurological and yearly eye examination are required.

Vitamin K

In case of prolonged cholestasis with steatorrhea vitamin K 5mg IM monthly should be given. Treatment of other complication of liver disease like ascites, portal hypertension, variceal bleed and encephalopathy should be done accordingly (10).

To summarise the scenario of NCS in India is disappointing at present because of late referral of the cases to centres where facilities to diagnose metabolic diseases and EHBA are available. This has been shown in table III. More than 80% of EHBA cases come for treatment when they have already crossed 2 months of age as shown in table III when it is difficult to establish the bile flow. The mistake is at various levels starting from undergraduate training to postgraduate training in pediatric medicine, unawareness about the seriousness of the problem, wastage of time on making diagnosis and treatment. These are not correctly practiced in peripheral hospital/medical colleges hence delay in referral of these cases. The algorithm III shows reasons for later referral of EHBA in India. There is lack of surgical expertise also to handle EHBA. We don't have the facilities of liver transplantation in our country. Cost factor and non-availability of cadaveric liver are main hinderances. In this context parents can help by giving piece of their liver to own produced baby. Hence, there
is need of "Yellow Alert" nation wide to detect these cholestatic babies and early referral to well equipped tertiary care centre where facilities to handle these babies are available. There is need for an Indian efforts to detect cholestatic babies, to make early diagnosis and prompt treatment to avoid occurrence of end stage liver disease given in algorithm IV.

Algorithm-III

LATE REFERRRAL OF EHBA IN INDIA

Healthy Baby

Ignorance of parents → All Doctors
Local Doctor or G.P. → Doctors to treat Jaundice
Pediatrician → Medical College

- Physiological Jaundice: Phototherapy
- Breast Milk Jaundice: Herbal Medicine
- Lack of facilities

Late referral to Tertiary Care Centre

Cirrhosis

Algorithm-IV

NEED FOR AN INDIAN EFFORT

CHOLESTASIS OF INFANCY

(High coloured urine, diaper staining, clay coloured stool & conjugated S. bilirubin > 20%)

Significant Hepatobiliary Disease

Urgent Diagnostic Evaluation
Early Specific Therapy
Prevent Morbidity Mortality

- Prompt referral to Tertiary care centre
- Pediatric Gastroenterology, Hepatology & Nutrition
- Era of LIVER TRANSPLANTATION

References