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Case series of device closure of PDA in extreme preterm neonates

In this case series we are reporting the safety and efficacy of transcatheter PDA (patent ductus arteriosus) closure in extreme preterm neonates using Amplatzer Piccolo Occluder.

Background:

A patent ductus arteriosus (PDA) is a persistence of the fetal connection (ductus arteriosus) between the pulmonary artery and aorta after birth, typically resulting in a continuous left-to-right shunt

Presence of a PDA beyond the first week of life occurs in as many as 50% of premature babies and in more than 80% of severely premature extreme low birth weight (ELBW) infants (<1,000 g at birth). The presence of hemodynamically significant PDA has been associated with increased morbidity and mortality in extreme preterm neonates like necrotizing enterocolitis, chronic respiratory disease, pulmonary hemorrhage, intraventricular hemorrhage, and death.

Surgical ligation of PDA is performed if pharmacological treatment of PDA is unsuccessful. Surgical ligation, while effective, has been associated with significant procedural and post-procedural complications and poor long-term outcomes, including worsening lung disease and poor neurodevelopmental outcomes

Recent clinical evidence has emerged suggesting that transcatheter closure of PDA can be performed safely and effectively in premature infants as small as 700 g or smaller.

The PDA morphology in extremely premature infants resembles its fetal counterpart (so-called F-type PDA morphology). It is typically long and tubular with a hockey stick configuration such that the Amplatzer Piccolo Occluder has favorable features (size,shape, delivery system) for closure of PDAs in premature neonates.

A clinical study evaluating the safety and effectiveness of the Amplatzer Piccolo Occluder was conducted that led to the approval of this device by the U.S. Food and Drug Administration (FDA) for patients ≥700 g.

In this case series of 5 neonates, we report the safety and efficacy of Amplatzer Piccolo Occluder to treat a hemodynamically significant PDA (hs-PDA) in extreme preterm neonates.

From April 2021 to June 2022, 5 neonates delivered ≤ 28 weeks who had persistent hsPDA despite 2 courses of medical management underwent transcatheter PDA closure.

Primary efficacy outcome was rate of PDA closure and primary safety outcome was rate of major complications.

Secondary outcome was rate of pulmonary or aortic obstruction at follow up.

Case series:

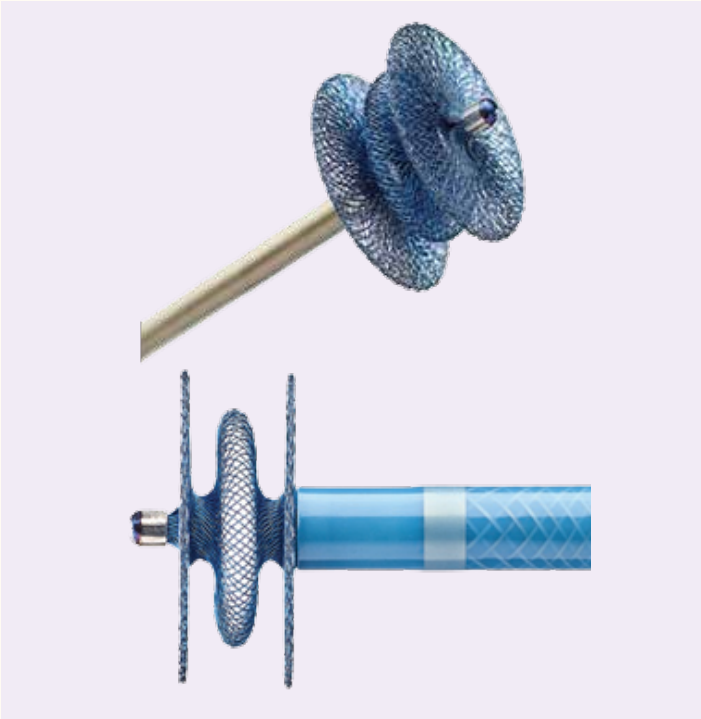
Five neonates with mean gestational ages of 26 weeks and with mean birth weight of 911 grams underwent transcatheter closure at mean postnatal ages of 27 days of life. Mean weight at the time of procedure was 960 grams.

Table: Clinical demographics of neonates undergoing transcatheter PDA device closure

	Case 1	Case 2	Case 3	Case 4	Case 5
Gestational age (weeks)	28	26+5	26+0	24+0	25+2
Birth weight (grams)	1138	1000	900	737	780
Postnatal age at procedure (days)	25	24	10	53	25
Postconceptional age (weeks)	31+4	30+1	27+3	31+5	28+6
Weight at procedure (grams)	1150	1050	880	815	905
Gender	Female	Female	Female	Female	Female
Outcome (survived/ died)	Survived	Survived	Survived	Survived	Survived
Echocardiographic characteristics					
Size of PDA- width (mm)	3.8	2.2	3.8	3.0	2.5
Type of PDA (conical vs tubular)	Tubular	Tubular	Fetal	Tubular	Tubular
Post procedure complications					
Clinically significant Left pulmonary artery stenosis	nil	mild	nil	nil	nil
Device migration/ embolization	nil	nil	nil	nil	nil
Residual shunt	nil	nil	nil	nil	nil

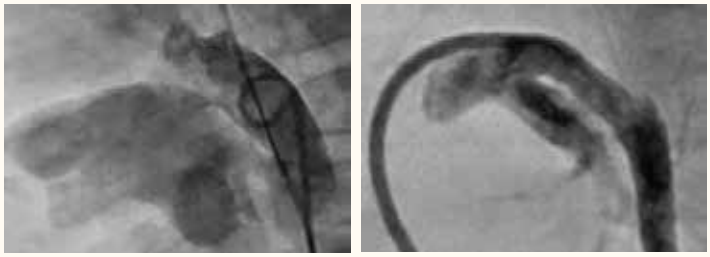
All 5 neonates (100%) has successful closure of PDA, one neonate (20%) had mild left pulmonary artery stenosis which was not clinically significant. All neonates (100%) on follow up at 2 months had no complications with no residual shunt.

AMPLATZER PICCOLO™ OCCLUDER

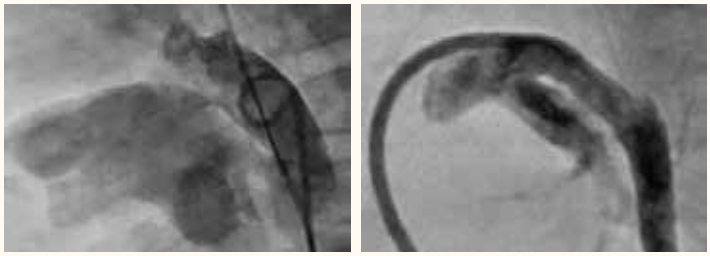


The Amplatzer Piccolo Occluder is a self-expandable, Nitinol mesh device with a central cylindrical waist and low-profile retention discs that are marginally larger than the waist, resulting in a nearly isodiametric device.

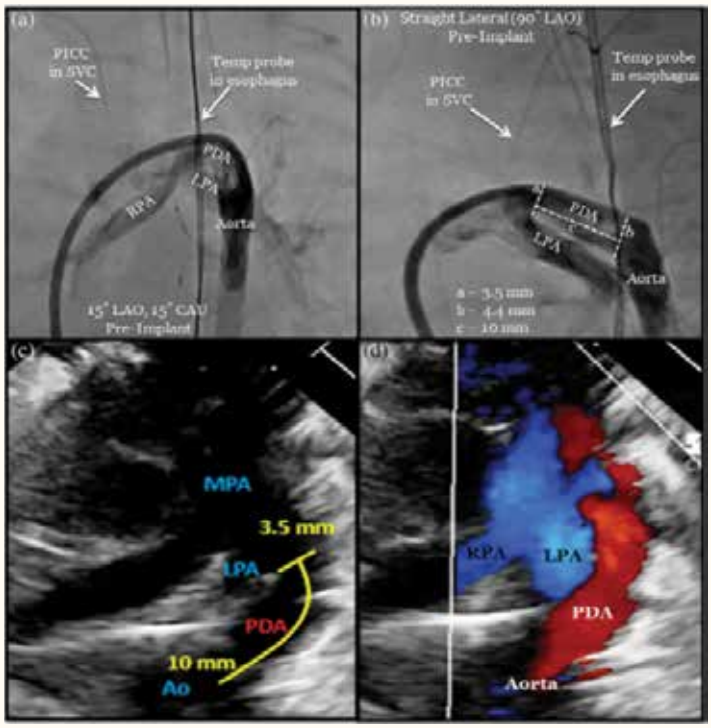
Implantation of PDA device under fluoroscopy



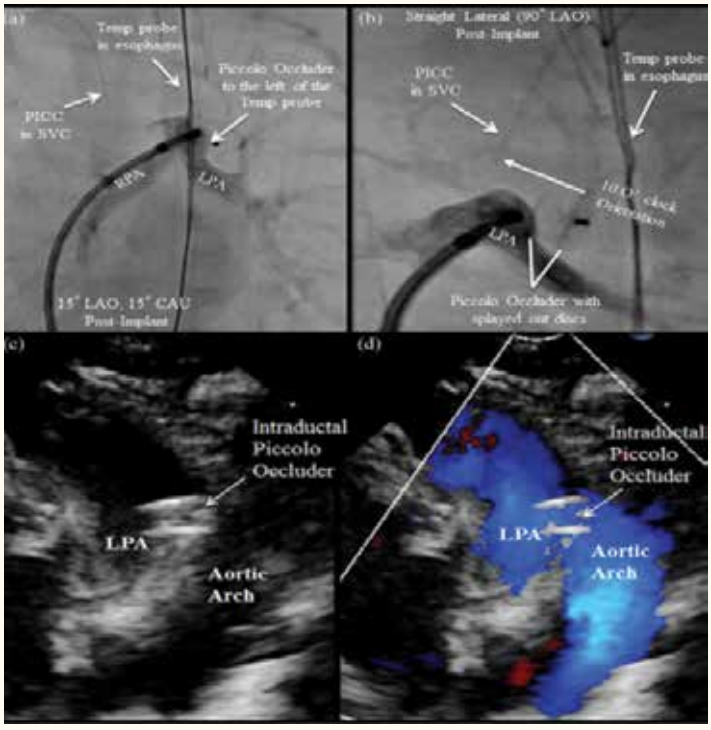
After implantation of PDA device



Before PDA device implantation



After PDA device implantation



Amplatzer Piccolo Occluder is an effective and safe alternative to surgical ligation among extreme preterm neonates with hsPDA despite 2 courses of pharmacological management.

The US IDE and CAP studies support the safety and effectiveness of the Amplatzer Piccolo Occluder, particularly in patients ≤2 kg.

Frequently Asked Questions

1. How do you identify PDA in Newborn?

PDA is identified on the basis of clinical signs such as hyper dynamic precordial activity (visible precordial pulsations in more than 2 rib spaces), bounding pulses, wide pulse pressures, palpable pulses in the palms of hands, hyperdynamic precordium, hepatomegaly, persistent tachycardia (>180 beats/min) and the presence of a pan systolic murmur or continuous murmur over the precordium. The most common finding a PDA in preterm neonates may be worsening requirement for mean airway pressure (MAP) or oxygen (FiO2) in a neonate recovering from RDS.

2. What are the indications of closure of PDA?

Opinions have varied on whether PDA can be considered a silent bystander versus whether it may be considered as a source of worsening cardio respiratory status in preterm neonates.

Various staging systems based on clinical as well as echocardiographic criteria have been proposed to decide whether a PDA requires treatment.

The following table summarises the role of echocardiographic variables in determining the hemodynamic significance of PDA.

3. What are the complications of untreated PDA?

Untreated PDA increases risk for BPD, NEC, renal dysfunction, IVH, death and long term complications like PVL, CP.

4. What are the advantages of using device closure over surgical closure of PDA?

Advantages are:

- Median time to return to baseline respiratory status is significantly shorter than the surgical closure.
- Lesser respiratory and hemodynamic compromise
- No risk of pneumothorax, chylothorax, vocal cord palsy, infection

5. What are the adverse effects of device closure?

Embolisation and risk of left pulmonary and aortic obstruction are the important adverse effects, particularly in extremely preterm neonates.

Table : Classification of PDA based on echocardiographic markers

Parameter	No PDA	Mild	Moderate	Large
Features of ductus arteriosus				
Transductal diameter (mm)	0	<1.5	1.5-3	>3
Ductal velocity Vmax (cm/s)	0	>2	1.5-2	<1.5
Antegrade PA diastolic flow (cm/s)	0	>30	30-50	>50
Pulmonary over circulation				
Left atrial/ aortic ratio	1.13 ± 0.23	<1.4	1.4-1.6	>1.6
Left ventricular/ Aortic ratio	1.86± 0.29	-	2.15±0.39	2.27±0.27
Mitral E wave/ A wave ratio	<1	<1	1-1.5	>1.5
IVRT (ms)	<55	46-54	36-45	<35
Systemic hypoperfusion				
Retrograde diastolic flow (%)	10	<30	30-50	>50
Aortic stroke volume (ml/kg)	≤2.25	≥2.34		
Left ventricular output (LVO) (ml/kg/min)	190-310	-	-	>314
LVO/ SVC ratio	2.4±0.3	-	-	4.5±0.6

Dr. Abhijeet Auradkar
Neonatal Fellow

Dr. Pranitha Reddy
Consultant Neonatologist & Pediatrician

Dr. Sudeep Verma
Consultant Pediatric Cardiologist

Hypernatremic dehydration mimicking peroxisomal disorders in a neonate

Introduction:

Hypernatremic dehydration (HND) is a rare but serious clinical condition in neonates. Hypernatremia is defined as serum sodium concentration > 150 mmol/L. Hypernatremia dehydration can be caused by decreased fluid intake, excessive fluid loss or excessive sodium intake. In a recent study, it was observed that lactation failure in primigravida mothers was one of the commonest reasons for hypernatremic dehydration in neonates with an incidence of 2.5% per 10,000 live births. The presenting complaints of hypernatremia were fever (34.6%), poor feeding (42.8%), loose stools (40.8%), lethargy (26.5%), decreased urine output (8.2%), and weight loss (75.5%); 24.5% neonates presented with neurological complaints and examination revealed a doughy feel of skin in 90 % of them. Hypernatremia itself or improper treatment may lead to intracerebral edema, subdural capillary haemorrhage, venous thrombosis, gangrene and death. Dehydration can cause pre-renal injury and may further progress into intrinsic renal failure, complicating the management.

Case report:

An early term (38weeks) male neonate was delivered by LSCS (Indication: failed induction) with birth weight 3100 grams to a 23 year old primi mother who conceived naturally with normal antenatal scans. Baby cried immediately after birth, did not require any resuscitation and was shifted to mother side. Baby was started on direct breast feeds. In view of inadequacy of mother's milk, baby was given cow's milk by the attenders. On day 3 of life baby had fever and was treated on OP basis. On day 7 of life baby again had fever, tachypnoea and decreased urine output. The baby weight was measured which was 2100 grams (32% weight loss from birth weight). Baby was admitted in private hospital. Baby was kept on nasal prongs oxygen and blood investigations showed raising creatinine. Baby also developed recurrent episodes of seizures for which baby was intubated and loading dose phenobarbitone was given. As baby had oliguria and raising creatinine, need for peritoneal dialysis SOS was explained to the attenders and referred to KIMS cuddles, Kondapur for further management.

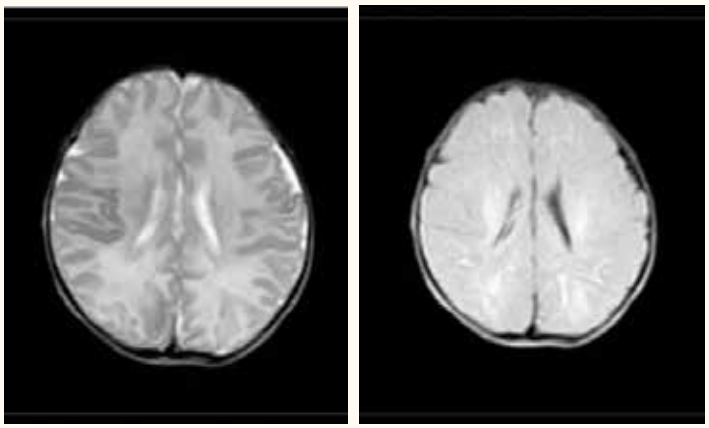
Baby brought to KIMS NICU on Bag with ET ventilation, placed under a radiant warmer and connected to mechanical ventilator on SIMV with minimal settings (PIP -14, PEEP -5, rate-40, Fio2-21%). On examination baby weight was 2110 grams, baby had tachycardia and no other signs of shock. Bilateral air entry was equal with shallow respiration. Neurologically baby was lethargic, hypotonic, weak cry on stimulation and anterior fontanelle was sunken. Baby had wrinkled appearance of skin with paucity of subcutaneous fat. Investigations revealed leukocytosis with neutrophilic predominance, thrombocytopenia (94,000/cumm) and CRP-1.2mg/l. Arterial blood gas analysis showed metabolic acidosis with pH-7.14, pCo2-27.8mmHg, pO2-39.6mmHg, HCO3-10.3 mmol/L and base excess -21.6mmol/L. Blood biochemistry revealed hypernatremia (172mmol/L), uremia (Blood Urea -292 mg/dl, Creatinine -6.6mg/dl), and transaminitis. Rest of the metabolic parameters were normal. USG KUB and renal doppler were normal.

In view of severe metabolic acidosis baby was given a bolus of NS 10ml/kg and sodium bicarbonate correction over 8 hours. Free water deficit and sodium excess were managed by gradual and slow correction over 48 hrs as per protocol. The serum sodium levels returned to normal by day 4 of admission. Baby had stress related hyperglycaemia with GRBS > 500mg/dl, hence treated with insulin infusion for 24 hours. Urine output and uremia gradually improved following IV fluid replacement. Baby was treated with Lasix infusion and antibiotics. Serum creatinine reached normal range (0.5 mg/dl) by day 5 of admission.

The baby required phenobarbitione and levetiracetam for the seizures. MRI brain showed large areas of white matter hyperintensities involving bilateral parieto-occipital white matter and splenium of corpus callosum (Figure-1) resembling neonatal peroxisomal disorders such as acetyl-coA oxidase deficiency. Upon review of literature, similar MRI findings could also be explained by hypernatremic dehydration in neonates. Very long chain fatty acid levels were normal. Baby was weaned off to CPAP by day 3 of admission. In view of mild PAH oral sildenafil was given. Baby was then weaned off to room air by day 8 of admission. By day 9 of admission, baby was on full oral feeds.

Baby was discharged on levipil and phenobarbitone was stopped. The weight of the baby was 2762 grams. On follow-up after 2 months, the baby's development was normal with no further seizure recurrence.

Fig. 1: MRI brain image showing bilateral parietooccipital white matter hyperintensities



Frequently Asked Questions

1. Define hypernatremia?

Hypernatremia was defined as serum sodium more than 150mEq/L and hypernatremia was graded as mild (150-155 mEq/L), moderate (156 - 160 mEq/L), severe (≥ 161 mEq/L).

2. What are the Causes of hypernatremic dehydration?

- Hypovolemic hypernatremia: Inadequate intake – lack of breastfeeding (often associated with high concentration of sodium in the breast milk which exaggerates hypernatremia), premature babies with excessive insensible water losses, radiant warmers, Diarrhoea and Phototherapy, Renal dysplasia, polyuric phase of acute tubular necrosis, Post obstructive diuresis
- Euvolemic Hypernatremia: Diabetes insipidus, CNS tumours, Meningitis or encephalitis, amphotericin, Aminoglycosides.
- Hypervolemic hypernatremia: Improperly mixed formula, Intravenous hypertonic saline, Hyperaldosteronism

3. What are the causes of Lactation Failure?

Maternal: Primi mother, elderly mother, Caesarean delivery, twins, inadequate knowledge, cracked nipple, inverted nipple, breast engorgement, poor attachment, maternal illness (preeclampsia, diabetes, hemorrhage, infection), obesity, mother- infant separation, working mother.

Neonatal: Early term and late preterm neonates due to ineffective sucking, SGA/IUGR, no effective latch in first 24 hours, cleft lip/palate, short frenulum, micrognathia, choanal atresia, neonatal asphyxia, excessive pacifier use etc.

4. How is hypernatremia corrected?

No consensus treatment guidelines exist, but most experts recommend a goal reduction rate of serum sodium levels of 0.5 mEq/L per hour with correction over 48 hours.

The treatment involves restoration of vascular volume with 10 to 20 mL/kg of isotonic intravenous [IV] fluid such as lactated Ringer solution with 130 mEq/L [130 mmol/L] of sodium or normal saline with 154 mEq/L [154 mmol/ L] of sodium) followed by a rehydration phase (the sum of the free water deficit and maintenance fluid requirements administered evenly over 48 hours)

In severe hypernatremia, the fluid restoration may need to be done with an IV solution that has a sodium concentration no more than 15 mEq/L (15 mmol/L) below the serum sodium concentration. For example, if the serum sodium at admission was 195 mEq/L, The desired sodium concentration of IV fluid is 180 mEq/L (195-15). This may need appropriate calculated volume of 3% NS to be added to regular 0.9% NS.

Calculation of the replacement fluid may be done in various ways – one of them is described below.

SAMPLE CALCULATIONS: HYPERNATREMIC DEHYDRATION		
Hypernatremic Dehydration		
Example: A 3-kg (pre-illness weight) child with 10% dehydration and serum sodium 159 mEq/L		
Requirement	**Formula**	**Sample calculation**
Maintenance fluid requirements	Holiday-Segar formula	100 ml/kg/d x3=300ml/24 hrs =12.5 ml/hr
Total fluid deficit	10 ml/kg for each percent dehydration	10 ml x 3 kg x 10% = 300 ml
Fluid requirement rate over 24 hrs		
300 ml/24 hrs = 12.5 ml/hr + 12.5 ml/hr maintenance = 25 ml/hr (600 ml/24 hours)		
Calculations for fluid selection		
Free water deficit	4 ml/kg x weight (in kg) x [serum Na+ (Meq/L - Desired Na+ (Meq/L)]	4 ml/kg x 3 kg x (159 Meq/L - 145 Meq/L) = 168 ml
Solute fluid deficit	Total fluid deficit – free water deficit	300 ml – 168 ml = 132 ml
Maintenance Sodium requirement	3 Meq per 100 ml of maintenance fluid	3 Meq x (300/100 ml) = 9 Meq Na+
Sodium deficit	8 – 10 Meq Na+ per each 100 ml of solute fluid deficit	10 Meq x (132/100 ml) = 13.2 Meq Na+
Total sodium requirement	Add maintenance sodium requirement and sodium deficit	9 Meq + 13.2 Meq = 22.2 Meq
Sodium required per liter	Divide total sodium by fluid deficit in litres	22.2 Meq/ 300 ml = 0.07 Meq/L
Fluid that best approximates sodium required per litre	Compare sodium needed to fluid composition; add dextrose and potassium per needs	D5 ½ normal saline (77 Meq/L) + 20 Meq KCL or KAcetate

5. Define Neonatal Acute Kidney Injury?

- Serum creatinine raised by more than or equal to 0.3 mg/dL within 48 hours.
- Percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline) or Decrease in urine output (documented oliguria of < 1ml/kg/hour over 24 hours)

6. What is the classification of AKI based on serum creatine and urine output?

Stage	Change in serum creatinine (SCr)	Urine ouput over 24 hours
0	No change or rise <0.3 mg/dl within 48 hours	>1ml/kg/hr
1	Rise in SCr by 0.3mg/dl within 48 hrs or Rise in SCr 150-200% of lowest previous value within 7 days	<1ml/kg/hr
2	Rise in SCr 150-200% of lowest previous value	<0.5ml/kg/hr
3	Rise in SCr 300% of lowest previous value or 2.5 mg/dl or recipient of dialysis	< 0.3ml/kg/hr

7. Types of AKI based on urine output?

1. Oligo-anuric (40%)
2. Non-Oliguric (60%)

Neonatal AKI is predominantly non-Oliguric and may be missed if serum creatinine is not monitored.

8. When to give Renal Replacement therapy?

1. When conservative therapy fails to treat AKI
2. Persistent hyperkalaemia
3. Metabolic acidosis (Ph<7.2 despite medical management)
4. Hyponatremia with volume overload
5. Hyperphosphatemia refractory to therapy
6. Inability to provide adequate nutrition due to fluid restriction.

Renal replacement therapy can be given by Peritoneal dialysis, Hemodialysis and Continuous renal replacement therapy.

9. What is adrenoleukodystrophy?

Adrenoleukodystrophy is an X-linked disorder associated with accumulation of saturated VLCFAs and a progressive dysfunction of adrenal cortex and nervous system. Mostly affects males. Definitive diagnosis is determined by demonstration of VLCFA excess. Other tests are MRI of brain, brain biopsy and genetic analysis. Treatment is corticosteroid replacement for adrenal insufficiency, Allogenic bone marrow transplantation for cerebral ALD.

Lorenzo's oil helps to lower elevated VLCFA levels.

10. MRI changes in Adrenoleukodystrophy?

Loes et al. described five different MRI patterns of adrenoleukodystrophy based on the involved anatomic locations and MR patterns of progression:

1. Deep white matter in the parieto-occipital lobes and splenium of the corpus callosum (66% of cases, chiefly in children); may include lesions of the visual and auditory pathways

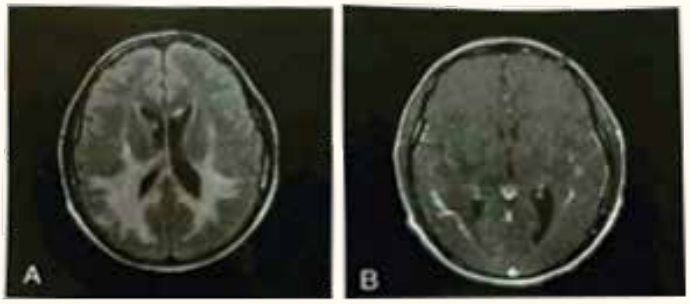


Fig. 104.5: Characteristic MRI findings in cerebral adrenoleukodystrophy. **A.** Symmetric T2 weighted MRI abnormalities involved the posterior white matter, including the corpus callosum. **B.** Contrast administration reveals a garland of enhancement.

2. Frontal lobe or genu of the corpus callosum (15.5%, mostly in adolescents)
3. Frontopontine or corticospinal projection fibres (12%, mostly in adults)
4. Cerebellar white matter (1%, mostly in adolescents)
5. Combined parieto-occipital and frontal white matter (2.5%, mostly children)

There tends to be cortical and subcortical U-fibre sparing.

Dr. Srujana Swarna
Neonatal Fellow

Dr. Singanamalla Bhanudeep
Consultant Pediatric Neurologist

Dr. Aravinda Lochani T
Consultant Neonatologist & Pediatrician

Infant with neonatal cholestasis

A 2 months old male infant product of non consanguineous marriage, born late preterm at 36 weeks' gestational age, presented to us with prolonged jaundice. The baby was born to a G2P1L1 mother by Elective LSCS with birth weight of 2300 grams. The baby cried immediately after birth and did not require any resuscitation at birth. At 24 hours of life, baby developed decreased feeding, lethargy, neonatal seizures in the form of jerky movements and cyanosis. The baby was shifted to the NICU, intubated and ventilated due to encephalopathy and was shifted to our centre.

The neonate had to be ventilated for 3 days followed by CPAP after the sensorium improved. The baby had multiple episodes of seizures and started on levetiracetam, phenobarbitone and phenytoin after ruling out hypoglycemia, hypocalcemia and dyselectrolytemia. Work up for inborn errors of metabolism showed mildly elevated serum ammonia (163 micM/L), normal lactate, anion gap and absent urine ketone bodies. Tandem mass spectroscopy (TMS) was essentially normal. Urine GCMS showed mild elevation of tyrosine and propionic acid. MRI brain showed mild cerebral edema. CSF analysis was not suggestive of pyogenic meningitis (2 cells/HPF, all lymphocytes,) although there was mild elevation of protein levels. Baby was discharged on oral levetiracetam with clinical examination showing mild axial hypotonia. The working possibilities remained viral encephalitis versus early onset epileptic encephalopathies, pending genetic evaluation.

Baby was on regular follow up on day 21 of life baby presented with umbilical swelling with discharge ? umbilical granuloma. USG abdomen showed a tubular structure of length 2.5mm connecting the anteroposterior aspect of urinary bladder to umbilicus likely patent urachus. The baby was on conservative management for the same.

At 50 days of life baby reported back to the OPD with whitish stools yellowish urine and recent onset jaundice. On examination, baby was having yellowish discolouration of skin activity good and vitals are stable, CVS -S1 S2 heard no murmur. Baby had hepatomegaly 5 cms below the RCM, soft in consistency and umbilical hernia was present .

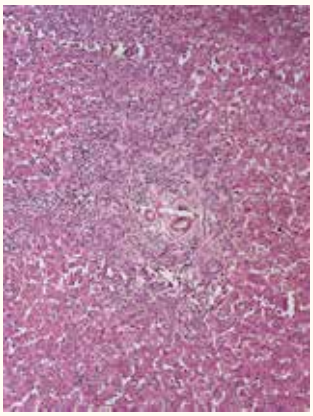
Evaluation revealed direct hyperbilirubinemia (TSB -11.6mg/dl with direct fraction 4.5 mg/dL), mildly elevated liver enzymes (SGOT-193 , SGPT-162), normal serum albumin (3.8 g/dL) and INR (1.1). Repeat USG abdomen to look for obstructive jaundice showed dilated common bile duct (10 mm), mild IHBRD and mild gall bladder sludge. There was no evidence of "triangular cord sign" and gall bladder was well distended which suggested that extrahepatic biliary atresia was less likely. GGT was elevated (347 U/L) suggestive of obstruction. Thyroid function was essentially normal. Urine routine examination, culture were not suggestive of urosepsis. The baby was given a brief trail of oral urso-deoxy cholic acid re-evaluated in 1 week.

On re-evaluation, serum bilirubin was persistently elevated with 10.11 mg% with direct fraction -5.86 mg%. The rest of the liver function remained similar with mildly elevated liver enzymes, normal synthetic liver function and elevated GGT. The infant was admitted for further workup in the form of a MRCP as there was a high likelihood of obstruction. In the absence of clear cut clues from MRCP, laparotomy with planned hepato-enterostomy with liver biopsy was planned. Blood counts showed CBP -8.4 g/dL, WBC- 28270/cu.mm, Platelet- 4.66 lacs/cu.mm suggestive of sepsis and echocardiography showed structurally normal heart.

A repeat USG abdomen followed by MRCP both revealed similar findings - a 5.4mm oval echogenic filling defect in distal CBD causing obstruction and upstream biliary dilatation suggestive of choledocholithiasis, well distended gall bladder with normal wall thickness, filling defect in gall bladder possible cholelithiasis and a small saccular diverticulum at the junction of cystic duct and common hepatic duct possible Type 2 choledochal cyst – suggesting the possibility of cholelithiasis and choledocholithiasis. The baby was taken up for laprotomy - intra operative findings showed dilated CBD as well as common hepatic duct (1 cm each), terminal CBD calculus and sludge causing obstruction and upstream biliary dilatation small type 2 choledochal cyst at the junction of cystic duct and common hepatic duct (Fig. 1). The baby underwent choledochal cyst excision + hepatojejunostomy and Roux en -y loop and liver biopsy was sent. Post operatively the baby was ventilated for 1 day and extubated to HFNC. Started on enteral feeds after 5 days and discharged after 8 days. Direct jaundice reduced significantly (TSB 2.6 mg/dL, direct fraction 1.5 mg/dL) and baby was noted to pass pigmented stools.

Fig.1 A: Dilated common hepatic duct and Common bile duct

Fig.1 B: Gall bladder sludge



Liver biopsy showed Portal tract expansion with extensive ductular proliferation. Native duct was unremarkable. These findings were supportive of obstruction as seen intraoperatively.

Frequently Asked Questions

1. What is the most accepted definition of direct hyperbilirubinemia?

Although there are discrepancies among various laboratories and techniques, a practical definition of cholestatic jaundice infant is one where direct bilirubin greater than 1.0 mg/dl if the total bilirubin <5mg/dl or a value of direct bilirubin that represents more than 20% of total bilirubin if the total bilirubin is greater than 5mg/dl.

2. What are the common causes of neonatal cholestasis?

The most common cause of cholestatic jaundice in the first months of life are biliary atresia and neonatal hepatitis. Neonatal hepatitis has referred to a histological appearance of widespread giant cell transformation.

In large Indian series hepatocellular causes were seen in 53%, obstructive causes in 38%, ductal paucity in 3% and other 6% cases were idiopathic.

Infants with cholestatic jaundice caused by bacterial sepsis , galactosemia ,hypopituitarism or gall stones often appear acutely ill . These disorders require early diagnosis and urgent treatment.

3. What are the important causes of cholestasis where early diagnosis can make a significant difference in outcomes?

Substantial observational evidence suggests that earlier diagnosis and surgical repair of extrahepatic biliary atresia led to better outcomes. The Kasai's Portoenterostomy appears to have the greatest likelihood of reestablishment of bile flow and the longest term of survival of infant native liver when performed before the age of 45 to 60 days. Conditions such as sepsis, galactosemia, hypothyroidism and panhypopituitarism must be recognised early to prevent progression.

4. What are the useful laboratory tests in a neonate with direct hyperbilirubinemia?

The investigatory approach should take into consideration the clinical condition and presentation of the child (Fig. 2).

The evaluation of cholestatic jaundice in infants between two and eight weeks of age should be undertaken in a staged approach. In a sick baby with cholestatic jaundice possibilities of galactosemia, toxoplasmosis, herpes, tyrosinemia, sepsis, malaria, etc. should be considered and ruled out. The next step is to distinguish biliary atresia from other causes of neonatal cholestasis, because early surgical intervention for biliary atresia results in improved outcome.

The further tests should be individualised rationally based on the results of above tests. If the level of serum alpha-1 antitrypsin is found to be low, Pi typing is indicated. If an obvious extrinsic obstruction (such as choledochal cyst) is present, referral for surgery is warranted.

5. What is the usefulness of imaging in a neonate with cholestasis?

Ultrasonography- It is most helpful in the diagnosis of choledochal cysts but can also suggest the diagnosis of biliary atresia; suggestive findings for the latter are the inability to visualize the gallbladder and the presence of the "triangular cord sign" (triangular or band like periportal echogenic density >3 mm in thickness). The latter is more specific than sensitive for the diagnosis of EHBA.

Scintigraphy- Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid analogues may provide some more information in distinguishing biliary atresia from neonatal hepatitis. Infants with biliary atresia usually have normal uptake of the isotope but absent excretion into the intestine, whereas those with neonatal hepatitis typically have delayed uptake but appropriate excretion. However, non-visualization of the gallbladder or lack of excretion can occur in patients without biliary atresia. Pre-treatment for five days with phenobarbital (5 mg/kg per day) increases the accuracy of this test by enhancing isotope excretion.

Additional tests such as MRCP (Magnetic Resonance Cholangiopancreatography) and ERCP (Endoscopic retrograde cholangiopancreatography) are not routinely recommended in view of limited data in neonates and young infants.

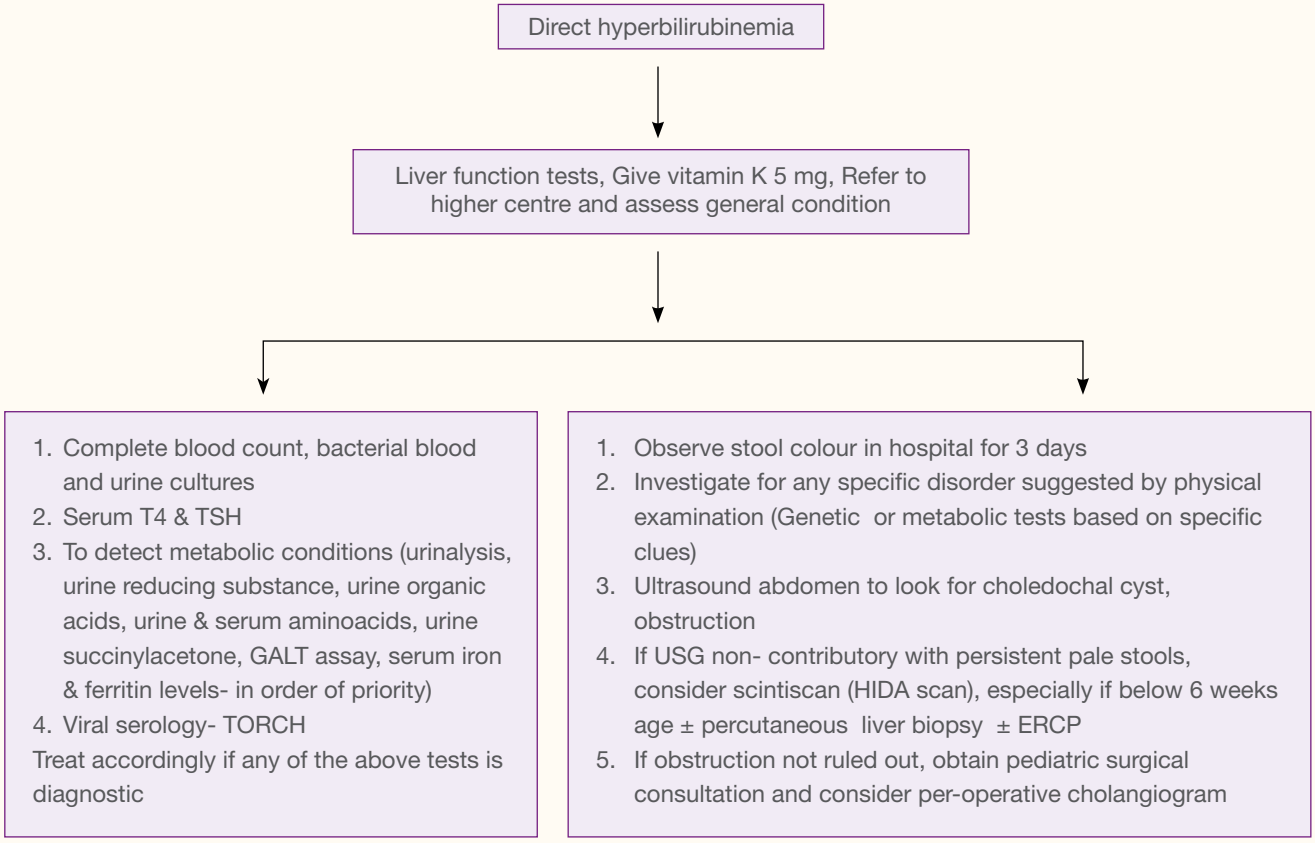
6. What does percutaneous liver biopsy add to the evaluation of a neonate with cholestasis?

The NASPGHAN guideline recommends that a percutaneous liver biopsy be performed in most infants with undiagnosed cholestasis, especially when obstruction cannot be reliably ruled out. Findings supportive of biliary atresia in the liver biopsy are - expanded and edematous portal tracts, bile duct proliferation, bile duct damage, and intraductular bile plugs. Liver biopsy specimens obtained early in the course of biliary atresia may be indistinguishable from hepatitis. Other diagnostic findings from a biopsy include PAS-positive granules in alpha-1 antitrypsin deficiency, ductal paucity in Alagille syndrome, necro-inflammatory duct lesions in sclerosing cholangitis, and other findings that are relatively specific for metabolic and storage diseases.

Conclusions

Neonatal cholestasis constitutes almost one-third of children with chronic liver disease in major hospitals in India. EHBA, neonatal hepatitis and metabolic causes are the most important causes in India. Early identification of the cause is essential for a favorable outcome. This requires specific biochemical tests, imaging studies and interpretation of histopathology by experienced personnel. To ensure early referral, there is an urgent need to sensitize pediatricians, obstetricians and other primary-care physicians on the need for early evaluation.

Fig. 2: Approach to investigating a neonate with cholestasis



Dr. Deepika Kurra
Neonatal Fellow

Dr. Jyothi
Pathologist

Dr. G. Manisha Reddy
Consultant Pediatric Surgeon & Urosurgeon

Dr Aparna C
Clinical Director - Neonatology & Sr. Consultant Neonatology & Paediatrics

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KIMS CUDDLES
MOTHER & CHILD CENTRE

KIMS Cuddles - An unit of KIMS Hospital Enterprises Pvt. Ltd.
1-112/86, Survey No 55/EE, Kondapur, Serlingampally, Hyderabad 500 084, Telangana, India.
Call: 040 - 4243 4243
hello@kimscuddles.com
www.kimscuddles.com