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MOTHER & CHILD CENTRE

Neonate with cyanosis and CCF

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Case report:

A Full term (39 weeks) male neonate was delivered by Elective LSCS (Indication: Previous LSCS) with birth weight 3400 grams to a 36 year old G2P1L1 mother who conceived naturally. All antenatal scans were normal. Baby cried immediately after birth, did not require any resuscitation and was shifted to mother's side. Baby was started on direct breast feeds. At 12 hours of life parents noticed respiratory distress. Baby was admitted in a NICU in a private hospital at Maharashtra in view of respiratory distress and bluish discoloration of skin. Baby was initially started on oxygen support via low flow nasal cannula. Vital signs were: RR – 65/mt, mild retractions, SpO2 -85% in room air. 2D Echo done on day 3 of life showed d-TGA (transposition of great arteries) with large subpulmonic ventricular septal defect -VSD (10 mm) with moderate unrestrictive secondary ASD. Baby was started on injection furosemide and empirical antibiotics and then referred to KIMS Cuddles NICU for further Management.

Baby was brought on DOL-3 to our unit on nasal prongs 2 L/mt and started on bubble CPAP (6 cms H2O/ FiO2 30%). On examination baby's weight was 3100 grams, baby had baseline oxygen saturation of 70% with tachycardia and grade 4 pan systolic murmur. Bilateral air entry was equal with tachypnoea and subcostal retractions (Downe's Score-3/10). Abdomen was soft with hepatomegaly (4cm under left coastal margin). Neurologically baby's cry, tone and activity was appropriate for age and anterior fontanelle was at the level. Chest X ray done showed cardiomegaly with bilateral perihilar haziness

Blood gas analysis showed mild respiratory alkalosis with metabolic acidosis with pH-7.34, pCO2-32.4 mm Hg, pO2-39.6 mm Hg, HCO3-17 mmol/L and base excess -7.2 mmol/L. 2D Echo done showed large subpulmonic VSD (left to right shunt shunt) with moderate ASD (8mm) BD with d-TGA. In view of features of congestive cardiac failure (cardiomegaly with respiratory distress with hepatomegaly) baby was started on IV furosemide and dobutamine.

At 18 hours of admission (DOL-4) baby was intubated and connected to mechanical ventilation on SIMV mode (PIP -18, PEEP 6 cms H2O/ FiO2 30%). In view of increase in respiratory distress associated with desaturation and bradycardia, baby was sedated with fentanyl infusion. On DOL-7 baby underwent arterial switch operation where aorta and pulmonary artery were transected just above the point where they leave the heart and reconnecting them to the appropriate ventricles and coronary arteries were re-anastomosed to the aorta in standard fashion and ventricular septal defect was patched under cardiopulmonary bypass. The ASD was also patched leaving a small defect to allow minimal shunting.

After the surgery, baby was shifted to NICU and connected to SIMV+VTV (VTe-28 ml (Tidal volume 8 ml/kg)/PIP max-28 cms H2O /PEEP-5 cms H2O /Rate-40/mt /Fio2-75%), nursed under radiant warmer with core temperature targeted at 36 oC. Bilateral pleural drains with mediastinal drain as well as peritoneal dialysis catheter were in situ. Right femoral artery line was placed with continuous invasive BP monitoring. Left femoral venous catheter was used for administering inotropes - Adrenaline (0.08 u/kg/min), Inj Milrinone (0.5ug/kg/min), Inj vasopressin (0.0005 U/kg/min) inj Sildenafil (1.6mg/kg/day), Inj calcium gluconate, inj Fentanyl, atracurium and antibiotics. X ray done on post operative day 2 showed bilateral perihilar haziness with normal sized heart

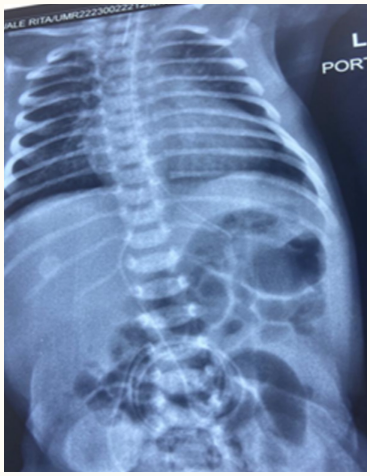

Figure-1: Chest radiography taken pre operative period showing cardiomegaly with bilateral perihilar haziness.

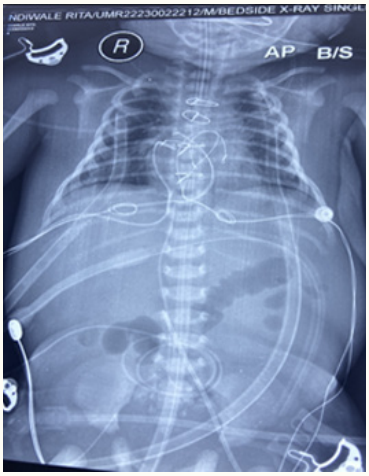

Figure-2: Chest radiography taken post operative period showing mediastinal drain and b/l pleural drains in situ.

Post operative echocardiography showed moderate MR with mild TR and mild PAH. Sternal closure was done on post operative day 2. As baby was edematous lasix infusion was started on post operative day 2 (DOL-9). Potassium correction was given as per protocol on post operative day 3 in view of hypokalemia (2.6MEq/l). I/v/o hypoalbuminemia and edema multiple albumin infusions were given. Ventilator settings were weaned and baby extubated to bubble CPAP (6/5/60%) by post operative day 4 (DOL-10). After optimizing perfusion and blood pressures between 5-50th centile inotropes were tapered and stopped over by 4 days. PD cycles were stopped on post operative day 3 and PD catheter was removed. Mediastinal drain and b/l pleural drains was removed on post operative day 3 & 4.. Femoral lines were removed on post operative day 6. Baby weaned off from CPAP to HFNC (5/30%) by DOL-18. Discharged after 20 days on oral furosemide, inj enoxaparin and oral sildenafil.

Frequently Asked Questions

1. In a neonate with cyanosis, how does X-ray and echocardiography help detect TGA as the cause?

Chest roentgenogram classically shows cardiomegaly with cardiac contours classically described as appearing like an egg on string (Figure-3). There is often an apparent narrowing of the superior mediastinum as the result of the aortic and pulmonary arterial configuration, i.e. parallel in D-loop transposition, with the main pulmonary artery posterior to the aorta.

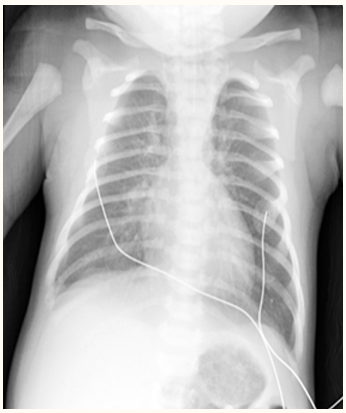

Figure-3: Chest radiography showing Egg on string sign

Transthoracic Echocardiography (Figure-4)

Parasternal long axis view: allows visualization of the great vessels traveling in parallel

- Main pulmonary artery branches posteriorly from the left ventricle and bifurcates into branch pulmonary arteries
- The aorta may be visualized anteriorly from the right ventricle

Short axis views: allows delineation of the spatial relationship of the great vessels and the coronary artery origins (Figure-4)

- Aorta will be anterior and slightly to the right of the pulmonary artery

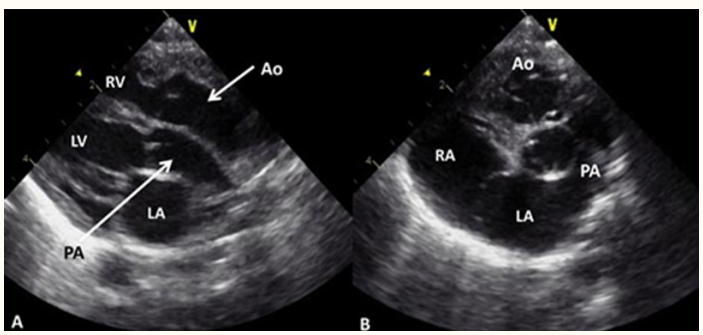

Figure -4: Long- (A) and short- (B) axis views of an infant with TGA. Note parallel position (A) of the PA and Aorta and on-end visualization of PA and Ao in B

2. What are the associated lesions with TGA?

- Ventricular septal defect (VSD) (40%)
- Pulmonary stenosis
- Overriding or straddling AV valves
- Hypoplastic aortic arch/Coarctation of aorta.
- Right ventricular outflow tract obstruction.
- Left ventricular outflow tract obstruction.
  - Coronary artery abnormalities Left Circumflex from the Right coronary artery
  - Single right/left coronary arteries
  - Inverted Coronary origins

3. Is there a role for non surgical management of TGA?

Two medical management measures may be used in TGA:

- PGE1 (Alprostadil): Keeps the PDA patent and may hence achieve increase in oxygen saturations or partial pressure of oxygen dissolved in arterial blood or both by 10% by increased mixing of blood from pulmonary and systemic circulations in TGA with intact ventricular septum. PGE1 can cause apnea, hypotension, fever
- Ballon Atrial Septostomy: Helps in increasing oxygen saturations in cases of insufficient blood mixing/ shunting and restrictive PFO or intact atrial septum. BAS may be associated with risk of vascular trauma, atrial arrhythmias, atrial perforation and tamponade

With medical management 90% of neonates with D-TGA are relatively stable and undergo electively-timed arterial switch surgery.

4. How is TGA corrected surgically?

a) D-TGA with intact ventricular septum or small VSD Arterial switch operation (ASO or Jatene operation):

Currently is the most frequent procedure. It consists in transecting the great arteries and switching them to the other semilunar valve. This way, the aorta with coronary arteries get translocated to the native-pulmonary artery valve and the pulmonary artery gets translocated to the native-aortic valve. Usually done during the first week of life, to avoid left ventricular deconditioning and risk of pulmonary hypertension (Fig. 5)

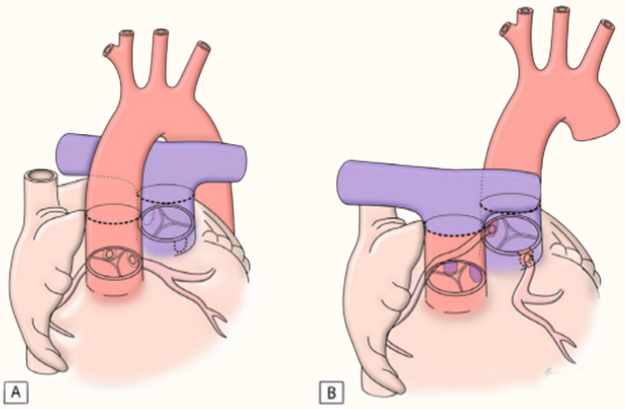

Figure 5: Arterial switch

Atrial switch operation

Mustard/ Senning procedure: Utilizes pericardial patch or atrial tissue to baffle systemic venous flow to mitral valve and pulmonary venous flow to tricuspid valve – when arterial switch is not feasible

b) D-TGA with intact ventricular septum or small VSD

Arterial switch is to be done before 1 month or earlier if there is refractory CCF. VSD closure is also done.

c) D-TGA with VSD and pulmonary stenosis:

Rastelli procedure: It consists of baffling the aorta to the left ventricle and using a right ventricle to pulmonary artery conduit. Baffling depends in the side of the VSD.

5) What must be the ideal timing of surgery?

TGA with Intact ventricular septum:

It is recommended that a primary ASO is performed from the first few days to 3 weeks of life and maximum up to 30 days to prevent left ventricular deconditioning.

Anatomy	Surgical Options	Comments
TGA/IVS	Arterial Switch (Jatene)	Neonatal period usually within 3 weeks of age
TGA/VSD	Rise in SCr by 0.3mg/dl within 48 hrs or Rise in SCr 150-200% of lowest previous value within 7 days	Usually neonatal repair

6) What are the early and long term post operative complications of arterial switch?

Early Morbidities: Cardiac arrest, myocardial ischemia esp during the critical phase of formation of neo-aorta, need for extracorporeal membrane oxygenation, delayed sternal closure, systemic infection (including sepsis, fungemia, endocarditis, and meningitis), necrotizing enterocolitis, seizure, stroke on MRI with clinical sequelae, diaphragmatic paralysis/paresis, reoperation before discharge, or readmission at 30 days.

The overall survival following arterial switch surgery is > 80%.

Long Term Post-Operative Sequelae	Incidence
Supravalvular pulmonary stenosis	10%
Supravalvular aortic stenosis	5%
Neoaortic root dilation,	Nearly universal
Neoaortic regurgitation,	Most (moderate or severe in < 10%)
Asymptomatic coronary occlusion,	2–7%
Sudden cardiac death	< 1%
Arrhythmia	2–10%
Aortic dissection or rupture,	Unknown

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A case of respiratory distress with PAH

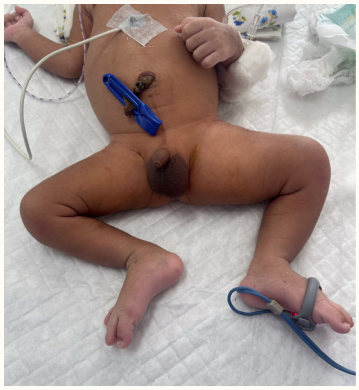
A single-live term male baby was born to 27 yr old G2P1L1 mother with marital life of 5 years with spontaneous conception. Antenatal history was uneventful. The baby was delivered through Elective LSCS in view of the previous LSCS elsewhere. Baby passed meconium in utero.

Baby cried immediately after birth and had a birth weight of 2750 grams. Soon after birth , baby developed respiratory distress and hence was initially started on oxygen through nasal cannula . Baby was referred to another private hospital where baby was started on high flow nasal cannula. In view of labile saturations with history of meconium stained liquor, possibility of PPHN was considered and baby was started on diuretics and sildenafil. Baby was started on antibiotics empirically after sending blood cultures.Sepsis was negative. 2D ECHO done on day 4 of life, revealed PDA with the size of 2.5 mm with left to right shunt with moderate PAH (RVSP-46mmHg).

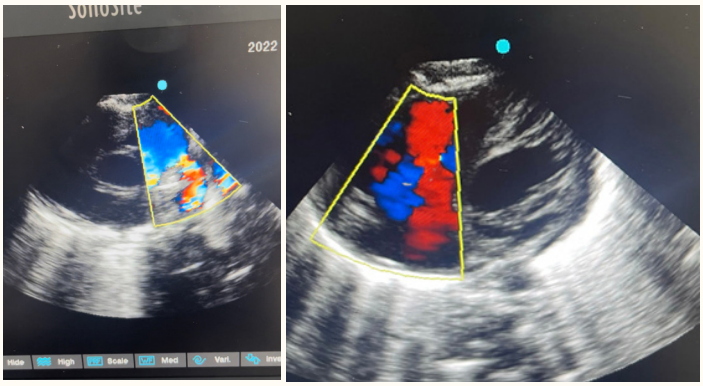
On day 5 of life, baby was referred to KIMS Cuddles neonatal unit in view of persistent respiratory distress. At admission, baby had respiratory distress with a downe's score of 3/10. Baby was started on CPAP with settings of PEEP-6/FiO2- 30%. Baby had heart rate of 170 per minute with wide pulse pressures, bounding pulses, continuous murmur, and hepatomegaly.

Blood gas at admission was normal. (pH- 7.365, pCO2- 38.6mm of hg, HCO3- 21.6, pO2-43mm of hg, BE=-3, lactate-2.5). x-ray was suggestive of bilateral perihilar haziness with cardiomegaly . Repeat 2D ECHO was done which revealed dilated right heart, small PFO with 2.5mm PDA with left to right shunt. There was mild TR jet and PAH(RVSP-38 mm hg). These features were suggestive of PDA with right heart failure . Baby was started on sildenafil for pulmonary hypertension and diuretic (furosemide) for CCF.

The baby had asymmetry of the lower limb and increased circumferential thickness of the left thigh as compared to the right side. Examination of the left limb showed slightly warm limb compared to right side, tenderness was present, there was no erythema. Bruit was also felt. Initially, septic arthritis was considered in view of clinical features of sepsis with elevated CRP.

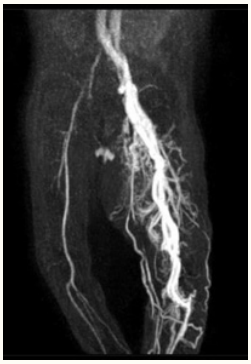


Picture 1: Clinical picture of baby produced with permission showing asymmetry of limbs with increased thickness of left limbs.

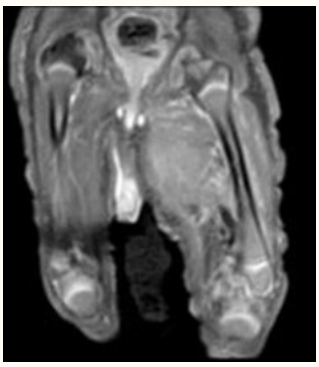


Picture 2 and 3: Echo showing PDA and PAH

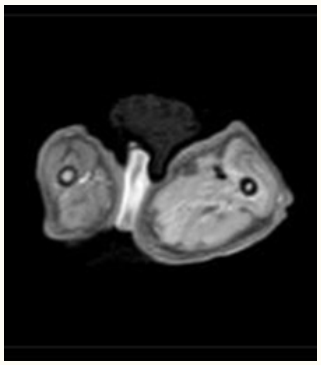
X-ray done revealed no evidence of increased joint space and effusion with increased soft tissue thickness on the left side. MRI showed hypertrophy of left thigh muscles with multiple intramuscular flow voids seen.on contrast arterial and multiple tortuous course of left iliac, femoral vessels (more in medial aspect), and subcutaneous tissues with the mild increased enhancement of thigh muscles suggestive of congenital arteriovenous malformations.



Picture 4: MR-Angiography showing collaterals from Iliac and femoral veins suggestive of AVM.



Picture 5: coronal view of left thigh contrast film - Showing discrepancy of both femurs (left>right), cortical thickening of left femur , hypertrophy of left thigh muscles(predominantly medial compartment).



Picture 6: Axial T1 contrast film showing hypertrophy of left thigh muscles , multiple dilated tortuous veins (Left iliac and femoral)

Pro-BNP levels were sent to know the cardiac dysfunction. (7210 pg/ml). D-Dimer(847.53) and fibrinogen(153 mg/dl) levels also sent to know extent of blood clot lysis which were within normal limits. Baby was gradually weaned off from respiratory support, started on oral diuretic. The baby was planned for surgical correction or embolization at later date.

Introduction

Arteriovenous malformations are high-flow congenital vascular abnormalities that result from disordered embryogenesis. AVMs are abnormal communication or shunting through a nidus of coiled and tortuous vascular connections that connect feeding arteries to drainivng veins due to a deficiency of interposed capillary bed between the two vessels from cellular and molecular changes affecting angiogenesis and inflammation that lead to their development . There may be over expression of genes involving vasculogenesis such as VEGF, angiopoietin-2, Notch4, and MMP-9 . Most AVMs are congenital. Some authors considered that they can also develop postnatally. The most common sites of AVM in infants and children are within the cranium, in the lung, in the liver, and also in the extremities.

The incidence of AVM is 1.34 per 1,00,000 person-years, where as the prevalence rate is quite higher because it's clinically silent in nature. It is only symptomatic in 12 % cases. The most common cause of mortality in these cases is significant haemorrhage (10-15 %) and morbidity varies from 30-50 % despite the best possible treatment.

The clinical manifestations of Peripheral AVMs depend on size of the fistulous communication, location , feeding and draining vessels. Due to shunting of blood from the high-pressure arterial system to low resistance venous system through large communication, systemic pressure drops, venous pressure increases leading to disruption of vessel walls .

Compensatory mechanisms manifest as tachycardia, widened pulse pressure, high output right heart failure. Local manifestations include haemorrhage, ulceration occur in some cases.

They can sometimes reduce blood supply to associated organs by Steal Effect.

Diagnostic modalities for confirming the disease are CT and MRI with or with out contrast. Angiography is a gold standard diagnostic modality helpful in diagnosing and planning treatment.

Treatment options of AVM include managing neonate with CCF. Definitive treatment includes catheter endo-vascular embolisation with sclerosant agents, Gamma knife radio- surgery and open vascular resection in some cases. Percutaneous and trans- vascular embolisation is considered to be first line therapy in advance state AVM. For transcatheter use, various mechanical occlusion devices (coils, vascular plugs) and liquid embolic agents are

available. The latter are divided into sclerosing agents (ethanol), polymerizing agents (cyanoacrylate

or ethylene-vinyl alcohol copolymer = EVOH) and particulate agents. To avoid relapse, complete occlusion of the vascular nidus has to be the goal of the embolization.

Frequently Asked Questions

1. What are some common syndromes associated with AVM ? Osler Weber Rendu Syndrome is associated with cerebral AVM. Cobb Syndrome is associated with spinal AVM.

   Klippel trenaunay Weber syndrome - lower limb AVM with bony and soft tissue swelling, varicose veins , port-wine stain.

   Parkes weber syndrome - giant limb hypertrophy due to AVM.

2. What are the risk factors associated with a higher risk of AVM rupture ?

   Prior haemorrhage, deep AVM location, exclusively deep venous drainage, and associated aneurysms.

3. What are the stages of AVM ? Schobinger score

   Stage I (quiescence): The AVM is asymptomatic. The overlying skin may be inflamed. Stage II (expansion): The AVM gets larger. A pulse can be felt or heard in the AVM. Stage III (destruction): The AVM causes pain, bleeding or ulcers. Stage IV (decompensation): Heart failure occurs.

4. Name grading system for AVM Spetzler-Martin grading system

Graded features	Points assigned
Size of AVM	
Small (<3 cms)	1
Medium (3-6 cms)	2
Large (>6 cms)	3
Eloquence of adjacent brain	
Non-eloquent	0
Eloquent	1
Pattern of venous drainage	
Superficial only	0
Deep	1
AVM grade 1-5 equals the total number of points	

5. What are the advantages of surgical method ?

Gold standard method

Fastest , most complete , immediate cure

Helps in Hematoma removal in acute haemorrhage.

Low post operative morbidity.

6. What are the differential diagnosis you can consider in a case of high output heart failure?

We need to rule out anemia , Fever, septic shock , PDA, AV Malformations , fluid overload if a baby presents with features of hyper dynamic circulation like tachycardia, bounding pulses, precodial activity .

7. What are the precautions to be followed while discharging such babies ?

Counsel the parents regarding risk of rupture . To review immediately in case of increase in limb swelling, discolouration of limb, cool peripheries, fast breathing . To avoid trauma and injections to the limb .

8. A term neonate presents with respiratory distress, macrocephaly, seizures, cranial bruit and high output Heart failure . What differential diagnosis do you consider in this case ?

Vein of Galen malformation is a shunt between prosencephalic vein , an embryonic precursor of vein of Galen and arteries supplying the brain. It leads to hemodynamic changes because of excess blood flow from these arteries into VOGM leading to high output heart failure. VOGM is one of the common AVM seen in infants.

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Down Syndrome with Autoimmune Enteropathy

INTRODUCTION:

Patients with Down syndrome are more susceptible to autoimmune pathologies, in particular endocrine or digestive diseases such as celiac disease. Autoimmune enteropathy is another form of digestive autoimmune disease, non-gluten-dependant, more often diagnosed in male neonates with immunodysregulation and polyendocrinopathy such as the Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome. Clinical manifestations are similar to celiac disease, but not improved after a gluten-free diet. Autoimmune enteropathy is frequently associated with other autoimmune diseases, such as thyroiditis, myasthenia gravis, lupus or immune deficiencies, as Common Variable Immunodeficiency. Pathological analysis of intestinal biopsies can frequently distinguish autoimmune enteropathy and celiac disease. Autoimmune enteropathy usually has an important lymphoplasmacytic infiltration of the mucosa and a lack of intraepithelial lymphocytes in the gastrointestinal mucosal surface, while celiac disease usually has a polymorph infiltration of the mucosa and an important intraepithelial lymphocytes infiltration. Nevertheless, the two pathological patterns may overlap. Here we report the case of a patient with Down syndrome associated with autoimmune enteropathy.

CASE REPORT:

An Early term 38weeks gestational age, female baby delivered by LSCS on 22/7/2022 at a private hospital in Warangal with birth weight of 2831 grams to a 31year old Primi mother following spontaneous conception. Baby was admitted in NICU on DOL-3 for phototherapy in view of neonatal hyperbilirubinemia. On examination baby had systolic murmur and saturation below 90% in all 4 limbs, 2D ECHO was done showed Double Outlet Right Ventricle with Pulmonary Stenosis, Baby was referred to KIMS CUDDLES for further management.

On examination baby had facial dysmorphism with flat round face, almond shaped upward slanting eyes, epicanthal folds, small depressed nose and small mouth, low set ears, brachycephaly, short neck, sandal gap suggestive of Downs phenotype, Karyotyping for Trisomy 21 was sent. On systemic examination, systolic murmur on cardiac auscultation was present, rest of the systemic examination is unremarkable.2D ECHO showed complete AV canal defect with DORV with PS. As baby is maintaining saturations between 85-92% advised to follow up after 2 weeks. Planned for Blalock Taussig shunt followed by intracardiac repair on further follow-ups.

On Day 26 of life baby presented with c/o mild tachypnea and loose stools since 5 days, decreased oral intake, irritability, vomiting and fever since 1 day. Baby had weight loss of 14% at admission. Baby had a HR-165/min, RR-62/min, acidotic breathing + BP - 79/48 mm of Hg (58) Abdomen was soft with no organomegaly. Cry & activity were dull. Hypotonia was present. Baby was febrile with temperature (100.4F). AF - Sunken, severe dehydration signs were noted with pallor and oral thrush. Bilateral femoral pulsations were well felt.

NICU COURSE:

Baby was admitted in NICU and nursed in a thermoneutral environment. Baby maintained saturations well at room temperature. No oxygen support was initiated. VBG done on day 1 of admission showed severe metabolic acidosis with respiratory acidosis (pH- 7.048, pCo2- 28, pO2- 29, base - -21, HCO3 - 7.4, lactate - 3.6) for which baby was started on NS bolus followed by IV fluids for correcting dehydration and ongoing losses along with maintenance fluids. Bicarbonate correction was given. Acidotic breathing slowly improved in next 8 hours. Repeat blood gas showed improvement in metabolic acidosis (pH- 7.3, pco2-27, pO2-29, lactate - 3.8, base - -11, HCO3- 14.9) and subsequent blood gases became normal. Baby had 1 episode of seizure at presentation, treated with anti-epileptic Levetiracetam and kept on maintenance dose.

2D Echo done at birth showed Cyanotic heart disease DORV with VSD with PS. Systolic murmur present and baby was maintaining saturations > 80 %. In view of poor perfusion, baby was started on dobutamine infusion which was tapered and stopped over the next 24 hours. Baby was hemodynamically stable during the later hospital stay.

CHRONIC DIARHHEA WITH DEHYDRATION:

Baby was admitted with complaints of loose stools with severe dehydration and severe metabolic acidosis. NS bolus given and fluids started as per protocol. Relevant investigations were done which showed raised CRP :200, CBP- WBC:24420, PLC:4.49 lakhs, Hb:17.3gm/dl, PCV:52.5, RBC:5.05, Serum creatinine 2, Stool for Reducing substances negative. Complete stool examination was normal.

Possibilities considered were infectious pathology for which baby was started on IV Meropenem and Fluconazole and given for 5 days. Blood culture showed no growth. Repeat CRP was 40mg/dl. As baby had bloody diarrhea Cow's milk protein intolerance was suspected and baby was started on elemental formula. Baby's diarrhea persisted even on half concentration elemental formula. Acquired Immunodeficiency was ruled out as baby's retroviral status was negative. Congenital immunodeficiency also seemed less likely as baby had no neutropenia or lymphopenia. Flowcytometry and immunoglobulin profile couldn't be done due to un-affordability.

Baby had both osmotic and secretory diarrhea as loose stools persisted even on keeping the baby nil

per oral. Now the possibilities considered were either Congenital enteropathy or monogenic Inflammatory bowel disease. Gastroenterologist opinion was taken. Baby underwent endoscopy and biopsy. Upper GI endoscopy revealed villous atrophy and decreased duodenal folds. Sigmoidoscopy showed loss of vascular pattern with erythema of mucosa with superficial ulceration suggestive of congenital enteropathy. Biopsy also showed moderate to marked villous atrophy, presence of small epithelial tufts on surface epithelium and lymphoplasmacytic infiltrates in lamina propria suggestive of congenital enteropathy. In contrast IBD picture would be of multiple deep linear ulcers and areas of narrowing. Baby was re-started on OG feeds and increased as tolerated. Down syndrome was confirmed on Karyotyping. Congenital enteropathy was confirmed on genetic evaluation. Baby was started on 2mg/kg/day of Prednisolone for congenital enteropathy for 2 weeks followed by tapering of the dose. After tapering Prednisolone baby was also started on Azathioprine at 1 mg/kg/day which was later increased to 2mg/kg/day.

Baby was discharged on full oral feeds with elemental formula which the baby tolerated well after starting treatment for congenital enteropathy. On follow-up after 2 weeks baby gained almost 500 grams weight and is thriving well.

Frequently Asked Questions

What is Down syndrome and its incidence?

Down syndrome is the most common chromosomal disorder, occurring with a frequency of 1:800 newborns. Human cells have a pair of 23 chromosomes. Trisomy is characterized by the presence of 3 chromosomes instead of the normal 2. Down syndrome is Trisomy 21. As cytogenetics shows Trisomy 21 is found in 95% cases, 1% cases are mosaic, 4% are due to translocations, most commonly involving chromosomes 21 and 14. Down syndrome is the most common cause of reduced intellectual ability

What is the Hall's Criteria for Down Syndrome?

- 10 cardinal signs
- Poor Moro reflex
- Hypotonia
- Flat facial profile
- Up slanting palpebral fissure
- Dysplastic ears
- Reductant loose neck skin
- Simian crease
- Hyperextensible joints
- Pelvic dysplasia
- Hypoplasia of 5th finger middle phalanx.

What anomalies are associated with Down Syndrome?

Neurological- Hypotonia, Developmental delay, Delayed closure of fontanelle, Seizures, Autism spectrum disorders

Congenital Heart Defects - such as endocardial cushion defects, AVSD, PDA, Tetralogy of Fallot, Mitral, tricuspid or aortic valve regurgitation, Endocarditis

Musculoskeletal - Joint hyper-flexibility, Short metacarpals and phalanges, Atlanto-axial instability, Hip dysplasia

Gastrointestinal anomalies - duodenal atresia, annular pancreas, Tracheo-esophageal fistula, Hirschsprung disease, Imperforate anus, Neonatal cholestasis, Celiac disease Endocrine- Hypothyroidism, Diabetes mellitus, Infertility, Obesity, Hyperthyroidism Hematological- ALL, AML

Antenatal screening for Down Syndrome?

First trimester screening: Between 11-13+6 weeks of pregnancy, combination of maternal age, free beta HCG, PAPP-A, and Nuchal translucency. Detection rate of 90-94%

Quadruple test- free beta HCG, unconjugated, AFP, inhibin A – 80% detection

Combined first and second trimester screening- dectection rate upto 95%

Diagnostic tests- Chorionic villus sampling, Amniocentesis

What is chronic diarrhea and its etiology?

Diarrhea with stool volume > 10 g/kg/day lasting for more than 14 days. Common causes are: Infectious (E coli, Giardia, Clostridium difficile, Cryptosporidium associated with HIV)

- Celiac disease,
- Allergy to cow's milk protein,
- Eosinophilic gastroenteritis,
- Lactose intolerance,
- Inflammatory bowel disease- peak incidence in childhood,
- Exocrine pancreatic disorders associated with cystic fibrosis- steatorrhea,
- Primary bile acid malabsorption
- Immune - Autoimmune enteropathy, primary and secondary immunodeficiencies, IPEX syndrome,
- Structural defects- Microvillus inclusion disease, tufting enteropathy, lymphangiectasia
- Electrolyte - Congenital chloride or sodium diarrhea, acrodermatitis enteropathica,
- Motility - Hirschsprung disease

What is Autoimmune enteropathy?

Autoimmune enteropathy (AIE) is a clinico–pathologic diagnosis that is characterized by severe intractable inflammatory diarrhea with intestinal biopsies showing villous atrophy, increased epithelial apoptosis, and mononuclear cell infiltration with or without the presence of anti-enterocyte antibodies. Patients with autoimmune enteropathy commonly present before 6 months of age

but can manifest at any age. These patients typically need prolonged immunosuppressive therapy. With recent technologic advances in genetic diagnostics, some patients presenting with AIE were identified to have specific diagnoses such as IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, and X-linked), IL-10 and IL-10R defects, and APCED (autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia).

What are intestinal and extraintestinal manifestations of Autoimmune enteropathy?

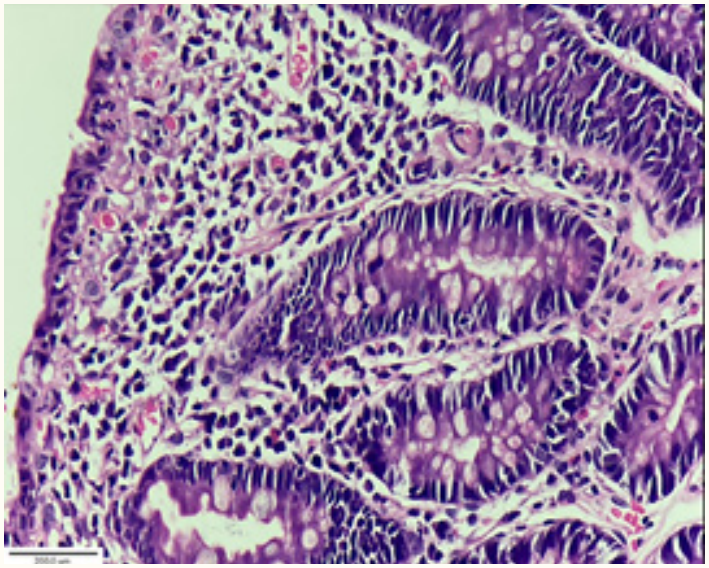
Children with AIE can have intestinal and extraintestinal manifestations. These infants have refractory diarrhea, with malabsorption, and anorexia, with severe weight loss, that requires treatment with total parenteral nutrition. The extraintestinal manifestations may include endocrine, renal, pulmonary, hepatic, hematologic, and musculoskeletal system involvement. The diagnostic criteria for AIE include chronic diarrhea for greater than 6 weeks with malabsorption, partial or complete blunting of the small bowel villi, deep crypt lymphocytosis, increased crypt apoptotic bodies, minimal intraepithelial lymphocytosis, and no other causes that may explain the villous atrophy. The diagnosis could also be supported by detecting anti-enterocyte (AE) or anti-goblet (AG) cell antibodies.

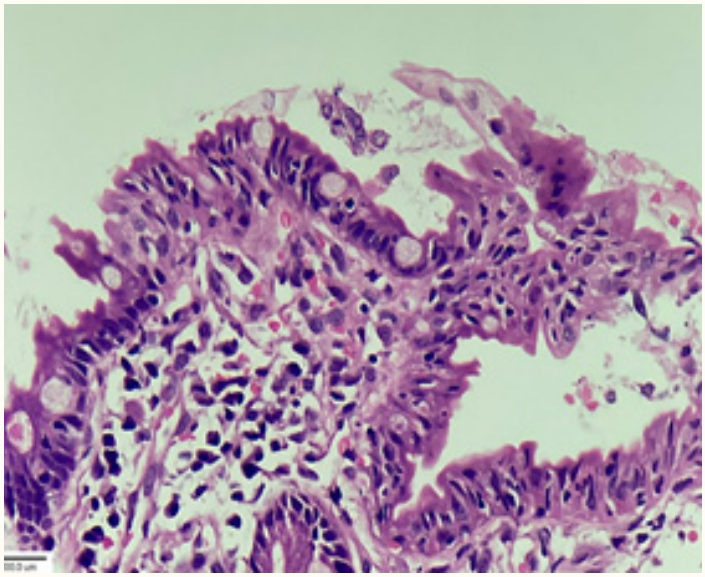
What are the clinical features of Autoimmune enteropathy?

Clinical features are characterized by severe and protracted secretory diarrhea starting for most in the first few weeks of life and leading to frequent episodes of dehydration, electrolyte imbalances, and malnutrition requiring parenteral nutritional support.

Management of Autoimmune enteropathy?

Many patients with AIE develop malnutrition, which must be addressed as part of the treatment plan. A trial of oral nutritional supplementation may be successful. However, for many patients with AIE, total parenteral nutrition is required. In addition, medical therapy is commonly used, most typically with corticosteroids (prednisolone). However, some patients (40%) are refractory to corticosteroids, and in these patients immunosuppressive therapy with azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, infliximab, and rituximab has been described and usually is successful in 20% of those cases. In addition, these drugs have been used as maintenance therapy in patients who are corticosteroid dependent. Remaining 20% may ultimately need bone marrow transplantation.





Biopsy images

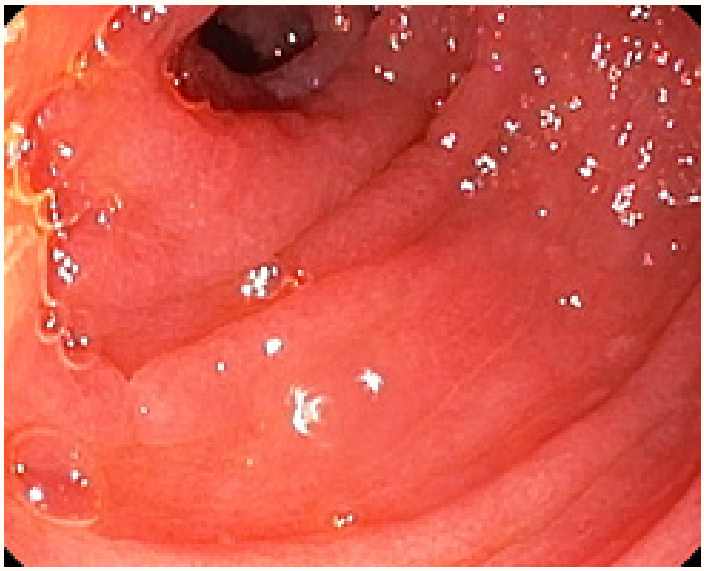
Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
CTLA4 (+) (ENST00000648405.2)	Exon 1	c.98T>C (p.Val33Ala) Large (>6 cms)	Heterozygous	Immune dysregulation with autoimmunity, immunodeficiency and lymphoproliferation (OMIM#616100)	Autosomal dominant	Uncertain significance

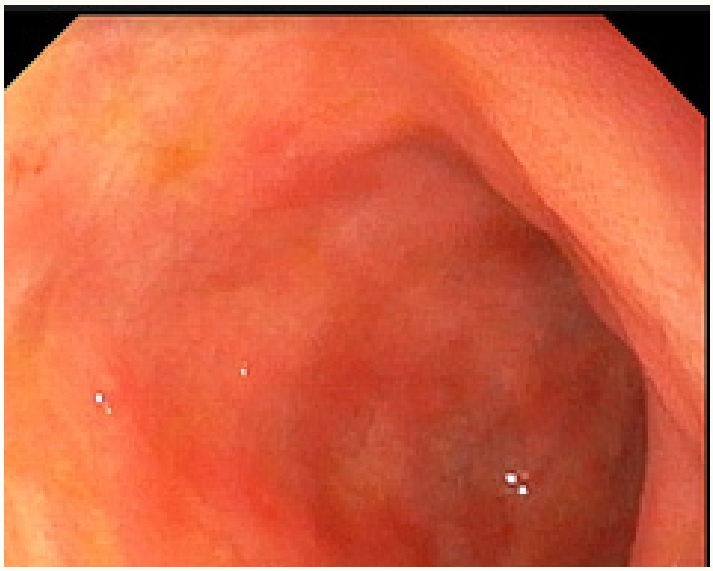
Parental testing is strongly recommended, and classification of the variant may change based on segregation analysis.

Copy Number Variants CNV(s)

Chromosome	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
Chromosome 21	chr21:g.(?_1)_ (46709983_?)dup	Microduplication	Heterozygous	Down Syndrome	-	Likely Pathogenic

Genetic report of Down syndrome and congenital enteropathy





Upper and lower GI endoscopy images

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