NICU TIMES

KONDAPUR

VOLUME-7

KIMS CUDDLES™
MOTHER & CHILD CENTRE

Foreword

Dear Esteemed Doctors,

I extend my heartfelt congratulations to KIMS Cuddles on the publication of its seventh edition of NICU TIMES. This stands as a testament to the dedication and passion of the entire team. Within these pages, you will find accounts of challenging and rare cases expertly managed.

It brings me satisfaction to witness the evolution of KIMS Cuddles into a team driven by it's pursuit of quality, making it an integral part of their ethos. Their commitment to professional excellence and personalized care is good.

I extend my sincerest commendations to Dr. Aparna C. and the entire team for their endeavors. May their journey ahead be marked with continued success.

I am confident that you will find this edition both informative and inspiring.

With warm regards,

Dr. B. Bhaskar Rao
Chairman & Managing Director
KIMS Group of Hospitals

Editor's Note

Dear Esteemed Readers,

It brings us immense joy to introduce the **Seventh edition** of our publication, the "**NICU Times**," crafted by the dedicated team at KIMS Cuddles, Kondapur.

In this edition, we are glad to present a diverse collection of challenging cases as case reports. The collection of cases in this issue ranges from post infective vasculitis related stroke, congenital primary immune deficiency presenting as pyrexia of unknown origin, a complex case of congenital hydrocephalus complicated by ventriculitis, neonate with coarctation of aorta masquerading as persistent pulmonary hypertension of newborn and an infant with cholestasis secondary to intrahepatic paucity of bile ducts.

We extend heartfelt gratitude to the experts from various allied departments like cardiology, cardiothoracic surgery, pediatric surgery, dermatology, and pediatric hemato-oncology. Additionally, we acknowledge the invaluable support from our branding team, instrumental in bringing this issue to fruition.

As pediatricians and neonatologists, we shoulder the significant responsibility of steering our nation towards enhanced neonatal survival rates and holistic well-being to achieve the ambitious goal of a single-digit Neonatal Mortality Rate (NMR) by 2030. At KIMS Cuddles, Kondapur we are unwaveringly committed to this objective. We firmly believe that sharing knowledge and collective learning will propel us closer to achieving this pivotal milestone.

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A RARE CASE OF CONGENITAL IMMUNODEFICIENCY

Case Details:

A 4 month old male infant with an uneventful birth history (born out of non-consanguineous marriage at term gestation by normal vaginal delivery with birth weight of 2.3 kgs) presented to KIMS Cuddles, Kondapur with recurrent episodes of high grade fever and noisy breathing for 10 days. Fever was well documented, high grade and not associated with chills or rigors. Baby had previous history of NICU admission for 6 days for the above complaints which was treated as pneumonia at an outside hospital (Chest X-Ray and other details were unavailable).

On admission baby weighed 5000 grams. Physical examination was unremarkable. Chest was clear. Baseline laboratory investigations revealed Anemia (Hb-8.7 grams/dL), leucocytosis (28330 cells/cu.mm), raised CRP (113 mg/L), ESR 10 mm/hr (normal), normal liver function and renal function tests, S. Ferritin - Normal (88 ng/mL), Malarial Parasite - Negative and unremarkable routine urine examination. Work up for dengue, enteric fever was negtaive. Urine and blood cultures were sterile, An arterial blood gas was normal. Chest X-ray was s/o Bilateral mild perihilar haziness. Ultrasound abdomen and 2D echocardiogram done for Kawasaki disease were normal. In view of clinical suspicion and persistent fever spikes, bone marrow aspiration and lumbar puncture were done. CSF sample findings revealed raised protein CSF - 86.3 mg/dL, total WBC count-5 cells /cu.mm. CSF c/s was sterile not suggestive of meningitis. CECT BRAIN done was normal. After a cross consultation with pediatric infectious diseases expert, IVIG 2 grams/kg was started with clinical suspicion of Atypical Kawasaki disease in view of persistent high grade fever and elevated acute phase reactants. Baby showed clinical improvement and was discharged.

Baby was re-admitted with complaints of fever after 2 weeks from date of discharge. On examination, BCG scar was normal with no increase in induration, with evidence of **hepatosplenomegaly**. Repeat routine CBP was sent, which showed anemia, leucocytosis and thrombocytosis. Repeat CRP was still elevated at 96.3 mg/dL, Procalcitonin high at 1.6 mcg/L. Triglycerides – 230 mg/dL, S. Ferritin continued to remain normal 89.3 ng/ml ruling out infection associated hemophagocytocis. ESR was raised (100 mm/hr). Work up for cytomegalo virus infection in the form of CMV PCR and Ebstein barr virus turned out negative, Gastric aspirates for tuberculosis were negative. Baby was on supportive therapy with IV fluids, antibiotics, steroids, antipyretics.

Baby was then extensively evaluated for other causes of fever - Brucella IgM, Malarial Parasite, HIV Gene Xpert were all negative. USG abdomen confirmed hepatosplenomegaly. Neurosonogram normal. There was no evidence of concealed collection of pus. Lymphocyte subset panel (CD4 and CD 19) was normal indicating absense of B cell and T cell mediated immune deficiencies. Repeat bone marrow smear as well as biopsy ruled out leukemia as well as hemophagocytocis. Rheumatologist opinion was taken and was advised to do consider steroids in view of suspicion of SOJIA (Systemic - Onset Juvenile Idiopathic Arthritis). Clinical exome sequencing was sent with a suspicion of immunodeficiency syndromes as well as periodic fever syndromes.

After a week of this admission, baby presented with decreased uptake of feeds, decreased activity, decreased urine output and 3 to 4 episodes of convulsions (GTCS type) with hypoglycemia, tachypnea, increased work of breathing, poor GCS and severe metabolic acidosis. Baby was intubated and started on ionotropic support, blood transfusion and peritoneal dialysis. Baby died due to severe sepsis with septic shock, multiorgan failure- encephalopathy, anemia, AKI, coagulopathy and severe metabolic acidosis.

Clinical exome sequencing was suggestive of hemizygous mutation involving CYBB gene suggestive of chronic granulamatous disease (below) The family was intimated and have been advised to undergo NBT dye reduction test for all family members and genetic studies for the elder female sibling as well as parents.

Disscussion:

Chronic Granulomatous disease (CGD) is a rare inherited disorder of the immune system that results in defective function of phagocytes. The disease manifests as recurrent or persistent life-threatening episodes of infections and hyperinflammation that often starts during the childhood. Affected individuals with CGD have deficient phagocyte NADPH oxidase activity that results in inefficient killing of bacteria and fungi inside the phagocytes. Exact incidence and prevalence of CGD is not known.

CGD is a primary immunodeficiency disorder characterized by defects in superoxide-generating systems of phagocytes leading to recurrent bacterial and fungal infections. Diagnosis of this disease requires a high index of suspicion along with prompt and aggressive treatment of infections. The presentation of this patient with recurrent, non remitting fever with hepatosplenomegaly with leucocytocytocis in early infancy points towards a primary immunodeficiency. The patterns of presentation differ from patient to patient in CGD.

CGD is a rare disorder and occurs in less than 1 in 25,000 individuals. The most common mode of inheritance is X-linked recessive. However, in 40% of patients with CGD, disease is inherited with an autosomal recessive pattern.

CGD normally presents in first few months of life, though age of onset can be as late as until adolescence or even adulthood. Skin, lungs and perianal tissue are the areas which are primarily involved in CGD. Laboratory findings in CGD include leukocytosis, anemia, increased ESR and hypergammaglobulinemia and the findings were similar in our case. Lung involvement in these patients may be in form of hilar lymphadenopathy, bronchopneumonia, empyema and lung abscess. Our patient had significant lung involvement showing bilateral subtle perihilar haziness on xray . It is known that abscesses can form in any organ of body, particularly in the liver, spleen, lungs and bones. Hepatomegaly is often quite prominent in such patients, as was the case in our patient. Infections in patients having CGD are usually due to catalase positive organisms like Staphylococcus aureus, Pseudomonas cepacia and Aspergillus species, but in our case culture was Negative.

Though various diagnostic tests have been used for CGD, the simplest of these is the NBT dye reduction test. In this test oxidase activity of leukocytes is tested during phagocytosis. This test gives percentage of neutrophils stained by the dye. This percentage is close to zero in affected cases, close to 100% in normal subjects, and 20-80% in heterozygotes. In our patient NBT was not done due to clinical suspicion of Atypical Kawasaki disease. Other tests used for diagnosis of CGD are absent chemiluminescence and immunoblot for NADPH oxidase production.

Prevention and cure of infections is the primary aim of management in CGD. Sulfamethoxazole-trimethoprim as prophylaxis is standard therapy nowadays for CGD and this treatment modality has revolutionized the management of this condition. Patients who remain on this therapy have significantly less infections necessitating hospitalization. Infections in these patients require vigorous as well as aggressive early antimicrobial therapy.

A short course of granulocyte transfusions has been used for persistent infection. Use of recombinant IFNy reduces the frequency of infections in CGD by stimulating the function of phagocytes. There is a risk of serious blood tranfusion reactions in patients with CGD who lack Kell associated red cell antigens. Therefore, a patient with CGD should be tested for the presence of Kell antigen before blood transfusion. Bone marrow transplantation has also been used in these patients. In vitro correction of gene defect has also been tried in B cells of these patients. Similar experiments in vivo are in progress.

Conclusion:

Chronic granulomatous disease is a life-threatening genetic immunodeficiency, which is diagnosed in the majority of patients between one and three years of age when they become clinically symptomatic. CGD must be considered in the differential diagnosis of children who present with recurrent bacterial and/or fungal infections. The diagnosis can be confirmed by a simple and inexpensive laboratory test and prophylactic long term cotrimoxazole has dramatically improved the long-term prognosis. Bone marrow transplantation remains the mainstay of treatment.

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DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	**BABY OF NAVYA**	Order ID/Sample ID:	**808689/8257160**
Gender:	Male	Sample Type:	Blood
Date of Birth / Age:	4 months	Date of Sample Collection:	9th December 2023
Referring Clinician:	Dr. Aparna C, Kim's Hospital Kondapur, Hyderabad	Date of Sample Receipt:	12th December 2023
		Date of Order Booking:	12th December 2023
		Date of Report:	8th January 2024
Test Requested:	**Clinical Exome**		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Baby of Navya, born of a non-consanguineous marriage, presented with clinical indications of pyrexia of unknown origin, anemia, hepatomegaly and hepatosplenomegaly. He is suspected to be affected with chronic granulomatous disease or leukocyte adhesion deficiency or familial mediterranean fever and has been evaluated for pathogenic variations.

RESULTS

LIKELY PATHOGENIC COPY NUMBER VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

No significant SNV(s)/INDELS for the given clinical indications that warrants to be reported were detected.

COPY NUMBER VARIANTS CNV(s)

Variant	Zygosity	Size (KB)	Disease (OMIM)	Inheritance	Classification[5]
chrX:g.(?_37685962)_(37810917_?)del	Hemizygous	124.96	Chronic granulomatous disease (OMIM#306400)	X-linked	Likely Pathogenic

The specificity of NGS based assays to detect large deletion is low and an alternate method of testing like MLPA/Microarray/PCR is recommended to confirm the same. However, we recommend discussing alternative testing methodology option with MedGenome Tech Support before proceeding with confirmatory testing.

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A CHALLENGING CASE OF POST VARICELLA VASCULOPATHY PRESENTING AS STATUS DYSTONICUS – COMPREHENSIVE REVIEW

Introduction:

Varicella zoster virus (VZV) is a neurotropic exclusively human herpesvirus.

Primary infection causes varicella (chickenpox), after which virus become latent in ganglionic neurons along the entire neuraxis.

One of the most serious complications of zoster is VZV vasculopathy.

The clinical spectrum of VZV vasculopathy may include intracerebral VZV vasculopathy, giant cell arteritis, and granulomatous aortitis.

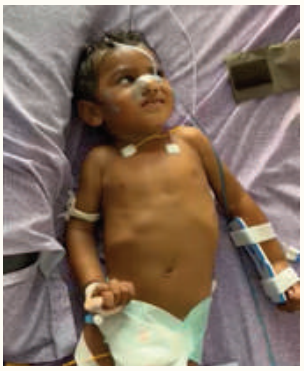
Case Details:

A 2 year old child presented with history of fever with hyper pigmented lesions all over the body and history of seizures (GTCS type) for 4 days. Child was apparently asymptomatic before with normal development and was able to perform all normal activities.Child was not immunised and BCG scar was absent on examination.

At presentation child was in altered sensorium, healed exanthematous rash was seen and dystonic movements were present associated with autonomic dysfunction. Possibilities considered were dengue encephalitis, Tuberculosis meningitis, viral meningoencephalitis and autoimmune vasculitis Child was initially started on IV Antibiotic, IV Acyclovir, Anti epileptic drug and on full maintenance fluids. In view of altered sensorium child was started on hyperosmolar therapy with hypertonic saline to decrease cerebral edema. Injection methylprednisolone was started in view of suspected autoimmune vasculitis.

Physical examination revealed altered sensorium with GCS 7/15, tachycardia, hypertension, hypertonia with exaggerated deep tendon reflexes, autonomic instability and dystonia. Cranial nerve examination was normal.

On day 3 of admission, child's sensorium improved and was alert but irritable with spastic generalised contraction for more than 2 hours associated with severe sweating, tachycardia and hypertension. Child was unresponsive to injection midazolam and was started on tablet Gabapentin and tablet clonidine for dystonia. Child had persistent dystonic movements and was started on tablet clonazepam following which child responded well to the treatment and was continued on these medications. Nasogastric feeds were started gradually and hiked as per protocol. During the hospital stay oral feeds were established and general condition of the child improved.



At admission

On follow up

Investigations:

Child had healed rash at presentation, workup for fever with rash done - to rule out dengue encephalitis, cerebral malaria and varicella encephalopathy.

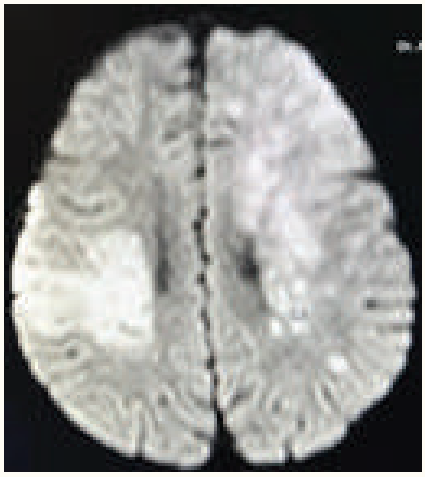
ESR and CRP was elevated. CBP was within normal limits. Dengue serology was negative, smear for Malarial parasite was negative. Workup done to rule out other causes of infectious CNS Vasculitis like tuberculosis was negative.

CSF Analysis was done which showed normal biochemical analysis, no cells or organisms and CSF culture showed no growth.

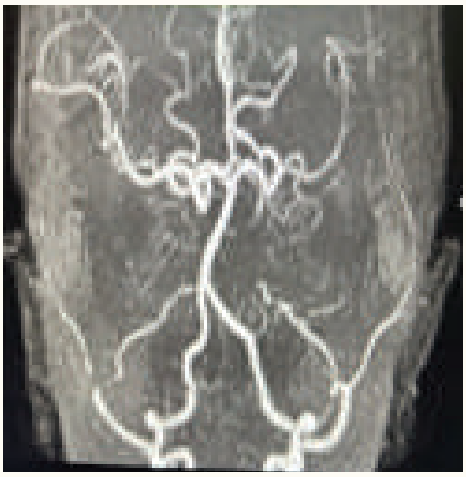
Varicella Zoster Antibodies was positive, CSF Varicella PCR was done which was negative.

MRI BRAIN done to localise the lesions showed Extensive areas of T2/FLAIR hyper-intensities T1 hypo-intensities with areas of restricted diffusion on DWI noted in right insular cortex right thalamus posterior limb of right internal capsule-left corna radiata and bilateral frontoparietal regions. On contrast there is significant enhancement in right side and patchy enhancement on left side. Possibilities include subacute infarcts (more likely) / infective etiology (less likely).

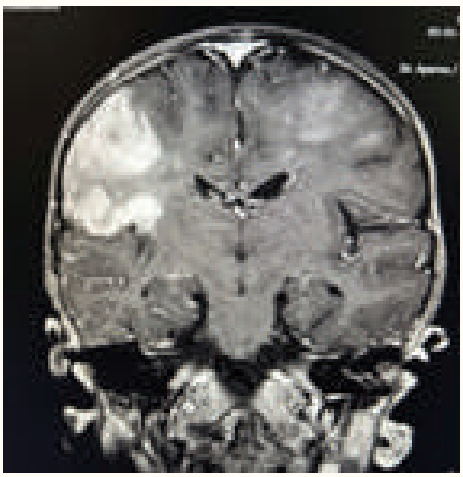
Non visualisation of both internal carotid arteries noted however reformation of bilateral MCAs and ACAs - likely complete occlusion/thrombosis.



Hyper-intensities in right insular cortex, thalamus, posterior limb of right internal capsule and bilateral frontoparietal regions



Non visualisation of both internal carotid arteries



Contrast enhanced MRI showing significant enhancement on right side

Discussion:
The onset of stroke or TIAs in children with varicella in recent months should alert the clinician to the possibility of VZV vasculopathy.

Most VZV vasculopathies develop within 6 weeks after zoster, the median interval for stroke is 4 months after varicella (1).

Predominant pathophysiology of varicella-associated stroke is likely VZV vasculopathy.

Post varicella Arteriopathy usually occurs in otherwise healthy, immunocompetent children and is usually monophasic, although progressive arteriopathy with recurrent TIA and stroke has been reported (1, 2).

A laboratory diagnosis of VZV vasculopathy is made by demonstrating either the intrathecal production of anti-VZV antibodies or the presence of VZV DNA in cerebrospinal fluid (CSF) using a quantitative polymerase chain reaction assay (PCR).

Only negative results in both anti-VZV IgG antibody testing and VZV PCR in the CSF would exclude the diagnosis of VZV vasculopathy (4).

Radiologically, PVA and VZV vasculopathy in childhood resemble the VZV vasculopathy described in immunocompromised patients and older adults, with large-vessel arteriopathy involving the anterior circulation reported most often in virologically-confirmed VZV vasculopathy in childhood (3).

Conclusion:
VZV vasculopathy should also be considered in patients with a stroke of unknown origin.

A laboratory diagnosis of VZV vasculopathy is made by demonstrating either the intrathecal production of anti-VZV antibodies or the presence of VZV DNA in cerebrospinal fluid (CSF) using a quantitative polymerase chain reaction assay (PCR).

Only negative results in both anti-VZV IgG antibody testing and VZV PCR in the CSF would exclude the diagnosis of VZV vasculopathy.

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A CASE OF NON-COMMUNICATING HYDROCEPHALUS WITH PSEUDOMONAS SUTZERI VENTRICULITIS

Introduction:

Ventriculitis is the inflammation of the ependymal lining of the cerebral ventricles, usually secondary to infection. It has other names, such as ependymitis, ventricular empyema, pyocephalus, and pyogenic ventriculitis [1]. It is an indolent but lethal infection and a source of persistent infection following meningitis treatment. Early diagnosis is essential for appropriate treatment. It is of particular concern in patients with external ventricular drains (EVDs) or intraventricular shunts.

Case Details:

A 3 months old boy born at 37 weeks of gestational age via LSCS with large head at birth - head circumference at birth was 40 cm which more than 97th centile. Antenatal scan done at 27 weeks of gestation age was suggestive of enlarged lateral ventricles about 13 mm each side with dilated 3rd ventricles.

MRI brain done on day 3 of life was suggestive of dilated lateral ventricles seen bilaterally with frontal right horns of 22 mm, left horn was 20 mm & IIIrd ventricle size of 12 mm with normal caliber 4th ventricle suggestive of obstructive hydrocephalus. Right ventriculoperitoneal shunt which was placed at 10 days of age at private hospital at Gulberga, Karnataka.

Baby presented to us at 3 months of age with a history of fever associated with vomiting for 5 days prior to admission. On examination the baby was irritable, had hypertension, sun-setting sign and refusal to feed. Head circumference of 44 cm which is more than 97th centile (Fig. 1).

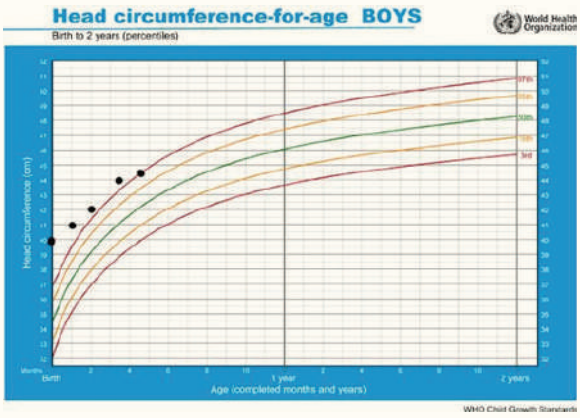

Figure. 1: Head circumference trend of the child

Baby was started on antibiotics Injection Meropenem and Injection Vancomycin. Ventricular tap done showed increased proteins of 1332 mg/dl, low glucose of less than 11 mg/dl, cell count of 380 cells with 70% polymorphs and 30% lymphocytes with cultures showed growth of carbapenem resistant Pseudomonas Sutzeri. Injection Colistimethate Sodium was added as per sensitivity pattern. Right ventriculoperitoneal shunt was removed and the Ommaya reservoir was placed. Daily ventricular tap was done via Ommaya reservoir and 15 to 20 ml CSF was drawn till anterior fontanelle depressed. CSF was analyzed 2-3 times a week to check for improvement in ventriculitis (Table 1).

Table 1: Serial CSF analysis

Day of admission	1	3	7	9	14
Protein	1332	435	444	391	282
Glucose	< 11	< 11	< 11	< 11	< 11
(mg/dL)					
Total Cell (cells/cumm)	380	75	72	70	160
Differential count	P70, L11	P80, L20	P75, L25	P70, L30	P80, L20

On 14 of admission CSF cultures still showed growth of Pseudomonas Sutzeri hence in view persistent CSF culture growth of Pseudomonas Sutzeri intraventricular Colistimethate Sodium was given via Ommaya reservoir. CSF was analyzed 2-3 times a week, there was gradual decrease in level of proteins and CSF culture was sterile 2 times which were sent after 7 days and 10 days of intra ventricular Colistimethate Sodium.

Table 2: Serial CSF analysis

Day of admission	18	21	21	23	25	27	29	30	31
Protein (mg/dL)	308	277	277	257	226	186	166	156	149
Glucose (mg/dL)	19	25	25	22	21	19	20	20	25
Total Cells (cells/cumm)	60	25	25	22	24	20	13	10	10
Differential count	P60, L40	P40 L60	P40 L60	L100	P10 L90	L100	P40 L60	P10 L90	L100

MRI Brain done on day 27 of admission showed communicating hydrocephalus noted of maximum diameter at septum pellucidum measuring 47 mm (Fig. 2, 3 and 4). Prominent posterior fossa with enlarged retrocerebellar space with communication with foramen of Magendie with thin septations within. Tenting of left superior cerebellum mega cisterna magna.

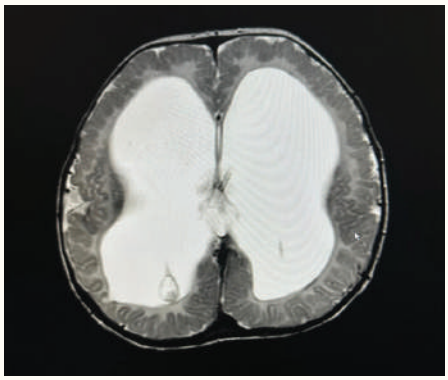

Figure 2: T2 axial image showing dilated bilateral ventricle

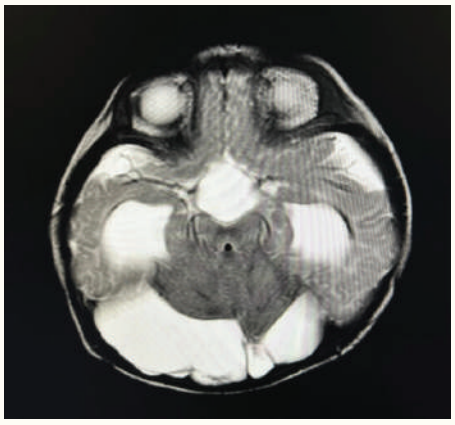

Figure 3: T2 axial image showing dilated third ventricle, temporal horns of bilateral third ventricle.

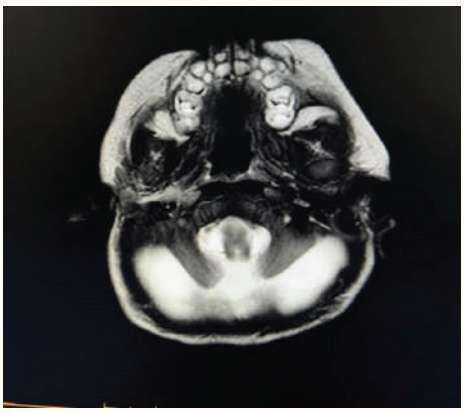

Figure 4: T2 axial image showing prominent posterior fossa with enlarged retrocerebellar space with communication with foramen of magendie

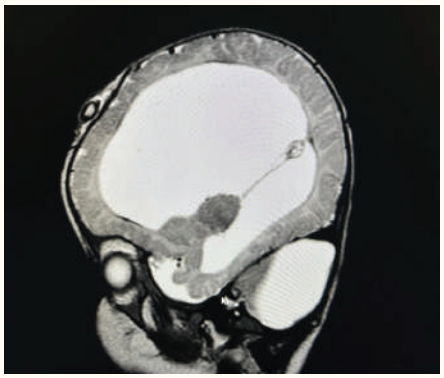

Figure 5: T2 sagittal image showing dilated bilateral lateral ventricles and prominent posterior fossa

With resolution in ventriculitis, a Programmable antibiotic coated ventriculoperitoneal shunt was placed on the left side. After 4 days the baby was discharged in stable condition.

Discussion:

Incidence of Ventricular catheter related ventriculitis is up to 45% [2]. In our case Pseudomonas Sutzeri growth seen in CSF cultures and intervenors Injection Colistimethate Sodium was added according to sensitivity pattern. After 14 days of intravenous Injection Colistimethate Sodium CSF cultures showed growth of Pseudomonas Sutzeri. Colistimethate Sodium penetration to the CSF is 15%-25% according to various studies in patients with meningeal inflammation. [3,4]. But it's very low (~5%), in patients without intense meningeal inflammation. Hence concomitant intrathecal administration of colistin seems warranted for the treatment of CNS infections from gram-negative bacilli. [5]

Conclusion:

In our case ventriculitis was resolved after giving both intravenous and intraventricular Colistimethate Sodium. The index child has been coming for follow ups with head circumference remianing stable at 50th - 97th centile at follow up with normal muscle tone and sensorium.

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AN UNUSUAL CASE OF NEONATAL CHOLESTASIS.

Introduction:

Neonatal cholestasis is a common neonatal liver disease which results in diminished bile flow and excretion, and is defined serologically as prolonged conjugated hyperbilirubinemia in neonates 1, 2.

A defect of the intrahepatic production or the transmembrane transport of bile, or a mechanical obstruction preventing bile flow leads to an accumulation of bile components in the liver, in the blood and extrahepatic tissues. The incidence of NC is ~1 in 2500 live births 31, of the various conditions that can present with NC, biliary atresia (BA) represents the major cause and has been reported to occur in 35-41% of the cases followed by progressive familial intrahepatic cholestasis (PFIC) (10%), preterm birth (10%), metabolic and endocrinological disorders (9-17%), Alagille syndrome (AS) (2-6%), infectious diseases (1-9%), mitochondriopathy (2%), biliary sludge (2%), and, finally, idiopathic cases (13-30%) (4,5).

Congenital diseases such as paucity of intrahepatic bile ducts (PIBD) can cause neonatal cholestasis 6,7). PIBD is a pathologic diagnosis defined as loss of intrahepatic bile ducts in more than 50% of portal tracts in a specimen that contains at least 10 portal tracts. Thus, diagnosis of PIBD needs a pathologic examination on a liver biopsy 8-10).

Case Details:

Full term, male baby, IUGR with birth weight of 1800 grams delivered by LSCS presented to hospital at one month of life, with complaints of persistent jaundice and clay coloured stools. On admission total bilirubin was 5.03 mg/dl (normal range 0.3 - 1.2 mg/di) with a direct bilirubin of 3.04mg/di (normal < 0.2 mg/di), SGPT/ALT 78 u/(normal range 13 - 45 U/L), SGOT/AST 117 U/L (normal 15 - 60 U/L), alkaline phosphatase 393 U/L (normal range 82 - 383 U/L). His serum gamma-glutamyl transferase was 145 U/L (normal 12-122 U/L). The patient was originally treated with phototherapy which did not result in improvement and on admission he was treated with phenobarbital, again with no improvement.

Patient metabolic workup (Ammonia, Lactate, TMS, Urine GCMS, TORCH profile) was sent, which were normal. The initial working diagnosis was biliary atresia and the patient underwent hepatobiliary scintigraphy which demonstrated good tracer clearance into the intestines - negative for biliary atresia. In abdominal sonography, liver is normal in size (6.4cm), shape and echotexture. No evidence of any focal solid or cystic lesions. No evidence of any intrahepatic biliary dilatation. Gallbladder is partially distended measuring 22x5mm, normally contracted in post prandial measures 22x2mm and is of normal size, shape and echo texture. As triangular cord thickness is not more than 4mm, gall bladderlength is not less than 15mm, no subcapsular flow on color doppler ultrasound, Biliary Atresia is ruled out.

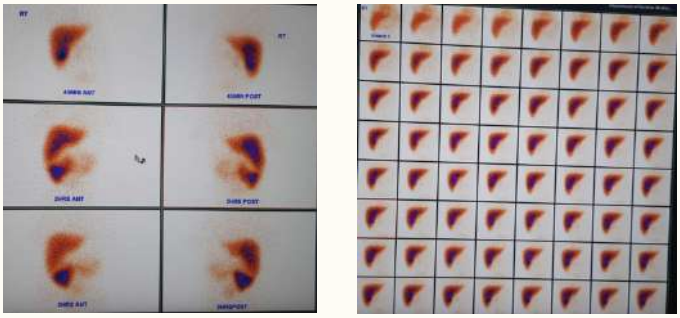


Figure 1: 4 week old male with non-syndromic paucity of intrahepatic bile ducts. Hepatobiliary scintigraphy obtained following intravenous administration of 1mCi Tc 99m-HIDA. Sequential dynamic images of the abdomen were acquired at 15sec per frame for 40min. Static images were acquired at 45, 120min and 24hours.

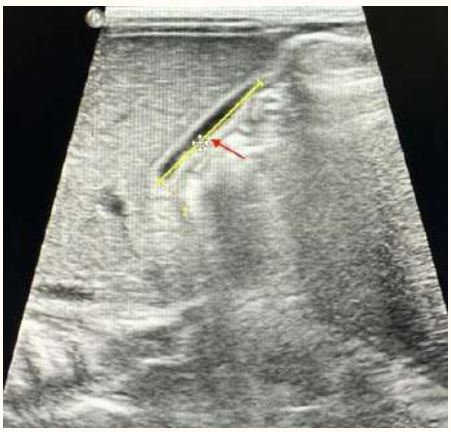
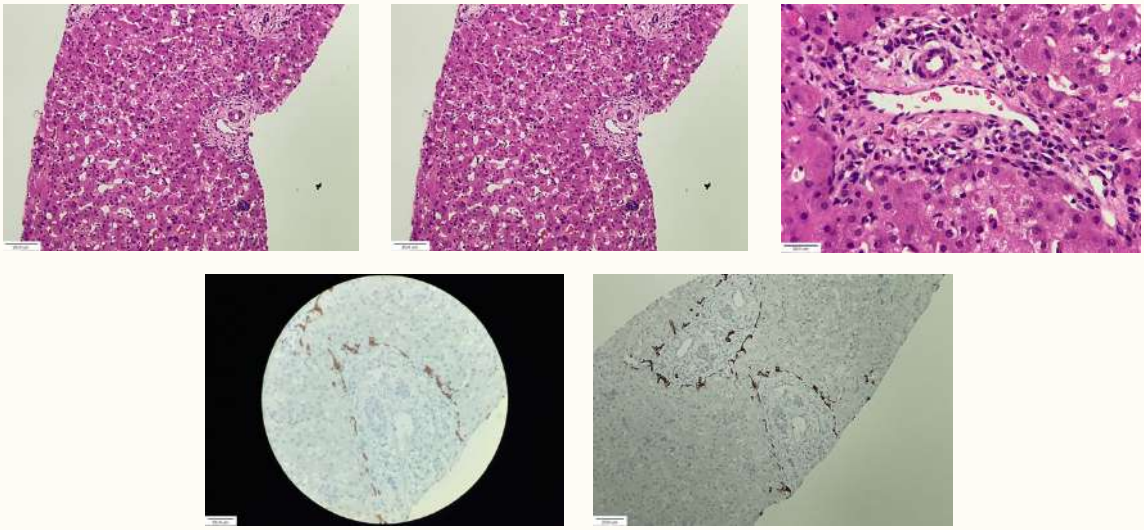


Figure 2: 4 - week old male with non - syndromic paucity of intrahepatic bile ducts. Sonogram of right upper quadrant of abdomen demonstrates normal appearance of the liver, gallbladder is normally contracted measures 22 x 2mm and is of normal size, shape and echotexture.

Patient underwent liver biopsy. Liver biopsy core show 13 portal tracts. Porto central relationship is well maintained throughout the biopsy. Portal areas show absence of portal tracts in 11/13 portal tracts. Portal venous radicles are of normal in calibre. No evidence of bilirubin stasis. Lobular parenchyma shows occasional focus of lobular hyalinization and giant cell transformation. Foci of extramedullary hematopoiesis noted. Foci of hepato canalicular cholestasis noted (zone 3 accentuation) No viral cytopathic changes seen. No evidence of storage cells. Further IHC with CK7 identifies paucity of bile ducts in majority of portal tracts and also identifies neo ductular proliferation in the periphery of portal tracts.



Other work up like Thyroid levels, Urine for Reducing substances, TORCH profile were done, which were normal. The patient underwent 2D ECHO, revelaed no cardiac abnormalities.

Ophthalmologic examination was normal and no osseous abnormalities were seen on skeletal radiography. The diagnosis of non-syndromic paucity of intrapatic bile ducts was made. The patient is being followed and his latest LFT (Liver Function Test) showed total bilirubin 1.55mg/dl with direct bilirubin of 0.83mg/dl. Plan for whole exomic sequencing is made on follow up.

Post natal age	4 weeks	5 weeks	6 weeks
Total Bilirubin	5.03 mg/dl	3.85 mg/di	1.55 mg/dl
Direct Bilirubin	3.04 mg/dl	2.21 mg/di	0.83 mg/di
Indirect Bilirubin	1.99 mg/dl	1.64 mg/di	0.72 mg/di

Discussion:

Alagille syndrome (AGS) is characterized by the paucity of interlobular biliary ducts and affects approximately one in 100,000 live births. The vast majority of patients present before six months of age with jaundice and failure to thrive or cardiovascular symptoms. Morbidity and mortality are linked to the severity of liver and/or cardiac involvement (11,12), Currently no cure exists for AGS, and medical management is directed at treating disease in each affected organ system (131, AGS is an autosomal dominant disease, with highly variable expression. Mutations in the JAG-1 gene on chromosome 20p12 are responsible for more than 90 percent of cases; others have mutations in NOTCH-2|14).

Both syndromic and nonsyndromic forms of AGS have been differentiated from other causes of intrahepatic cholestasis in infancy. A liver biopsy often depicts bile duct paucity; however, this finding alone is not specific for AGS 15), in the nonsyndromic form, the bile duct pathology is identical; however, there are no extrahepatic findings and currently there is no clinical, biochemical, radiological, or histological test specific for AGS and diagnosis is based solely on the clinical phenotype 18).

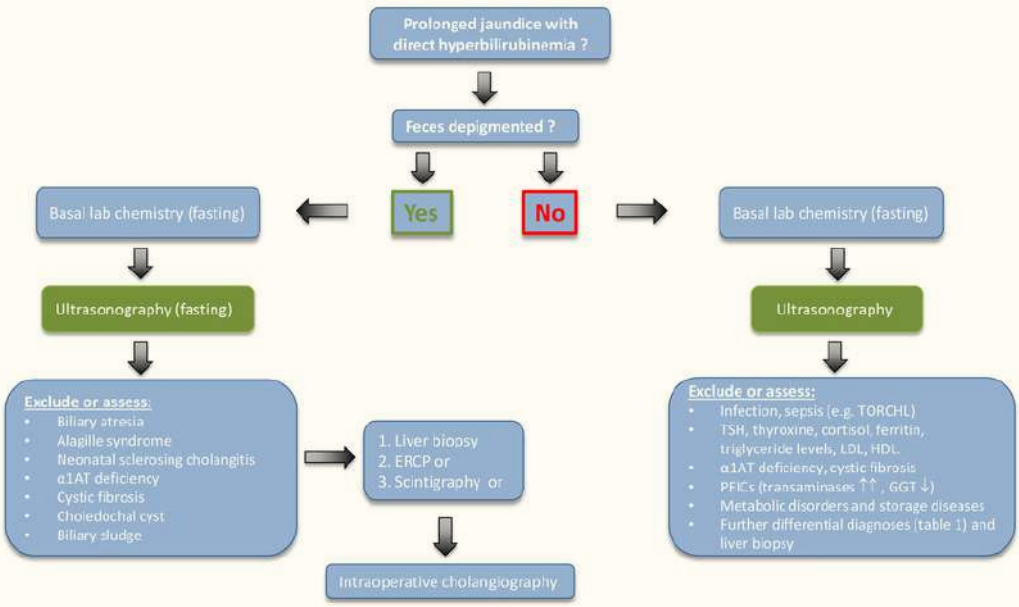
In the syndromic form of AGS, congenital heart disease has been reported in up to 90% of cases. The most common heart abnormalities involve the pulmonary valve, pulmonary artery, and its branches with the most common finding being peripheral pulmonary stenosis 191. Ophthalmological findings include defects of the anterior chamber (posterior embryotoxon, Axenfeld's anomaly, or Rieger anomaly), and retinal pigmentary changes 20. In addition, evaluation of the biliary anatomy using diagnostic modalities including hepatobiliary nuclear scintigraphy, magnetic resonance cholangiopancreatography (MRCP), or endoscopic retrograde cholangiopancreatography (ERCP) can aid in a proper diagnosis.

Patency of the extrahepatic biliary tree can be assessed by cholescintigraphy and patients with AGS will often show delayed visualization of the gastrointestinal tract 211. MRCP fails to demonstrate the absence of bile ducts because these are barely visible in normal subjects.

However, MR sequences without and with gadolinium injection show clear structural abnormalities of the liver, with a combination of tumor-like nodules centered on a hypertrophic portal vessel and areas of major atrophy generating a bright signal on T1 images 161. In the case of AGS, ERCP will display marked diffuse narrowing of the extrahepatic biliary ducts and uniform narrowing of the intrahepatic ducts with reduced arborization (22).

In addition, ultrasonography (US) can display evidence of portal hypertension and can help to establish indications for hepatic transplantation (181, Although these findings alone are not specific for AGS, in a cholestatic child, they help in establishing a diagnosis of AGS (18), Therefore, diagnostic testing is important to exclude other causes of neonatal cholestasis and to evaluate for associated malformations.

Diagnostic algorithm for neonatal cholestasis



Basal lab chemistry for neonatal cholestasis:
Blood cell count with reticulocytes, total and fractionated bilirubin, coagulation parameters (incl. INR, ATIII), hemolysis parameters, liver transaminases incl. GGT, plasma bile acids, lipase, glucose, lactate, ammonium, CrP.

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A CHALLENGING CASE OF PERSISTENT PULMONARY HYPERTENSION WITH COARCTATION OF THE AORTA & PATENT DUCTUS VENOSUS

Introduction:

Persistent pulmonary hypertension (PPHN) of the newborn occurs when pulmonary vascular resistance remains abnormally elevated after birth, resulting in right-to-left shunting of blood. The prevalence of PPHN has been estimated at approximately 2 cases per 1000 live births. [1]. Coarctation of the aorta is a narrowing of the descending aorta. This defect generally results in left ventricular pressure overload. CoA accounts for 4 to 6 percent of all congenital heart defects with a reported prevalence of approximately 4 per 10,000 live births [2]. Ductus venosus is a connection between portal vein and inferior vena cava that closes functionally in first minutes after birth and true obliteration is completed in 15-20 days. Failure of closure of ductus venosus results in diversion of portal blood into the systemic circulation and is a type of congenital portosystemic shunt.[3]

Case Details:

An early term (37 weeks), twin 2, male baby, IUGR with birth weight of 2000 grams delivered by LSCS with perinatal asphyxia requiring intubation developed severe hypoxia. Baby was transferred to our NICU with saturation of 65% on Mechanical Ventilator - SIMV mode with settings of PIP- 22/PEEP- 6/Rate-40/ FiO2-100%, hence we started on High Frequency Oscillation mode of ventilation after administering surfactant. Oxygenation index at 6 hours of life was 26 on HFOV with settings of MAP - 14/ Delta P-28/ frequency-10/ FiO2 - 100% and hence we started inhaled nitric oxide. Sildenafil, levosimendan and bosentan were added subsequently.

Baby had poor perfusion with hypotension hence we started on inotropes, requiring highest inotropic requirement at 48 hours of life with inj. Dobutamine 10 mcg/kg/min, Inj. noradrenaline- 0.5 mcg /kg /min, Adrenaline 0.5 mcg/ kg/ min, vasopressin 0.0005 IU/ kg/ min, which were gradually tapered and stopped by day 5 of life.

Echocardiography revealed dilated right atrium and right ventricle with right and left ventricular hypertrophy with large PDA of 8 mm with bi-directional flow with coarctation substrate.

Baby had Maximum OI of 47.4 and inhaled nitric oxide was increased to 40 ppm at 48 hours of life. As OI was in declining trend, baby was weaned to Volume target ventilation with SIMV on day 3 of life, inhaled nitric oxide was tapered and stopped by day 8 of life. Oral Sildenafil was continued.

Baby had hepatomegaly, direct hyperbilirubinemia at 24 hours of life with total bilirubin of 6.41 mg/dl, direct component 2.37 mg/dl. On work up elevated liver enzymes were seen (SGPT 93 U/l, SGOT 874 U/L, Alkaline phosphatase 214 U/L), TORCH profile was normal, ultrasonography of abdomen revealed hepatomegaly. We have started cholestatic regimen in view of direct hyperbilirubinemia. Direct hyperbilirubinemia was gradually increasing with highest being on day 13 of life with total bilirubin of 35 mg/dl, direct component 15.85 mg/dl.

In view of persistent requirement of ventilatory support, CT angiography was done on day 12 of life which showed hypoplasia of distal aortic arch with large PDA associated with persistent ductus venosus with hepatomegaly and cardiomegaly.

Baby underwent ductus venosus device closure on day 13 of life and PDA ligation with coarctation repair on day 17 of life. Echocardiographic done postoperatively on day 18 of life, showed no residual coarctation of the aorta / PDA, mild PAH, dilated right atrium and right ventricle.

Following this we could extubate and started on NIMV by day 18 of life, weaned to Bubble CPAP by day 20 of life, to HFNC day 22 of life and to room air on day 24 of life. Direct hyperbilirubinemia was in decreasing trends.
Baby was discharged on day 27 of life in stable condition.

DAY OF LIFE	1 Days	3 Days	4 Days	13 Days	15 Days POD 3	19 Days POD 7	22 Days POD 10	29 Days POD 17	60 Days POD 48
Total Bilirubin	6.41	16.86	13.47	35	29.81	18.68	19.21	11.7	2.48
Direct Bilirubin	2.37	8.56	7.98	15.58	16.42	12.10	11.83	5.86	1.16
Indirect Bilirubin	4.04	8.3	5.49	19.42	13.39	6.58	7.38	5.84	1.32

Discussion:

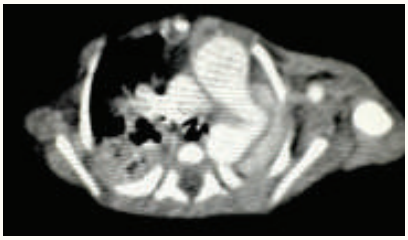
PPHN is suspected when there is difference in preductal and post ductal saturations, but confirmatory test is echocardiography showing increased right ventricular pressure measured through tricuspid regurgitation. In case of severe PPHN we may demonstrate right to left shunting through PDA and or foramen ovale. Coarctation of the aorta can be suspected when there is difference in blood pressures in lower limbs versus upper limbs. Echocardiographic features of coarctation of the aorta in parasternal short axis view shows hypoplastic aorta and PDA showing right to left shunt.

In our case large PDA was shunting just distal to coarctation of the aorta masking the severity of coarctation of the aorta mimicking severe PPHN with PDA showing right to left shunt. PPHN and severe coarctation of the aorta share the same picture of a large PDA with right-to-left shunt, they should differentiated. In our case we performed CT angiography which showed hypoplastic aorta and large PDA. Surgical ligation of PDA and coarctation of the aorta repair helped baby to wean off from oxygen support.

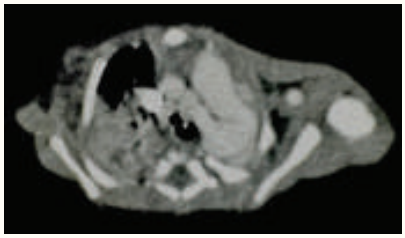
Common causes of Direct Hyperbilirubinemia are biliary atresia, hepatitis and rarely like in our case may due to congestive cardiac failure and patent ductus venosus. Direct hyperbilirubinemia reduced in our case post ductus venous closure.

Conclusion:

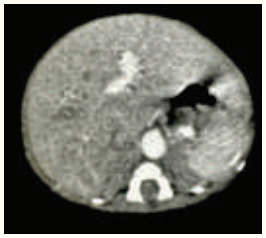
Though PPHN and severe coarctation of the aorta share the same picture of a large PDA with right-to-left shunt, these two diseases have to be differentiated using modalities like CT angiography followed by appropriate management. We should keep patent ductus venosus in mind as a rare cause of direct hyperbilirubinemia in neonates and infants. Early detection of the shunt and proper management leads to a good prognosis and prevention of serious complications.



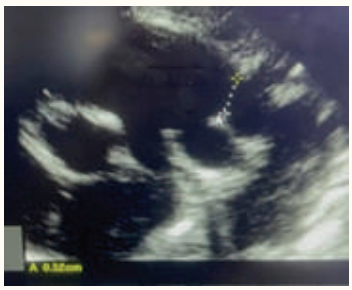
CT Angiogram: Hypoplasia of distal aortic arch



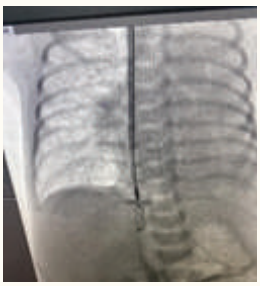
CT Angiogram: large PDA



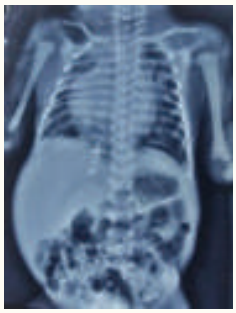
CT Angiogram: Shunt between IVC and portal vein



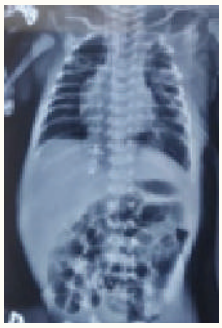
Echo: Parasternal short axis view showing 5 mm PDA



Ductus venosus device closure



Post device closure X ray showing Cardiomegaly



Post CoA repair X ray showing decreased Cardiomegaly

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