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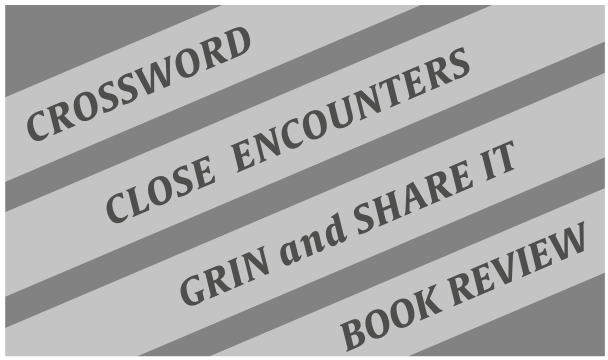

HIGHLIGHTS OF THIS ISSUE

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Indian Pediatrics Case Reports

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Contents

Contents (contd.)

It's Raining Stories - Hallelujah

This is the third issue of Indian Pediatrics Case Reports, and I am proud to announce that we have started getting many more high-quality submissions now. Given that we are in the middle of the monsoons, and is it raining cats and dogs outside, I cannot think of a better title than the one that has been given. It is in continuation with the themes of the previous editorials, and based on a popular Geri Halliwell song!

Let me share some observations that I have made with respect to the content of this issue that I believe are in alignment with what we had envisioned for our journal.

1. *Story background*: Out of the 12 selected case reports, 8 (75%) are from the private setup. This includes medical colleges, multi-specialty hospitals, smaller hospitals, and centers. Four (25%) are from Government medical colleges. This means we have caught the interest of private practitioners and they have started sharing their stories with us. We would also welcome contributions from practitioners working in smaller settings. You may not realize it, but you have a wealth of clinical material that can benefit our readers.

2. *Range of stories*: We have cases covering a myriad of dimensions: general pediatrics, infectious diseases, pediatric sub-specialties, fetal medicine, neonatology, orthopedics, and pediatric surgery.

3. *Crux of the stories*: The case reports published in this issue include: (i) Uncommon presentations of common disorders: sternal tuberculosis, acute pancreatitis in coronavirus infection, manifestations of bereavement, childhood apraxia of speech in autism, aplastic anemia in systemic lupus erythematosus (SLE), recurrent infections in SLE, neonatal Scrub typhus, and a right ventricular abscess following traumatic osteomyelitis; (ii) Common masquerades of uncommon conditions: desaturation during feeding due to 20p duplication syndrome, fatty liver due to cholesteryl ester storage disease, acute gastroenteritis due to cecal duplication; and (iii) Rare disorder: Neonatal Marfan's syndrome. I can appreciate additional facets: 91.6% were national and 8.4% international; 75% involved multi-disciplinary collaboration; and the establishment of diagnosis was made by genetic testing in 25%

People tend to think that a case report has to be something extremely rare. Only one of the cases is an extremely rare condition. We look for uniqueness and novelty certainly, but it can revolve around any dimension of a clinical condition; expanding the clinical phenotype, establishing the diagnosis, or using some novel or innovative line of management that has been adapted to the challenges of the circumstances in which we work in.

4. *Promoting budding writers*: The stories have been written by authors at different levels of competency in terms of writing scientific literature that may not necessarily reflect their years of experience in pediatrics. That is the magic of adult learning. You can embark upon the intoxicating adventure of writing whether you are in the spring, summer, autumn, or winter of your career. We at IPCares are here to guide you on your journey, provided the storyline is honest and riveting.

I really look forward to receiving feedback from our readers. We are yet to inaugurate the section "Letter to the Editor" because we have not received any feedback from our readers related to previously published articles. The same applies to the neonatology quiz and clinical crossword. We are seriously thinking of discontinuing the latter. Hence, this request comes straight from the heart of everyone in our team; please do write to us and tell us what you think about our various sections.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Acute Severe Necrotizing Pancreatitis: A Manifestation of Multisystem Inflammatory Syndrome in Children?

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Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) is commonly being diagnosed among children, 2–8 weeks following a severe acute respiratory syndrome (SARS)-CoV-2 infection. Several cases of pancreatitis have been reported with SARS-CoV-2 infection in adults but only one in a 10-year-old girl with MIS-C. **Clinical Description**: During the coronavirus disease (COVID) pandemic, a 1-year-old girl presented with high-grade fever for 3 days and vomiting and abdominal pain for a day. Her parents had contracted SARS COVID-2 infection 5 weeks earlier. At admission, she was febrile, drowsy, had tachycardia, tachypnea, and hypotension. Salient examination findings included bilateral nonpurulent conjunctivitis, diminished air entry and crepitation's in the left basal zone, distended abdomen with guarding and tenderness in the left hypochondrium and epigastrium. The diagnostic criteria of MIS-C were fulfilled, but not for classical or incomplete Kawasaki disease. Biochemical markers and radiological findings confirmed acute severe necrotizing pancreatitis. No other etiological cause of pancreatitis could be identified. **Management**: Intravenous immunoglobulins were started as per protocol. Steroids were withheld in view of the pancreatitis. The child showed dramatic resolution in fever and rapid improvement in clinical and biochemical parameters. **Conclusion:** Pancreatitis may be a presentation of MIS-C, either due to a direct cytopathic effect or secondary to a hyper-inflammatory response. A high index of suspicion should be kept in children with fever and severe pain abdomen with recent history of COVID-19 infection in the patient or close contacts.

Keywords: Abdominal pain, COVID-19, inflammatory syndrome, pancreas

Acute pancreatitis in infants and young children is usually attributable to viral or idiopathic causes. Coronavirus disease 2019 (COVID-19) has been reported to cause pancreatic injury in 8.5%–17.3% of adults with severe acute respiratory syndrome (SARS) CoV-2 infection.[1] Since the angiotensin-converting enzyme 2 (ACE-2) receptors are high in the pancreas, it is plausible to believe that CoV-2 infection can be a potential cause of acute pancreatitis in children as well. A few case reports from the west have described pancreatic involvement in children with acute COVID infection.[2-4] A single case report of COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) presenting as pancreatitis was found on an extensive scientific literature search.[5] However, whether acute pancreatitis can be considered, a presentation of MIS-C is still uncertain.

We report the case of a young child who presented with an acute febrile illness with prominent gastrointestinal (GI) symptoms and who was diagnosed with MIS-C and acute necrotizing pancreatitis. Management was customized accordingly.

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Clinical Description

A 14-month-old girl child presented to the emergency department of our hospital during the second wave of the COVID pandemic in May 2021. She had a history of high-grade fever for 3 days. During this period, she had become lethargic, and her oral intake had progressively decreased. This was followed by multiple episodes of nonbilious vomiting for 1 day. She had episodes of crying, which her parents perceived to be due to abdominal pain.

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There was no history of loose motions, intake of any meals from external sources, drug intake, yellowish discoloration of the eyes, rashes, or seizures. The frequency of passage of urine was unaffected. There was a significant past history of her parents having developed fever with upper respiratory symptoms 5 weeks earlier and testing positive for SARS CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) test. Around the same time, the child had also developed fever and loose stools for 2 days for which she was symptomatically treated and recovered. The child was developmentally normal and immunized for age.

At admission, the patient was febrile (38.5 C), had tachycardia (heart rate160/min), tachypnea (respiratory rate45/min) with hypotension (blood pressure 60/40 mmHg, <5th centile for age, sex, and height), SpO^2 of 96% in room air. Her weight and length were 9.8 kg and 78 cm, respectively (between 50th and 75th centile). General physical examination revealed some pallor and bilateral nonpurulent conjunctivitis. There was no icterus, clubbing, lymphadenopathy, or rash. The oral cavity was normal. Salient findings on systemic examination included diminished air entry in the left basal zone with crepitations; normal heart sounds with no audible murmur; and a mildly distended abdomen with guarding and tenderness in the left hypochondrium and epigastric region, hepatomegaly (4 cm below the right costal margin in the mid clavicular line with a span was 8.5 cm), and normal bowel sounds. The Glasgow Coma scale was 12/15 (E4, V4, M4). There was no evidence of any cranial nerve involvement, focal neurological deficit, or meningeal irritation. Details of laboratory parameters are depicted in Box 1.

Box 1: Laboratory parameters of the patient at admission

Hemogram: Hb 8.8 g/dl, Total leukocyte count 14.860 × 10^3/uL; 83.9% neutrophils, 10% lymphocytes; Platelets - 388,000/mL
Markers of acute pancreatitis: Lipase - 13,552 U/L, Amylase - 282 U/L
Venous blood gas analysis: pH - 7.383, lactate - 1.78 mmol/L, bicarbonate - 17.8 mmol/L
Kidney function test: Urea - 32 mg/dl, Creatinine - 0.3 mg/dl
Liver function test: Bilirubin total - 2 mg/dl, Bilirubin direct - 0.5 mg/dl; AST - 80 U/L, ALT - 40 U/L, GGT - 292 U/L, Albumin - 3.86 g/dL; random blood sugar - 111 mg/dl
Acute phase reactants: CRP: 23.5 mg/dL (normal <10 mg/dl); Interleukin-6: 30 pg/ml (normal range <6 pg/ml); Ferritin: 128 ng/ml (normal 6.24-137 ng/ml); ESR: 66 mm/h
Markers of inflammation: Procalcitonin: 2.79 ng/mL (normal 0-0.05 ng/ml)
Lactate dehydrogenase - 423 U/L (Normal 120-246 U/L)
Evidence of coagulopathy: PT: 14 s, INR 1.47; D-dimer: 5167 ng/mL (normal 0-500 ng/ml)
Cardiac biomarkers: Troponin I 0.014 ng/ml (normal 0-0.034 ng/ml), CPK - 153 U/L (normal 30-135 U/L); Pro BNP 491pg/ml (normal 0-125 pg/ml)
Evidence of COVID infection: SARS COVID antibody IgG 99.1 AU/ml (positive >15 AU/ml); COVID RT PCR negative (twice); stool for COVID RT PCR negative

Hb: Hemoglobin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PT: Prothrombin time, CPK: Creatine phosphokinase, RT PCR: Reverse transcription-polymerase chain reaction, SARS: Severe acute respiratory syndrome, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-Glutamyl transferase

In the setting of a COVID pandemic, the onset of an acute febrile illness associated with GI symptoms (pain abdomen and vomiting), history of past COVID like illness and positive contact with COVID-infected individuals, nonpurulent conjunctivitis, hypotension, and a tender abdomen was highly suggestive of the possibility of MIS-C. Other differentials that were considered were dengue shock syndrome, scrub typhus, acute pancreatitis, and incomplete Kawasaki disease (KD). Investigations were planned accordingly.

Management and outcome

The child was managed with intravenous fluid as per standard protocol. She was evaluated by rapid COVID RT-PCR test which was negative, after which she was shifted to the intensive care unit. Box 1 lists the reports of the preliminary laboratory investigations. Blood cultures were sterile. NS1 and viral serology were negative for Dengue. Confirmatory tests for malaria and scrub typhus were negative. An abdominal ultrasound revealed an acute edematous pancreatitis with early necrosis in the anterior body of the pancreas with peripancreatic fluid collection, moderate ascites, and bilateral pleural effusion. A computerized tomography (CT) scan confirmed acute necrotizing pancreatitis, peripancreatic inflammation, and an enlarged pancreas showing intraparenchymal necrosis (up to 40%) with a modified CT severity index of up to 10 [Figure 1]. Mild bilateral pleural effusion with underlying areas of atelectasis and patchy consolidation of the left lung base were noted. The viral serology panel for the common causes of acute pancreatitis (cytomegalovirus, coxsackievirus, adenovirus, measles, and rubella) was negative. It was important to rule out KD, especially due to the presence of bilateral nonpurulent conjunctivitis. The echocardiogram demonstrated normal heart chambers, valves, biventricular function, coronaries, and related indices. There was no pericardial effusion. Since the clinical and

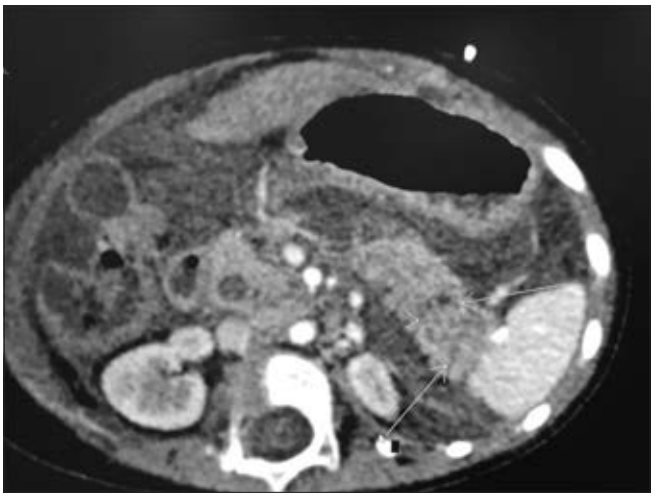

Figure 1: Axial contrast abdomen depicting intrapancreatic necrosis in body and tail region (yellow arrowhead)

Table 1: Satisfaction of the World Health Organization criteria of multisystem inflammatory syndrome in children-C in the patient

WHO parameters	Patient's clinical profile
Children and adolescents 0-19 years of age with fever >3 days AND two of the following	Age: 1 year Fever: 3 days
Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet)	Bilateral nonpurulent conjunctivitis
Hypotension or shock	Hypotension
Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP)	Elevated NT-Pro BNP
Evidence of coagulopathy (PT/aPTT, ↑D-dimers)	Elevated PT, D-Dimer
Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND	Vomiting and abdominal pain
AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin AND	CRP, ESR, procalcitonin elevated
No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes AND	Urine culture, blood culture were sterile dengue profile (NS1, dengue IgM, and IgG), scrub typhus IgM, malaria antigen, typhidot IgM - negative
Evidence of COVID-19 (RT-PCR, antigen test, or serology positive) or likely contact with patients with COVID-19	SARS COVID IgG titer elevated History/of COVID like illness 5 weeks back History/of parents COVID positive 5 weeks back

WHO: World Health Organization, ECHO: Echocardiography, CRP: C-reactive protein, IgM: Immunoglobulin M, IgG: Immunoglobulin G, SARS: Severe acute respiratory syndrome, RT-PCR: Reverse transcription-polymerase chain reaction, COVID-19: Coronavirus disease-2019, ESR: Erythrocyte sedimentation rate, PT: Prothrombin time, NT proBNP: N-terminal pro B type natriuretic peptide, PTT: Partial thromboplastin time

Table 2: American heart association criteria for incomplete Kawasaki disease and our patient profile (criteria not fulfilled)

Incomplete Kawasaki disease	Patient's clinical profile
Fever 5 days and less than 4 classical features of Kawasaki disease OR	Age: 1 year Fever duration: 3 days
Unexplained fever in infants >7 days AND	
CRP 3 mg/dl and/or ESR 40 mm/h AND	CRP and ESR high
ECHO positive OR	
ECHO negative AND	ECHO-normal
At least 3 of the following	
Platelet count 450,000/mm^3	Platelet count 388,000/mm
Anemia for age	Hb-8.8 g %
Albumin 3 g/dl	Albumin 3.86 g/dl
Elevated ALT level	ALT normal 40 U/L
WBC 15,000/mm^3	WBC 148,60/mm^3
Urine 10 WBC/hpf	Urine no WBC/hpf

CRP: C-reactive protein, ECHO: Echocardiography, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, ALT: Alanine aminotransferase, WBC: White blood cell

laboratory profile satisfied the World Health Organization criteria [Table 1],[6] MIS-C with severe pancreatic necrosis was kept as the final diagnosis. The diagnostic criteria for KD and incomplete KD [Table 2] were not fulfilled.

As per standard protocol, intravenous immunoglobulin (IVIG) was given at 2 gm/kg over 48 h. The child became afebrile within 24 h, with improvement in vital parameters and decline in inflammatory markers (C-reactive protein: 9.3 mg/L, ferritin: 70 ng/ml, NT-Pro-BNP66 pg/ml, and lactate dehydrogenase: 371 U/L, lipase: 373 U/L). Clear liquids were started followed by fat-free diet on the 3rd day, which was well tolerated. Prophylactic low molecular weight heparin was started, and aspirin added subsequently in view of thrombocytosis. She was discharged on the 10th day, with no peripancreatic collection or complications. Postillness follow-up remained uneventful with documentation of a normal echocardiography repeated at 2 weeks.

Discussion

Ever since the pandemic began, there has been extensive research on the effect of COVID-19 on various organ systems, with documentation of evolving evidence of their involvement. The expression of ACE-2 receptors is very high in the endocrine part of the pancreas, in comparison to the exocrine pancreas.[7] Pancreatic injury due to the coronavirus has been attributed primarily due to direct invasion and consequent cytopathic effect.[8] However, other mechanisms of pancreatic injury have also been proposed like systemic inflammatory response or ischemia.[9] A few case reports have described acute pancreatitis as the presenting feature of COVID-19 infection in children.[3,4] A recent study of 8159 hospitalized children in New York found a significant difference in the incidence of acute pancreatitis in children with COVID-19 (1.8%), in contrast to those who were not infected (0.14).[3]

It has been postulated that viral particles may remain within the GI tract for a long time after the initial COVID-19 infection. In MIS-C, increased mucosal permeability of the gut allows these SARS–CoV-2 antigens to leak into the bloodstream, triggering a cytokine storm and hyperinflammatory response. This could trigger acute pancreatic injury, similar to that described in KD. It is well established that KD and atypical KD like syndrome is seen quite frequently in children infected with SARS-CoV-2 virus.[9,10]

Our patient had acute severe necrotizing pancreatitis, the diagnosis of which was established based on clinical,

biochemical, and radiological grounds. One may argue that in the setting of a pandemic, most pediatric patients will have SARS CoV-2 immunoglobulin G antibodies, however, our patient also satisfied the diagnostic criteria of MIS-C. Another interesting aspect that was noted was that fever is not the usual presenting symptom of acute pancreatitis. It usually occurs a few days afterward secondary to the inflammatory process. In this case, fever was the initial symptom, and the other common viral causes of acute pancreatitis were negative. We preferred to use IVIG over high-dose steroids due in our case as steroids may aggravate and complicate the severe necrotizing pancreatitis. We believe that this case supports the theory that acute pancreatitis could be a manifestation of MIS-C that may rapidly progress to severe pancreatitis as seen in KD unless appropriate intervention to control the cytokine storm is not initiated in time. Treating pediatricians should keep a high index of suspicion of pancreatitis in children with fever and acute abdomen, especially when associated with a temporal history of COVID infection in the household.

Lessons learnt

- Severe pancreatitis may be a presenting complaint of MIS-C.
- A high index of suspicion for pancreatitis should be kept in children presenting with acute abdominal pain and diagnosed with MIS-C, as IVIG would be preferable over steroids in the management.
- COVID-19-related pancreatitis can be severe with necrosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Right Ventricular Cardiac Abscess Secondary to Traumatic Osteomyelitis: Hematogenous Dissemination from Metaphysis to Myocardium

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Abstract

Background: A cardiac abscess is a suppurative infection involving cardiac tissues as myocardium, endocardium, and valves (native or prosthetic). The abscess could form as a direct extension of a preexisting cardiac focus such as bacterial endocarditis or from a distant septic focus leading to bacteremia. **Clinical Description:** We report an immunocompetent 3-year-old-child with a structurally normal heart presenting in septic shock secondary to right ventricle (RV) myocardial abscess. The abscess developed following hematogenous spread from neglected posttraumatic osteomyelitis of the left ankle and the causative organism was identified as methicillin sensitive *Staphylococcus aureus*. **Management:** Prompt action by a multidisciplinary team helped in reaching the diagnosis, effective management of septic shock, emergency open heart surgical removal of the septic mass, and concomitant lower limb arthrotomy saved the child from a bad outcome. **Conclusion:** This case reiterates the need for aggressive treatment of the open skeletal wound to prevent bacteremia and complications such as myocardial abscess. In a child presenting in septic shock, a quick point-of-care echocardiography is critical in ruling out possible underlying cardiac conditions such as bacterial endocarditis, myocardial abscess, or pericardial effusion. A high index of clinical suspicion is required to make a prompt diagnosis and aggressive medical and surgical intervention for good outcomes.

Keywords: Myocardial abscess, point-of-care echocardiography, posttraumatic osteomyelitis, septic shock

A cardiac abscess is a rare and fatal suppurative infection involving cardiac tissues as myocardium, endocardium, native or prosthetic valve and develops as a sequela of infective endocarditis in repaired or unrepaired congenital and/or acquired heart disease.[1] It was first reported by Cossio *et al.* in an adult in 1933, as a delayed complication of bronchopneumonia.[2] The abscess formation could be a direct extension of preexisting cardiac focus such as bacterial endocarditis or arise from distant septic foci secondary to seeding during bacteremia.[1,3,4] In these cases, myocardial abscesses are usually multiple and small in size and can also involve other organs such as the kidneys, lungs, and brain.[5] Other predisposing factors leading to myocardial abscesses include penetrating chest trauma, cardiac interventions, or acute myocardial infarction which are infrequently seen in children.[5] Less commonly, it is secondary to bacteremia from a distant septic focus.

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We present the case of a 3-year-old child with right ventricular myocardial abscess secondary to traumatic osteomyelitis, whose successful outcome can be attributed to the smooth collaboration between members of a multidisciplinary team (pediatrician, radiologist, cardiologist, and cardiothoracic vascular surgeon).

Clinical Description

A 3-year-old girl sustained trauma to her left ankle. This was treated conservatively with wound cleansing, analgesics, and

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local application of antibiotics. Within 10 days, a festering open wound developed at the same site with purulent bloody discharge [Figure 1] and she was prescribed oral antibiotics (amoxycillin-clauvulanate) and called after 1 week for review. The child was not brought back for 3 weeks. At presentation in the emergency, her parents gave a history of high-grade fever and severe respiratory distress for 3 days and decreased urine output for 2 days. On examination, the child was febrile (103°F), had tachycardia (heart rate 150/min), tachypnea (respiratory rate 50/min) had chest indrawing, feeble peripheral pulses, prolonged capillary filling time (>3 s), and blood pressure of 60/27 mm Hg (below 10th centiles). Her oxygen saturation was 92% in room air.

The child had an infected open wound on the left ankle that was discharging pus [Figure 1]. Salient systemic examination findings included cardiomegaly and a gallop rhythm; lethargy (Modified Glasgow Coma Scale 11), with normal sized and normal reacting pupils and absence of focal neurological signs, and soft tender hepatomegaly (3 cm beneath right subcostal margin in the mid-clavicular line). The arterial blood gas showed metabolic acidosis with respiratory (pH 7.2, pO2 60 mm Hg, pCO_2 28 mmHg**,** base deficit minus 5, and elevated lactate of 5 mmol/L). The child had hyperglycemia (blood sugar 160 mg/dl) and normal serum electrolytes. A diagnosis of septic shock with right-sided congestive heart failure was made, and a possibility of traumatic osteomyelitis was kept.

Management and Outcome

Treatment was initiated as per the standard protocol for septic shock; intravenous fluid, noradrenaline infusion, oxygen, broad-spectrum intravenous antibiotics (Ceftriaxone and Amikacin). Preliminary laboratory investigations showed raised C-reactive protein (116 mg/L), leukocytosis (total leukocyte count 26,400/mm^3 with neutrophilic predominance and toxic granules), and hemoglobin 10.3 g/dl with normal platelet counts (2.3 lakhs/mm^3). The child had mildly deranged liver (SGOT 56 unit/l, SGPT 60 unit/l), and renal function tests (blood urea 62 mg/dl and serum creatinine 1.2 mg/dl). Blood and local wound cultures were sent before starting antibiotics. Chest X-ray showed moderate cardiomegaly with right atrial enlargement. Magnetic resonance imaging of the left leg showed osteolytic changes in left lower tibia [Figure 2]. Clinical and laboratory investigations were in concordance making a final diagnosis of septic shock, multiorgan dysfunction including cardiac involvement secondary to posttraumatic osteomyelitis of lower end of tibia of the left leg.

Point-of-care echocardiography revealed the absence of septal defects, normal cardiac valves, mild pulmonary arterial hypertension with pulmonary artery systolic pressure of 35 mm Hg and small pericardial effusion (5 mm) without tamponade. The entire right ventricle (RV) cavity was occupied with thick, mobile, shaggy, heterogeneous, echo dense mass (4 cm × 8 cm) extending from the free wall of RV to its outflow tract [Figure 3 and Video 1 (video available from: *https://www.ipcares.org/articles/2021/1/3/images/IndianPediatrCaseRep_2021_1_3_166_325078_sm5.mp4*)]. There was severe RV dysfunction (tricuspid annular plane systolic excursion 4 mm, fractional area change 20%) with mildly reduced left ventricular (LV) contractility (LV ejection fraction 50%). A provisional echocardiographic diagnosis of large vegetation attached to RV myocardium along with infiltration to RV wall suggestive of a RV abscess was made. Electrocardiogram (ECG) showed sinus tachycardia, right ventricular hypertrophy by voltage with no conduction abnormality. High-resolution computed tomography (HRCT) of the chest with angiogram confirmed the diagnosis of RV abscess. A final diagnosis of RV abscess secondary to posttraumatic osteomyelitis and septic shock was made. Antibiotics were upgraded to include vancomycin.

The child's condition deteriorated and had to be intubated. Emergency cardiac surgery was performed by a multi-disciplinary team within 12 h of admission in view

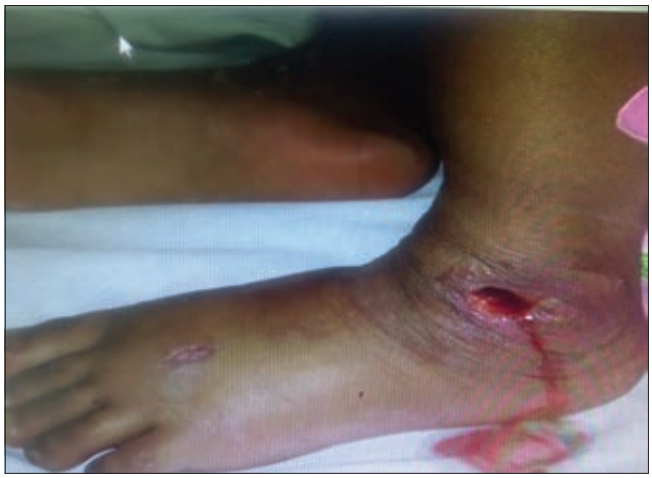

Figure 1: Lateral aspect of left lower limb showing ulcerating wound located at the lower end with swelling of the foot

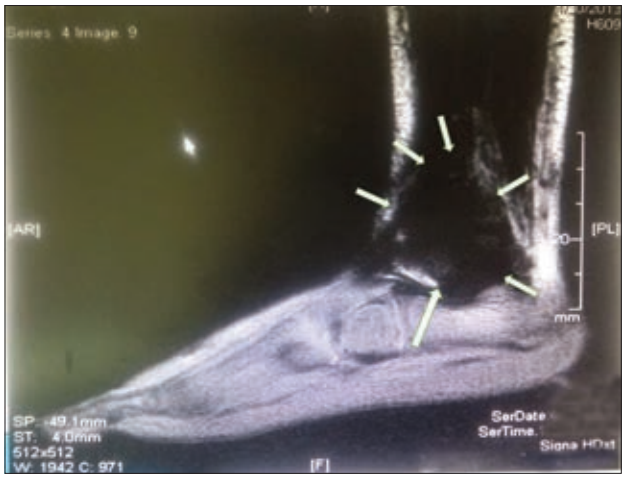

Figure 2: Magnetic resonance imaging of left lower tibia showing osteolytic lesion (arrows)

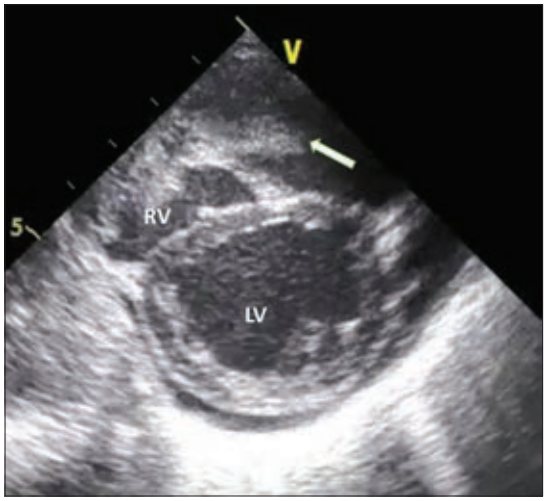

Figure 3: Two-dimensional echocardiography from parasternal short axis view at the level of ventricles showing big vegetation (arrow) attached to RV myocardium

of refractory septic shock secondary to a cardiac abscess with ventricular dysfunction. The RV abscess with a large vegetation attached to the RV myocardium was confirmed intraoperatively. A huge purulent cystic mass adherent to the RV free wall (40 mm × 30 mm) was found extending from the moderator band to infundibulum. No vegetation or clots had embolized to the pulmonary arteries. Simultaneous open heart surgical removal of the septic mass and arthrotomy of the left ankle joint was done. The cardiac abscess and marrow from medullary cavity of left tibia were sent for culture and histopathology. These grew methicillin sensitive *Staphylococcus aureus*.

The child was successfully extubated on the 2nd postoperative day and weaned off inotropes by the 6th day. There were no postoperative events and she was discharged after 3 weeks of intravenous vancomycin and ceftriaxone followed by oral antibiotics for another 6 weeks. The child has been under follow-up since the last 7 years. Serial postoperative echocardiograms showed complete resolution of abscess, no valvular damage, normal cardiac function, and normal ECG. There is slight asymmetry between left and right lower limb length, although she can perform all her routine activities effortlessly.

Discussion

A cardiac abscess is a suppurative infection involving cardiac tissues. A review of the literature by Shah *et al*. described 16 patients with perivalvular abscesses associated with bacterial endocarditis during a 20-year period.[3] The patients' ages ranged from 8 to 21 years, and 40% were due to *S. aureus*. The incidence of this complication is rare in children in comparison to adults, in whom up to 30%–40% of patients with myocardial abscess have native valve bacterial endocarditis.[4] Garg *et al*. demonstrated 7% of 192 patients with infective endocarditis had cardiac abscesses.[6] Children with *Staphylococcus bacteremia* have a 12% incidence of infective endocarditis, out of whom 90% have an underlying congenital heart disease.[4,7]

In this case, a 3-year-old immunocompetent child with a structurally normal heart, presented in septic shock secondary to the development of a large RV myocardial abscess with RV dysfunction. The primary focus of infection was partially treated posttraumatic osteomyelitis of left ankle joint. Blood culture and culture from surgical debridement of local wound grew methicillin sensitive *S. aureus*. A multidisciplinary approach and use of point-of-care echocardiography in a child with septic shock led to the early diagnosis of the myocardial abscess. Standard indications for surgical intervention in cardiac abscesses include severe heart failure, severe valve dysfunction, prosthetic valve infection, invasion beyond the valve leaflets, recurrent systemic embolization, large mobile vegetations, or persistent sepsis despite adequate antibiotic therapy for more than 5–7 days.[8] In our case, the child with large RV abscess presented in septic shock and had rapid clinical deterioration despite attempted medical stabilization that was salvaged only by an emergency open heart surgery and left lower leg debridement.

Lessons learnt

- Posttraumatic osteomyelitis needs care of wound and aggressive treatment by intravenous antibiotics
- Inadequate treatment may lead to hematogenous spread as in present case leading to RV abscess and septic shock
- Point-of-care echocardiography in emergency helped in diagnosing the intracardiac focus of infection confirmed by HRCT angiography

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Infantile Sternal Tuberculosis: A Rare Condition

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Abstract

Background: Tuberculosis (TB) of sternum is one of the rarest forms of skeletal TB. Incidence of sternal TB has been calculated to be <1.5% amongst osteo-articular TB, with very few cases reported in infants. Due to its subtle signs and symptoms, early diagnosis of this entity becomes a challenge. **Clinical Description:** We reported case of 6-month-old boy who presented with complaints of progressively increasing swelling at the anterior chest wall. Radiological, histological, and microbiological investigations helped establish a diagnosis of infantile sternal TB. **Management:** Drainage of the lesion and excision of affected necrotic tissue was done. Culture and histopathological examination were suggestive of tubercular osteomyelitis of sternum. Weight adjusted antitubercular medications were given for 1 year. At 3 years of follow-up, the lesion had healed well without any recurrence, sinus formation or local deformity. **Conclusions:** High index of suspicion and detailed diagnostic work up are required for early diagnosis and management of infantile sternal tuberculous osteomyelitis.

Keywords: Infantile, osteomyelitis, sternal, tuberculosis

About 2.8 million new and relapsed cases of tuberculosis (TB) are diagnosed each year in India. Among them 10% are below the age of 15 years.[1] Pulmonary TB is the most common type of TB.[2] Skeletal affection of Mycobacterial TB is unusual with the overall incidence reported as 0.87%.[2] Tuberculosis of the sternum is one of the rarest forms of skeletal TB, with a calculated incidence of <1.5% among osteoarticular TB.[3] Around 164 cases of sternal tubercular osteomyelitis have been reported in scientific literature till date.[4] The countries from where most of these cases originated were India (95), South Africa (14) and USA (10). Majority of cases reported were primary (67.3%) followed by secondary (20.8%) and postoperative (11.9%) in origin.[4] Postoperative cases were noted mostly after cardiac surgeries. Due to the subtlety of signs and symptoms, early diagnosis is a challenge.

We report a case of tubercular osteomyelitis of the sternum in a 6-month-old boy. The purpose of this report is to create awareness among clinicians so that they consider sternal TB as a differential diagnosis of anterior chest wall swelling in an infant.

Clinical Description

A 6-month-old boy was referred to us with a progressively increasing swelling on his chest for 1.5 months. The swelling was painless, without any signs of local inflammation or any active discharge. There was no history of fever, cough, weight loss, or any other constitutional symptoms. There was no history of local trauma or swelling anywhere else in the body.

The baby was delivered at full term by lower segment caesarean section with a birth weight of 3.92 kg and an uneventful perinatal period. His immunization was complete till date. Bacille Calmette-Guerin vaccination was administered on the 1st day of birth. Patient was vaccinated as per the age. There was no significant past history or positive history of contact with TB in the family. Developmental milestones were appropriate for his age. The infant was being exclusively breast fed.

At admission, the child was stable with normal vital parameters. The weight was 5.5 kg (−2 standard deviation [SD]), length

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65 cm (−1 SD), and head circumference 41.8 cm (−1 SD). Local examination revealed a swelling of size 2 cm × 2 cm, over the lower part of sternum [Figure 1]. It was nonmobile, nontender, nonerythematous, nonfluctuant and hard in consistency [Figure 1a]. The overlying skin was normal and there was no discharging sinus. No pallor or lymphadenopathy was observed. The respiratory examination was normal and there was no hepatosplenomegaly. There was no other contributory findings on the rest of the systemic examination.

Management and Outcome

Salient laboratory reports included leukocytosis (total leukocyte count 19,900/mm^3), increased erythrocyte sedimentation rate 30 mm in the 1st h, normal C-reactive protein and liver function tests. HIV status was negative for both the child and the mother. An ultrasonogram of the swelling confirmed the presence of a hypo-echoic area in the left side of the anterior chest wall that was communicating with the anterior mediastinumas a horse-shoe shaped swelling around the wall of sternum. A high-resolution computed tomography scan of the thorax was planned to delineate the anatomy further. This showed a cystic swelling lying over the lower part of the sternum that extended to the left retrosternal region, with erosion of the adjacent surface of the sternum and costal cartilage [Figure 1b]. Underlying pleura, lungs and pericardium were not infiltrated. There was no mediastinal lymph node enlargement. Fine-needle aspiration cytology (FNAC) of the swelling reported pink, amorphous, caseous, necrotic background with few epithelioid clusters, polymorphs, and leukocytes suggestive of infection by *Mycobacterium*. Based on the clinical profile and investigations, we kept a diagnosis of sternal TB and started the infant on four-drug oral anti-tuberculous therapy (ATT) as per standard protocol. A multidisciplinary approach including pediatrician, pediatric orthopedic surgeon, and cardiothoracic surgeon managed the case.

As the swelling persisted for 6 weeks without regression, the cardiothoracic vascular surgeon advised drainage of the cystic lesion along with excision of the affected adjacent tissue. A 4 cm transverse incision was placed over the swelling, pus drained, and wide debridement performed with excision of osteomyelitic cartilage [Figure 2a and b]. Retrosternal soft tissue including mediastinal fat was also debrided. The left internal mammary artery was sacrificed. Pericardium and pleura were devoid of any infective tissue. Thorough saline wash was given and wound was primarily closed over a negative pressure suction drain. Retrieved fluid was sent for bacterial and tuberculous cultures and cartridge based nucleic acid amplification test (CBNAAT), which was positive.[5] The wound remained healthy postoperatively and sutures were removed 15 days' postsurgery.

The treatment plan that was decided on was ATT to continue for 1 year; 2 months intensive phase and 10 months maintenance phase. Pyridoxine (10 mg/day) was continued for the entire duration of ATT.[3] Regular monthly follow ups were done for the first 2 months followed by 3 monthly follow-ups till 1 year of age, and subsequently, 6 monthly follow ups till 3 years. At the final follow-up at 3 years, the lesion healed completely without any signs of residual pain, swelling, or sinus formation. Child demonstrated growth and development within normal range.

Discussion

Out of the 164 cases of sternal tubercular osteomyelitis reports till date, the youngest age of presentation was 9 months in a Japanese child.[4,6] The diagnosis was confirmed by biopsy and the child was managed with first line ATT for 9 months.[6,7] The majority of other cases were beyond infancy. To the best of our knowledge, our case is the youngest child diagnosed with sternal tubercular osteomyelitis. Reactivation of the latent loci of mycobacterium is the most common cause of sternal TB. The usual routes of spread are hematogenous and lymphatics.

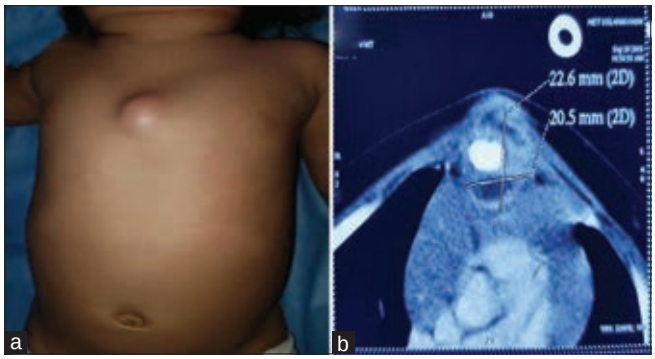

Figure 1: (a) A midline globular swelling of 2 cm × 2 cm × 1 cm over the lower part of sternum at the time of presentation. (b) Dimensions of the swelling on axial section of computed tomography scan

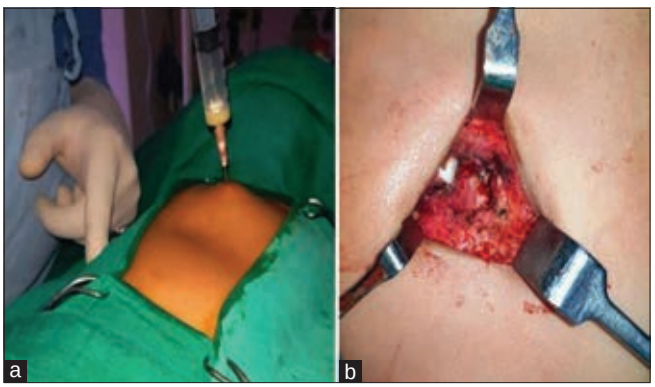

Figure 2: (a) Aspiration of frank pus from the swelling. (b) The necrotic granulation tissue being removed from the swelling

Subclinical contamination and immunocompromised condition can also be the possible pathogenesis.[4] Direct seeding from mediastinal lymph nodes and through inhalation have also been mentioned.[6,8] Like most of the previous case reports, the primary reason of the infection in this case could not be ascertained.

The differential diagnosis of chest wall swellings includes pyogenic infections, metastasis, malignancy, brodies abscess, and granulomatous lesion. Unlike pyogenic osteomyelitis, in tuberculous lesions there is a slow destruction of the cartilage and hence the delay in diagnosis. Thus, TB of the sternum can present with an indolent, painless swelling without any constitutional symptoms, as was seen in this case. Sternal TB can also present with a painful swelling associated with erythema, warmth, tenderness, and enlarged lymph nodes. If timely diagnosis is not made, any form of sternal TB can result in bone deformity, fracture, draining abscess or sinus formation.

The diagnosis of sternal TB is usually delayed owing to slow growing character of organism. Chest radiograph is not contributory in detecting early bone changes, periostitis, osteopenia, or fractures. Magnetic resonance imaging (MRI) scan can detect abscess formation, bone marrow invasion and extent of soft tissue mass, even better than CT scan.[9] However, due to logistic issues, we could not get MRI and had to proceed with the CT scan. FNAC and excisional biopsy can confirm diagnosis. CBNAAT is a cartridge-based nucleic acid amplification test for rapid diagnosis of TB and assessing sensitivity of isoniazid and rifampicin.[5] Khan *et al*. described two cases of multi drug resistant sternal TB in their series of 14 sternal TB. Two patients required surgical treatment apart from first-line ATT and one patient with advanced disease developed pectus excavatum. None of the patients were HIV positive.[8,10]

Incision and drainage of the pus along with excision of the cystic wall is the ideal choice of treatment. Debridement of the affected tissue and histopathological examination can be of great help in diagnosing atypical presentations of TB. To conclude, a high index of suspicion and detailed diagnostic work up is required for early diagnosis of infantile sternal tuberculous osteomyelitis. To the best of our knowledge, this is the youngest patient (6 months) of sternal TB reported in literature till date.

Lessons learnt

- A high index of suspicion and detailed diagnostic work up is required for early diagnosis of infantile sternal tuberculous osteomyelitis
- An inter-professional team approach including pediatrician, pediatric orthopedic surgeon, and cardiothoracic surgeon ensures best results with minimal complications
- Incision and drainage of the pus along with excision of the cystic wall along with anti-tubercular drugs is the ideal choice of treatment in case of abscess formation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Neonatal Scrub Typhus – A Sepsis Mimic

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Abstract

Background: Scrub typhus is the most prevalent rickettsial infection in India. It is caused by *Orientia tsutsugamushi*. Although there are few reports suggesting vertical transmission from the mother to baby, it is extremely rare. **Clinical Description:** We describe a 1-day-old baby who was referred to us for respiratory distress and diagnosed as meconium aspiration syndrome, the clinical features of which resolved by the 10th day. The baby developed fever on the 11th day of life and was detected to have developed pallor and hepatosplenomegaly. History revealed maternal fever preceding and continuing well beyond delivery. **Management:** Late-onset sepsis was initially suspected in the baby. After reviewing the maternal history, transplacental transmission of scrub typhus was considered. Immunoglobulin M enzyme-linked immunosorbent assay was positive in the mother–baby dyad, but polymerase chain reaction for scrub typhus was negative. However, both exhibited a dramatic response in resolution of fever with doxycycline in the former and clarithromycin in the latter. On follow-up, the baby was well and gaining weight. **Conclusion:** Proper history and early initiation of management are important for reducing the morbidity and mortality of newborns with scrub typhus.

Keywords: Polymerase chain reaction, scrub immunoglobulin M enzyme-linked immunosorbent assay, transplacental infection

Rickettsial infections are re-emerging causes of acute febrile illnesses throughout Asia. Scrub typhus, caused by *Orientia tsutsugamushi*, is the most prevalent rickettsial infection in India.[1] Manifestations of scrub typhus include hepatitis, meningitis, cardiac dysfunction, and triggering of preterm labor in pregnancy. The primary mode of transmission is through the bite of the trombiculid mite larvae.

We describe a mother–baby dyad manifesting with persistent spikes of fever. Rare modes of transmission in neonates include transplacental and postnatal transmission. Vertical transmission from mother to newborn was reported for the first time in 1992.[2] An exhaustive literature search revealed only three more newborns with scrub typhus till date.[3-5] Establishing diagnosis in the neonatal period is challenging, given the low index of suspicion, nonspecific signs and symptoms, and lack of diagnostic tests with high sensitivity and specificity. If undiagnosed, there is significant morbidity and mortality.[6] In contrast, with timely diagnosis, treatment is easy, affordable, and there is often a dramatic response to antimicrobials.[1,5]

Clinical Description

A baby boy was referred to our newborn unit from a private hospital for respiratory distress that developed soon after delivery. He was born to a 33-year-old third gravida (with two previous abortions) at 39 weeks of gestation. The antecedent antenatal period had been uneventful. The mother had been screened for toxoplasma, rubella, cytomegalovirus, and herpes simplex virus, which were negative. The mother developed fever 4 days before birth. There were no localizing signs and symptoms, and the preliminary investigations were inconclusive. The mother was started on broad-spectrum antibiotics. Delivery was by an emergency cesarean section in view of meconium-stained liquor. The baby cried immediately at birth at a nearby hospital and weighed 2.79 kg. The baby was received in our tertiary care institution at 4 h of life. At admission, the baby had severe respiratory distress but was normothermic and hemodynamically stable. The baby was electively intubated for acute respiratory failure and started on synchronized intermittent mandatory ventilation with

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peak inspiratory pressure/positive end expiratory pressure of 20/4, respiratory rate of 40/min, and FiO_2 of 80%. Two provisional diagnoses were considered; meconium aspiration syndrome (MAS) and congenital pneumonia. The baby was started on intravenous fluids and antibiotics after sending relevant investigations.

Management and outcome

The hemogram revealed normal hemoglobin (Hb) of 14 g/dL leukocytosis with a total leukocyte count (TLC) of 22,400/mm^3 and normal platelet counts. Chest X-ray showed multiple patchy nonhomogenous opacities [Figure 1]. A negative sepsis screen and sterile blood culture ruled out congenital pneumonia. Hence, the diagnosis of MAS was retained. The baby was extubated on day 7 of life and started on continuous positive airway pressure. Nasogastric feeds were initiated. On day 8, status improved further, but the SpO_2 could not be maintained above 94% in room air. A normal two-dimensional echocardiography ruled out persistent hypertension of the newborn, a known complication of MAS. By the 10th day, the baby was active, displayed good spontaneous movements, the oxygen requirement had resolved, and the baby was started on paladai feeds.

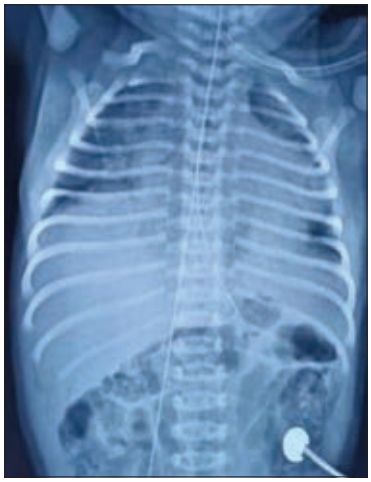

Figure 1: Multiple patchy opacities in both lung fields suggestive of meconium aspiration syndrome

On the 11th day of life, the baby developed recurrent spikes of high-grade fever without any other localizing symptoms. The baby was hemodynamically stable, but it was noted that he had developed hepatosplenomegaly (liver span 7 cm and spleen palpable 3 cm below the left subcostal margin. Broad-spectrum antibiotics (vancomycin and meropenem) were started suspecting late-onset nosocomial sepsis and/or meningitis, after sending a repeat septic workup. These revealed anemia with a drop in Hb levels to 11 gm/dL, normal TLC (7200/mm^3) and platelets (2.85/mm^3), elevated C-reactive protein (102 mg/dL), and increased transaminase levels (Serum glutamic oxaloacetic transaminase (SGOT) 259 U/L, Serum glutamic pyruvic transaminase (SGPT) 194 U/L). Blood culture was sterile. The cerebrospinal fluid analysis (CSF) was normal with the absence of leukocytes, protein 72 mg/dL, sugar 53 mg/dL, and sterile CSF culture. The fever persisted [Figure 2].

In the meantime, it was discovered that the mother's fever had not abated and she had been hospitalized. Her reports had shown thrombocytopenia and leukopenia, and parenteral antibiotics had been started considering postpartum septicemia. Antifungals had been added when there was no symptomatic relief. Pleural effusion was identified on a chest radiograph. Scrub typhus was suspected, immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) was sent, and oral doxycycline was started. Diagnosis was confirmed by a positive serology report and supported by dramatic resolution of fever. In these circumstances, we considered transplacental scrub typhus infection in the baby and investigated accordingly. He was started on parenteral clarithromycin (15 mg/kg/day) empirically, while awaiting the reports. The fever disappeared within 24 hour [Figure 2] and did not recur. The baby's IgM ELISA for scrub typhus was also positive, though the scrub polymerase chain reaction (PCR) (sent on day 9 of fever) was negative. Clarithromycin was continued for 10 days. At discharge on day 32 of life, the baby was breastfeeding well and displayed adequate weight gain.

Discussion

Scrub typhus is endemic in the regions of South India and Northeast regions. Although there is definite increase in prevalence of scrub typhus in children in recent years, there

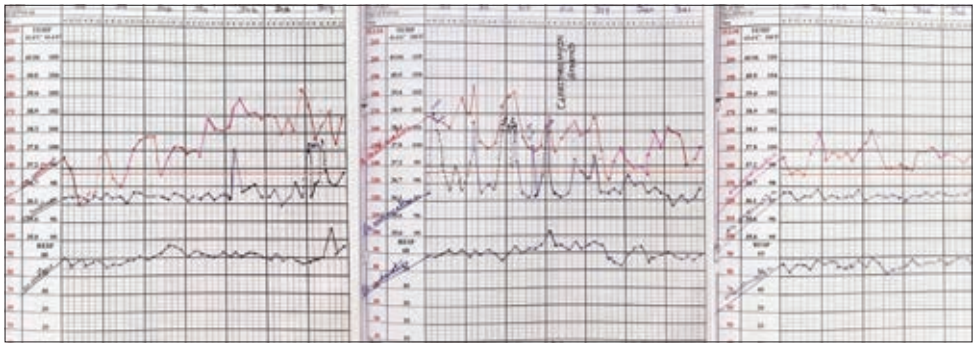

Figure 2: Charting of Vitals showing the pattern of fever and the lyse of fever after starting clarithromycin

is limited literature regarding infection in newborns. Usually, affected children present with fever, respiratory distress, abdominal distension, poor feeding, lethargy, seizures, and hepatosplenomegaly. These manifestations commonly mimic severe sepsis.[7] Diagnosis of scrub typhus is established by IgM ELISA and confirmed by PCR, preferably nested PCR. The Weil Felix agglutination test was has fallen into disrepute due to poor specificity and sensitivity. In this case report, the explanation for a negative real-time PCR in both mother and baby despite having reactive scrub typhus IgM antibodies may be low sensitivity (44.8%), in contrast to nested PCR(82.2%).[8] The routes of transmission of scrub typhus are transplacental, perinatal blood-borne, and postnatal infection.[2] Transplacental infection is the vertical transmission from mother to fetus, in which IgM ELISA will be positive for the baby.[1] Perinatal blood-borne infection may not have IgM positivity. Postnatal infection is when a baby acquires the infection from a tick bite that may occur ticks attach to clothes when the have been put to dry after a wash. This was ruled out in this case as the baby had been admitted in the Neonatal intensive care unit (NICU) since birth.

The case described by Wang *et al*. was initially considered to be aseptic meningitis.[2] Suntharasaj *et al*. reported positive IgM antibodies in a preterm baby of 34 weeks gestation.[3] Postnatal transmission was suspected in a 19-day-old resident of Delhi with positive IgM ELISA and scrub PCR. The mother was asymptomatic and negative for both tests, but a relative had visited from Assam and it was speculated that a tick could have got stuck on the luggage.[4] Another unusual source of postnatal transmission was suspected due to application of "*vasambu*," a medicinal herb commonly used in South India for home remedies of young infants. It was assumed that chiggers may have been present in the plant.[5]

Prompt diagnosis and early initiation of management are critical in reducing mortality and morbidity of newborns with scrub typhus. Although doxycycline is the drug of choice, it is avoided in newborns because of the possible side effects, and azithromycin and clarithromycin are used instead. Since there are a few cases of azithromycin causing infantile hypertrophic pyloric stenosis,[9] we chose to treat our patient with parenteral clarithromycin.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the parent. The legal guardian has given his consent for the images and other clinical information to be reported in the journal. The guardian understands that the name and initials will not be published, and due efforts have been made to conceal the same, but anonymity cannot be guaranteed.

Lessons learnt

- The possibility of transplacental infection of scrub typhus should be considered in newborns with persistent fever and hepatosplenomegaly
- Scrub typhus mimics sepsis
- Reviewing maternal history can give important clues to diagnosis in newborns.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Aplastic Anemia Complicating Systemic Lupus Erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with a myriad of hematological manifestations. Pancytopenia occurs in 10%–50% of cases in these patients. Rare cases of aplastic anemia have been reported with SLE but mostly in adults. **Clinical Description:** A 6-year-old child presented with fever and painful multiple joint swelling for 6 months. Examination revealed pallor and polyarthritis involving small and large joints. Hemogram, bone marrow aspiration, and biopsy established the diagnosis of aplastic anemia. Since the clinical phenotype encompassed a childhood-onset multisystemic (musculoskeletal and hematological) chronic illness with constitutional symptoms, we considered included connective tissue disorders (CTDs), systemic-onset juvenile idiopathic arthritis with macrophage activation syndrome, hematological malignancy, and disseminated tuberculosis as differentials. Investigations confirmed the diagnosis of SLE. **Management:** The patient was treated with pulse doses of intravenous methylprednisolone for SLE and daily oral cyclosporine and supportive transfusions for aplastic anemia. She showed improvement in the constitutional symptoms and hematological parameters within 6 weeks. The arthritis resolved within 6 months of therapy, after which she was continued on low-dose steroids, hydroxychloroquine, and methotrexate. **Conclusion:** In cases of aplastic anemia with atypical features of CTDs such as arthritis, uveitis, oral ulcers, rash, and photosensitivity should be worked up for underlying autoimmune disorders.

Keywords: Aplastic anemia, cyclosporine, methylprednisolone, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic, potentially fatal, autoimmune, inflammatory disease of unknown etiology that leads to tissue and cell damage by pathogenic autoantibodies and immune complexes. It is characterized by multiorgan involvement, an unpredictable course, and very high mortality in the pediatric age group. Hematological manifestations such as anemia, leukopenia, lymphopenia, thrombocytopenia, and antiphospholipid syndrome are commonly reported in SLE and are included in the diagnostic criteria for the disease. Anemia is seen in up to 50%–70% of patients of SLE.[1] Anemia of chronic disease is the most common cause. Other factors include inflammation, renal disease, blood loss, hemolysis, medications, dietary insufficiency, infection, hypersplenism, myelofibrosis, and myelodysplasia.

Aplastic anemia is a very unusual manifestation of SLE[1] that occurs due to an impaired erythropoietin response and formation of antibodies against erythropoietin.[2,3] We report a girl with SLE and aplastic anemia. A literature search found 15 cases of previously published case reports of aplastic anemia with SLE. All of these were seen in adults, except for a single patient with neonatal lupus.

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Clinical Description

A 6-year-old girl presented with recurrent episodes of fever and painful swelling of multiple joints for 6 months. The joints involved were bilateral knees, ankles, elbows, and the small joints of both hands. These were accompanied with morning stiffness and severely decreased range of motion. The episodes of fever were high grade, occurred twice a month, had variable duration of 7–10 days, and were not associated with night sweats. There was no history of associated rash, eye redness, photosensitivity, or oral ulcers. There was a history of gradual onset of progressive pallor for a month that was accompanied by multiple petechial rashes. There was no history of bleeding from any site, recurrent episodes of sore throat, or appearance

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of nodular swellings. There was no history of decreased urine output or reddish discoloration of urine, jaundice, breathlessness, or palpitations. The child had decreased appetite and listlessness. The child was hospitalized 1 month after the onset of illness. On reviewing the documents, it was discovered that she had evidence of pleural and pericardial effusion, as well as ascites. There was no history of contact with tuberculosis.

On examination, she was undernourished. She was febrile and hemodynamically stable. The weight, height, and body mass index was 13.4 kg, 108 cm, and −2.49 Z score (thinness), respectively. General physical examination revealed pallor and generalized petechiae. Throat examination was normal. There was no icterus or lymphadenopathy. Bilateral knee, ankle, and elbow joints were swollen and tender with decreased range of movements. There were no deformities or contractures. Per-abdomen examination did not reveal any hepatosplenomegaly. Respiratory, cardiovascular, and central nervous system (CNS) examination was normal.

The clinical phenotype encompassed a childhood-onset multisystemic (musculoskeletal and hematological) chronic illness with constitutional symptoms. The differentials that were considered included a connective tissue disorder (CTD) (SLE, mixed CTD, or overlap syndromes) and systemic-onset juvenile idiopathic arthritis with macrophage activation syndrome [MAS] due to the presence of pallor and petechiae, a hematological malignancy, and disseminated tuberculosis.

Salient hematological findings were pancytopenia based on counts (hemoglobin 4.6 g/dL, total leukocyte count 900/μL, platelet count 3000/μL, and reticulocyte count 0.5%) and peripheral smear which did not reveal any atypical cells. Since this was suggestive of hypoproliferative marrow, a bone marrow aspiration (BMA) was performed. The report showed suppressed erythroid series with a predominant normoblastic reaction, with maturation arrest of myeloid series and absent megakaryocytes. Since bone marrow cellularity cannot be commented upon in a BMA, a bone marrow biopsy was done that revealed decreased cellularity of 30%. Since there were features of MAS, work-up for hemophagocytic lymphohistiocytosis (HLH) was planned (serum ferritin, fibrinogen, and triglycerides) although it was lower down in the list of differentials. The levels of these biomarkers were normal.

Results of the inflammatory parameters included an elevated erythrocyte sedimentation rate of 55 mm/1st h and raised C-reactive protein. The reports of investigation sent for the evaluation of CTDs were as follows: positive antinuclear antibody (ANA) by immunofluorescence, high titers (197.94 IU/ml) of anti-double-stranded DNA (dsDNA) and negative for phospholipid antibody (IgG, IgM), anticardiolipin antibody (IgG, IgM), lupus anticoagulant, and direct Coombs test. Slit lamp examination excluded uveitis. In view of the clinical phenotype (including the past history of polyserositis) and laboratory findings, a diagnosis of childhood SLE was made. Relevant clinical and laboratory evaluation for multisystemic involvement excluded renal, hepatic, and CNS involvement. The final diagnosis was childhood SLE with aplastic anemia.

The patient was treated with pulse doses of intravenous methylprednisolone for SLE. Daily oral cyclosporine was added to this standard protocol for the associated aplastic anemia, in addition to supportive treatment with multiple packed red blood cell and platelet concentrate transfusions. Within 6 weeks of therapy, she showed improvement in constitutional symptoms and hematological parameters. Her arthritis showed symptomatic resolution within 6 months of therapy, and she was continued on low-dose steroids, hydroxychloroquine, and methotrexate (which were started after resolution of pancytopenia). The child has been under follow-up for the last 10 years and has not shown any evidence of disease progression.

Discussion

The etiology, pathogenesis, clinical manifestations, and laboratory findings of SLE in children are similar to that seen in adults. A diagnosis of SLE in childhood is based upon the American College of Rheumatology (ACR) criteria which requires the satisfaction of four out of 11 criteria for establishing diagnosis. In children, these criteria display sensitivity and specificity of 96% and 100%, respectively. Although these criteria are excellent guides, clinicians should use their clinical judgment in children if all these are not fulfilled, as many features evolve over time, and may not be found initially. The diagnosis of SLE was made in our patient in view of presence of arthritis, polyserositis, positive ANA, and anti-dsDNA, and hematological criteria (leukopenia and thrombocytopenia).

Pancytopenia is a rare hematological manifestation of SLE, the underlying mechanism of which is still unclear. Cytotoxic T cells are primarily responsible for immune-mediated destruction of bone marrow precursor cells.[4-6] Autoantibodies in SLE act against the pluripotent stem cells and lead to bone marrow suppression.[7] In addition, impaired apoptosis and defective clearance of these cells can also contribute to pancytopenia, similar to children with HLH. These apoptotic cells are likely to be a source of autoantigens in SLE as they express many of the nuclear autoantigens that are found in SLE. Impaired clearance of these particles can lead to dysregulated immune activation, causing disease activity. A high proportion of bone marrows obtained from patients with SLE contain apoptotic debris.[8] Overall hypocellularity, morphological dysplasia, increased fibrosis, and bone marrow necrosis were common findings in patients with SLE with pancytopenia, suggesting a primary bone marrow involvement in the tissue pathogeny of the disease, probably mediated by autoantibodies, immune complexes, and activated cytotoxic T cells.[9]

This case was unique in many aspects. This child was diagnosed as SLE despite the absence of classical features, such as malar rash, oral ulcers, photosensitivity, or renal disease. She did not have all features at presentation, and

polyserositis was identified only after careful review of past history and documents. We did not administer antithymocyte globulin, which is usually used in severe aplastic anemia, as the etiology of the pancytopenia was autoimmune in nature. In cases of aplastic anemia with atypical features of CTDs such as arthritis, uveitis, oral ulcers, rash, and photosensitivity should be worked up for underlying autoimmune disorders.

Lessons learnt

- In a patient with prolonged fever and polyarthritis, SLE must be considered as a differential diagnosis even in the absence of malar rash, ulcers, photosensitivity, or renal disease in a child.
- Though the ACR criteria for SLE are excellent guides, clinicians should use their clinical judgment in children if they are not fulfilled, as many features evolve over time, and may not be found initially.
- In aplastic anemia with SLE, a favorable outcome is seen with the management of SLE with methylprednisolone and treatment of aplastic anemia with cyclosporine, without the need for antithymocyte globulin.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Novel Heterozygous Mutation of CIITA Gene Presenting with Recurrent Infections and Systemic Lupus Erythematosus

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Abstract

Background: The expression of major histocompatibility complex (MHC) molecule is essential for homeostasis of the immune system. The expression of MHC-II is regulated by the master regulator for transcription, the Class II transactivator (CIITA) gene. Homozygous mutations affecting the CIITA gene result in bare lymphocyte syndrome type-II, but the clinical manifestations of heterozygous mutations are not well reported. **Clinical Description:** Herein, we describe the roller coaster course of a 6-year-old child who had presented with recurrent infections in infancy and systemic lupus erythematosus (SLE) in toddler age, who was later found to have heterozygous mutation in the CIITA gene. **Management:** The child was managed with immunosuppression for SLE and monthly intravenous immunoglobulin replacement therapy and daily cotrimoxazole prophylaxis for features of immunodeficiency. **Conclusion:** This case report aims to provide more insight into the clinical features associated with heterozygous mutations of CIITA.

Keywords: Autoimmune, bare lymphocyte syndrome, immunodeficiency, major histocompatibility complex, systemic lupus erythematosus

The expression of major histocompatibility complex (MHC) molecule is essential for homeostasis of the immune system. Tissue-specific expression of MHC-II is regulated at the level of transcription. Four transacting genes control and coordinate the MHC-II expression are Class II transactivator (CIITA), RFX5, RFXANK, and RFXAP.[1] The master regulator for transcription of the MHC-II gene is CIITA. Homozygous mutations in any of these four genes result in bare lymphocyte syndrome type-II, a rare genetic disorder characterized by a lack of expression of MHC-II antigens, which lead to a combined immunodeficiency disorder.[2] However, manifestations of heterozygous mutations of these genes have not been well described.

We present this case to highlight the presenting features of heterozygous mutation of CIITA gene in a toddler where he presents with features of immunodeficiency and systemic lupus erythematosus (SLE).

Clinical Description

Our index child was the sixth-order child born to a third-degree consanguineous couple with a birth weight of 3 kg. The family history was significant in the form of two female siblings who succumbed to severe sepsis and meningitis before 1 year of age. A male sibling had a history of recurrent episodes of severe anemia requiring blood transfusion since the age of 18 months and finally succumbed by 2 years of age. The index child presented to us at 15 months of age with complaints of fever, respiratory distress, reduced activity, and feeding for 3 days, suggestive of lower respiratory tract infection. He had a stormy infantile period with recurrent episodes of lower respiratory tract infection, persistent diarrhea, and failure to thrive since the age of 9 months, necessitating multiple hospitalization and intravenous injections. None of the signature organisms

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pertaining to immunodeficiency could be isolated during the evaluation of these episodes. His weight at 15 months was 7.5 kg (−3.05 Z), length was 74 cm (−2.41 Z), and weight for length was −3.29 Z, suggesting severe acute malnutrition. The child was febrile (101°f) and tachypneic (54 breaths/min) with normal perfusion and saturation on 4 L/min oxygen supplementation being 97%. General examination revealed mild pallor without any evidence of jaundice, lymphadenopathy, cyanosis, clubbing, or edema without evidence for any micronutrient deficiency. Respiratory examination revealed normal breath sounds and diffuse bilateral crepitations. His systemic examination was unremarkable. Laboratory reports did not reveal any lymphopenia, thrombocytopenia, or neutropenia. The liver and renal function tests, evaluation for tuberculosis and human immunodeficiency virus, repeated bacterial cultures of blood, urine, and stool samples, stool evaluation for parasitic infestation, and chest roentgenogram were all unremarkable. The duodenal and colonic biopsies were planned in view of persistent diarrhea and failure to thrive which revealed features consistent with eosinophilic enteritis.

The child presented again at 4 years of age with severe pallor (hemoglobin 3.6 g/l), failure to thrive, hepatosplenomegaly, and congestive cardiac failure. His mother reported intermitted episodes of persistent diarrhea and bronchopneumonia in the last 3 years, which were managed conservatively by his primary care physician.

Management and Outcome

Evaluation for immunodeficiency disorders was performed at 18 months of age. Lymphocyte subset analysis by flow cytometry revealed: absolute lymphocyte count - 2700/μl, CD4 cells - 12% (322/μl; reference range 1900–2900 μl), CD8 cells - 43% (1154 μl; reference range 667–1473/μl), B cells - 7% (188/μl; reference range 160–370/μl), NK cells - 14% (376/μl; reference range - 50–4000/μl). Serum immunoglobulin evaluation by nephelometry showed: IgG - 18.6 g/l (reference range 5.33–13.78 g/l), IgM - 1.01 g/l (reference range 0.28–2.18 g/l), IgA - <0.246 g/l (reference range 0.24–1.01 g/l), and IgE - <4.4 IU/ml. Thus, the CD4 cell count and serum immunoglobulin A levels were reduced for his age. A possibility of combined immunodeficiency was considered. However, further functional and genetic evaluation for immunodeficiency could not be performed as the child was lost to follow-up.

On next presentation at 4 years of age, he had spherocytosis with reticulocytosis, hemoglobinuria, decreased serum haptoglobulin, and elevated lactate dehydrogenase, suggestive of intravascular hemolysis with positive direct Coomb's test. The child also had stage-I hypertension and proteinuria (1+) with low serum C3 levels (42 mg/dl). Hence, a possibility of SLE was entertained and worked up. Serum antinuclear antibody and anti-double-stranded DNA were positive (4+). However, the serum albumin (3.3 g/dl), serum cholesterol (122 mg/dl), serum creatinine (0.53 mg/dl), blood urea (39 mg/dl), aspartate transaminases (23 IU/l), and alanine transaminases (28 IU/l) were within normal limits. Renal biopsy showed evidence of class-II lupus nephritis. He did not have other systemic manifestations of SLE such as cutaneous features, arthritis, neurological changes, serositis, and antiphospholipid antibodies. The presence of absence of cutaneous and neurological manifestations excluded complement deficiency-induced lupus as our differential diagnosis. European League Against Rheumatism/American College of Rheumatology 2019 criteria[3] to diagnose SLE were fulfilled (score = 25; score ≥10 classifies SLE with 96% sensitivity and 93% specificity). The child was treated with intravenous methylprednisolone pulse therapy followed by oral prednisolone and mycophenolate mofetil for 4 weeks. Laboratory evaluation (complete hemogram and urine analysis) after 4 weeks confirmed that the child was under remission. The dose of prednisolone was tapered gradually and mycophenolate mofetil was continued with oral hydroxychloroquine.

During the 3rd month of the steroid taper, there was an isolated hematological flare of SLE (hemoglobin - 3.3 g/l). For this isolated hematological flare, he was treated with intravenous methylprednisolone pulses and 4 weekly doses of injection rituximab. Mycophenolate mofetil maintenance was continued, and he remains in a state of clinical remission status till now.

Since the index child had presented with features of combined immunodeficiency disorder initially and features of SLE later, further evaluation was done to identify the immunodeficiency disorder. Clinical-exome sequencing by next generation sequencing testing revealed a heterozygous missense variation in exon 13 of the CIITA gene, resulting in the amino acid substitution of leucine for valine at codon 94. Although this mutation is not described previously in literature, the *in silico* prediction of the variant was damaging by SIFT and mutation tester. Quantitative activity of MHC-II molecules can be assessed by human leukocyte antigen (HLA)-DR expression on monocytes, and qualitative activity of MHC-II molecules can be assessed by antibody response to vaccines. Flow cytometric evaluation for HLA-DR expression on monocytes was performed. It was observed that 87% of the monocytes expressed HLA-DR antigen [Figure 1a and b], dismissing a quantitative defect. Antibody titer to vaccination revealed a deficiency of antibodies against tetanus toxoid after 6 weeks of immunization that confirmed a qualitative defect in the MHC-II molecule. The child was initiated on monthly intravenous immunoglobulin replacement therapy, and daily cotrimoxazole prophylaxis for the past 1 year as a bridge till stem cell transplantation is performed.

Discussion

The CIITA gene encodes a protein called the MHC-II transactivator. Homozygous mutations in this gene result in bare lymphocyte syndrome which severely cripples the immune system and leads to a combined immunodeficiency disorder. The CIITA is considered as a transcriptional coactivator as it does not directly bind to DNA. It exerts its

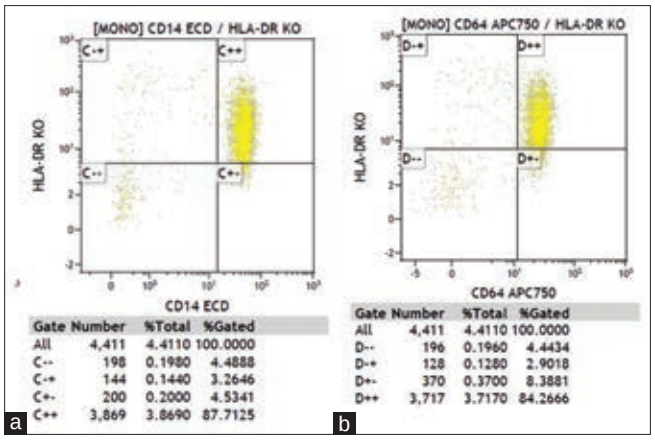

Figure 1: (a) Peripheral flow cytometry - CD14-gated monocytes - 87% express human leukocyte antigen-DR. (b) Peripheral flow cytometry - CD64-gated monocytes - 84% express human leukocyte antigen-DR

function through the activation of transcription factor RFX5. The CIITA protein acts as a positive regulator of MHC-II complex gene transcription and is therefore referred to as the master control factor for the expression of these genes. Our case adds insight to the clinical manifestations of heterozygous CIITA gene mutation. Functional activity of MHC-II molecule is very vital in antigen presentation functioning and T cell and B cell interaction. This child had most of the features of MHC-II deficiency - failure to thrive, recurrent respiratory tract infections, protracted diarrhea, hypogammaglobulinemia, and CD4 lymphopenia due to defective T and B cell functioning. There have been reports of cases with recurrent infections secondary to heterozygous mutation of one of the four transacting regulators of MHC-II expression.[4] All of these cases lacked expression of HLA-DR on monocytes. These cases highlight the quantitative defect of MHC-II protein due to CIITA mutation. In addition, CIITA gene is also responsible for the qualitative function of MHC-II.[5] A single amino acid deletion has been reported to be sufficient to abolish the activity of CIITA *in vivo*.[6] The HLA-DR expression was normal in our patient, which confirms the quantitative presence of MHC-II. Presence of low antibody titer to vaccine response could probably be due to poor T and B cell interaction, resulting in poor antibody response to subunit protein vaccines. This makes us speculate these immunodeficiency manifestations in our index child as secondary to CIITA mutation. However, animal model studies with functional assays were not done to confirm the same. Autoimmune cytopenias have been described in cases with heterozygous mutations of CIITA, but features of SLE have not been reported so far.[7] The presence of MHC-II is paramount for central tolerance in preventing the development of autoreactivity. Three mechanisms have been described to silence the development of autoreactive cells at the first checkpoint in bone marrow - deletion, anergy, and receptor editing.[8] All these factors together could have triggered SLE in this patient.[9] This has been emphasized by the fact that CIITA mutation has been identified as one of the susceptible genes for SLE by genome-wide association studies.[10]

Most children with homozygous mutation of the CIITA gene succumbed to underlying infection by 5 years of age without bone marrow transplantation.[2] Since our index child managed to survive till 5 years without bone marrow transplant, we hypothesize that the heterozygous mutations, though significant to cause immunodeficiency, may be less lethal.

To conclude, homozygous mutations of CIITA have been well known to cause primary immunodeficiency. However, heterozygous mutation causing clinically significant immunodeficiency is less reported. In this case, a novel presentation of primary immunodeficiency with autoimmunity adds a new facet to existing literature.

Lessons learnt

- Childhood SLE in children having its onset < 5 years of age can be monogenic in origin. CIITA gene mutation, even in heterozygous form, can present with features of SLE.
- Heterozygous mutation for CIITA gene can present with features of immunodeficiency but with a severity lesser than homozygous mutation.
- Children with cellular or humoral immunodeficiency can present with both the clinical features of immunodeficiency and autoimmunity.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Multidisciplinary Early Intervention in a Child with Autism and Childhood Apraxia of Speech

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Abstract

Background: Childhood apraxia of speech (CAS) is a neurological pediatric speech sound disorder, in which the precision and consistency of movements underlying speech are impaired in the absence of neuromuscular deficits. It is a common comorbidity in autism spectrum disorder (ASD) and requires detailed analysis to identify the typical errors in speech. **Clinical Description:** A 25-month-old boy presented with speech delay. The evaluation revealed absence of meaningful speech, impaired nonverbal communication and social skills, repetitive atypical behavior, and sensory issues with normal hearing. Although autism was suspected, the diagnosis could not be established, and intervention was started based on strengths and weaknesses. There was minimal improvement and discordance between receptive and expressive language was noted. Manifestations evolved over 15 months until a diagnosis of ASD was established by standard protocol. CAS was diagnosed at almost 4 years when a few meaningful words had developed and errors in oral movements, articulation, and phonological development were identified. **Management and Outcome:** Initially, the child received multidisciplinary management customized according to the strengths, weaknesses, and needs of the child. There was minimal improvement in communication, social interaction, and overall functioning. Identification of autism and slight changes in intervention did not bring about any remarkable changes. Once CAS was identified, and the focus of management changed there was a remarkable improvement in speech, and mild improvement in other aspects. **Conclusion:** Nonverbal or minimally verbal children with autism should be evaluated for CAS, especially if there is discordance between expressive and receptive language.

Keywords: Childhood apraxia of speech, pediatric speech sound disorder, phonology

Childhood apraxia of speech (CAS) is a neurological pediatric speech sound disorder, in which the precision and consistency of movements underlying speech are impaired in the absence of neuromuscular deficits.[1] Essentially, this means that the sequence of movements involved in speech production is impaired, which disrupts a child's ability to produce sounds, syllables, words, or sentences precisely, consistently, and rhythmically.[2] Not only is the sound production impaired, but also there is inappropriate prosody, i.e., the normal rhythm and intonation of speech.

CAS occurs in 0.1%–0.2% children,[2] with higher prevalence in boys compared to girls, the ratio being 2–3:1.[3,4] Although the magnitude is uncertain, CAS is frequently seen in nonverbal or minimally verbal children with autism spectrum disorder (ASD). These are children who have no meaningful speech even by the age of 5 years and comprise around 25%–30% of children with ASD.[5] On extrapolating, this percentage to the prevalence of ASD in Indian children between 2 and 6 years (1.0%),[6] and the magnitude of the 0–6-year-old population according to the 2011 census (15.87 crore),[7] it is evident that there will be a huge number of children with both ASD and CAS. If CAS goes unrecognized and is not addressed in the individualized education plan, neurodevelopmental outcomes will get adversely affected. Most pediatricians encounter children with ASD in their practice, nowadays. Not only should they be able to suspect ASD in children with developmental/behavioral issues, make

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a clinical diagnosis and refer them to experts, but they should also provide continuity of health care including checking adherence to the management.

We present the evolution of manifestations and management of a toddler who presented with speech delay and was eventually diagnosed as ASD with CAS. This condition has traditionally been considered to be the domain of the expertise of speech and language pathologists. We believe that pediatricians who provide health care to children with ASD (especially minimally verbal children) should be aware of this relatively unknown disorder.

Clinical Description

A 25-month-old boy presented to our center with delayed speech. The child did not speak any meaningful words and only uttered syllables. He did not point when he needed something but would drag his mother toward the object of desire and use her hand for indicating it. He displayed difficulties in understanding gestures. Although the parents had not appreciated any delay in other domains, we identified impairment in social skills. Apart from occasional smiling, he avoided social interactions. The parents thought he was shy and would outgrow it.

On probing, further, we also elicited the presence of atypical behavior. He was fascinated by patterns on surfaces (i.e., on the furniture or walls) and would stare at them for hours. He frequently ground his teeth and plucked his hair. He would get agitated and cover his ears at loud sounds such as horns or the whistle of a pressure cooker. There was no history of seizures or impairment in vision, hearing, chewing, swallowing, or locomotor abilities.

The child was born of a nonconsanguineous union, at term, by a cesarean section (the indication being fetal distress). Details of the Apgar Score were unavailable, but there was no history that suggested hypoxic-ischemic encephalopathy. The birth weight was 2.4 kg. He developed neonatal jaundice at 48 h, received phototherapy, and was discharged by the 5th day of life. Neither the past history nor family history was contributory. The parents belonged to the upper socioeconomic strata and were working professionals. We deemed the stimulation being given at home to be quantitatively and qualitatively adequate. The child had undergone brainstem-evoked response audiometry, an ophthalmologic evaluation, and a thyroid profile previously, all of which were normal. The weight, height, and head circumference were within normal limits. Examination of the oral cavity and throat was unremarkable. The child did not display dysmorphism or neurocutaneous markers. Extended neurological and systemic examinations were normal. Since the clinical phenotype comprised delayed communication (verbal and nonverbal) and social interaction, atypical behavior, sensory issues, and normal hearing, autism was suspected.

A multidisciplinary evaluation was performed. The Vineland Social Maturity Scale revealed a Social Quotient (SQ) of 84.96 (average social functioning), but the profile was uneven, with significantly more delay in self-help, eating, and communication skills. Diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) were not satisfied, and the Childhood Autism Rating Scale (CARS) score was 27.5 (nonautistic). Table 1 lists the speech and language assessment. According to the receptive expressive emergent language test, the receptive language (RL) age was 12–14 months, whereas the expressive language (EL) age was 7-8 months. Vestibular, auditory, and tactile sensory issues were identified. Despite synthesizing all information, a specific diagnosis could not be established, which is quite common in young children with special needs, sans locomotor impairment. We decided to formulate a multidisciplinary IP based on our functional assessment, monitor his progress, and reassess. The parents were explained about the child's strengths, weaknesses, and needs and the importance of incorporating intervention strategies into their daily routine.

Management and outcome

The intervention plan (IP) was multidimensional. Occupational therapy focused on improving eye–hand coordination, fine motor skills, and perception of depth and space. Sensory integration was employed for sensory issues. At the onset, speech and language therapy aimed at improving cognitive prerequisites for learning language (e.g., developing eye contact, attention and concentration, imitation of body movements and vocal behaviors, improving comprehension and expression, improving social skills, and oral skills). A linguistic approach included facilitating oral sensory and oral-motor development. The scope of language ability was expanded by teaching the child how to make a different sound, the rules of using these sounds, and their sequences. Behavior modification strategies were shared to help parents create a more conducive learning environment and avoid triggering inappropriate behaviors. Regular parental feedback was obtained regarding the child's changing needs and overall learning. Compliance with instruction was good.

Table 1 lists the various changes that occurred during follow-up. Minimal improvement was observed in communication, social interaction, and independence in activities of daily living. Goals of the IP were modified periodically, according to the mastery attained in skills. Reevaluation at 3.25 years revealed a decrease in SQ (62.5) to mild subnormal levels. The DSM-5 diagnostic criteria of ASD were satisfied, and the CARS score was 30 (mildly to moderately autistic). The intervention continued, after factoring in the additional ASD. However, improvement still did not occur as expected given the severity of autism and good parental adherence to the IP. Problems in verbal expression and articulation were identified on the emergence of a few single words with meaning in the 4th year. A detailed analysis demonstrated the typical error patterns of speech involving oral movements, articulation, and phonology (production of meaningful speech), which confirmed CAS [Table 2]. Subsequently, the intervention was modified with emphasis on speech-based, oral-motor skills,

Table 1: Speech and language characteristics pre- and post- intervention plan

Age	2.1 years	3.25 years	4 years	4.5 years
Phase	Pre-IP	~ 1-year post-IP	~ 2 years post-IP	~ 6 m post CAS IP
Mode of communication	Nonverbal; reduplicated babbling Hand over hand pointing	Nonverbal, better comprehension and receptive vocabulary	Predominantly verbal; persistence of nonverbal sounds for basic needs	Verbal communication Need-based with single words with meaning (hand over hand stopped)
Oral-peripheral use	Movements of all oral structures restricted: blowing, sucking and chewing limited. Occasional aspiration	Mild improvement in oral-sensory and oral-motor skills; partial chewing; occasional aspiration	Unintelligible words; weak intra-oral pressure; poor consonant production; syllable structure fairly developed	Improved intra-oral pressure and better speech intelligibility
Cognitive prerequisites for language learning	Poor imitation, joint attention and joint referencing; lack of imitation of sounds	No improvement in imitation skills; reliance on visual cues (e.g., pointing by the nearest person) had reduced	Started imitating non-speech movements, but poor imitation of speech movements; spontaneous production of few words with oral movements; word production on command or on imitation very poor	Immediate imitation of few speech sounds; good progress in eye-contact, attention, concentration, and joint-attention skills
Pragmatics	Occasional social smile; limited socialization and play skills	Mild improvement in social and play skills; frequent parallel play; greeting others restricted	Minimal progress in socialization	Social smile, greeting and requesting more spontaneous. Sharing of experiences in ADL emerging
Comprehension	Followed, single-step commands visual prompts	Followed simple, single step commands with minimal visual prompts quicker	Could understand, two step commands with visual prompts e.g., "bring your bag and keep the book inside it"	Comprehension of two step commands without cues. Occasionally followed yes/no questions
Receptive and expressive language	Expressed by crying/and hand-over-hand pointing. Receptive vocabulary consisted of common household objects and their functions	Reliance on visual cues less. Receptive vocabulary consisted of common household objects, body-parts, fruits, vegetables, vehicles, etc.	Expression of needs by pointing; spontaneous expression by naming pictures and single words. Vocabulary-common nouns, verbs, adjectives, prepositions, numbers, rhymes, colors and shapes	Comprehended and expressed more new words in a natural manner with fewer prompts
CAS	Not observed	Not observed	Observed	Observed, but less

CAS: Childhood apraxia of speech, IP: Intervention plan, ADL: Activities of daily living

Table 2: Features of childhood apraxia of speech noted in child at ~4 years

Features of childhood apraxia of speech
Inconsistent errors on consonants and vowels on repeated production of syllables and words (for "pen" - pe, en, en, pen, pe, pen)
Better performance in single sounds ("a") versus sounds in a sequence ("mama")
Better performance in single sounds and syllables versus in a sequential combination (for e.g., "water" has 2 syllables "wa" and "ter" but 4 sounds/w/,/a/,/t/ and/r/)
Groping behaviors on attempting to produce speech sounds or coordinate articulators for purposeful movement
More difficulties in word production with longer and more complex syllables (resulting in omissions)
Greater ease in producing automatic frequently used phrases (e.g., "my name is.") versus spontaneous speech or new (not previously practiced) phrases
Intonation: Inappropriate stress on syllables within words (i.e., lexical stress)
Limited range of consonant and vowel sounds
Problems with imitation noted; however good receptive vocabulary
Associated problems: Delayed language development, expressive language problems (e.g., confusion in word order), problems in pragmatics, oral motor clumsiness in blowing, chewing, sucking, feeding difficulties, hypo or hyper-sensitivity in oral cavity

and verbal communication. The history was revisited, but no apparent cause for the CAS could be determined.

The recognition of CAS and change in intervention resulted in a slow but steady improvement that had been missing before. Substantial improvement was seen in comprehension, receptive, and expressive vocabulary and naming [Table 1], with two-word phrases appearing at 4.5 years. Figure 1 depicts the changes in EL and RL during follow-up. Progress was not as remarkable for the cognitive prerequisites for language learning, sensory concerns, independence in ADLs, and social interaction.

Discussion

CAS can be congenital or acquired (intrauterine or early childhood stroke and traumatic brain injury), occur within complex neurobehavioral disorders such as ASD, fragile X syndrome, Rett syndrome, or idiopathic. The etiology is not

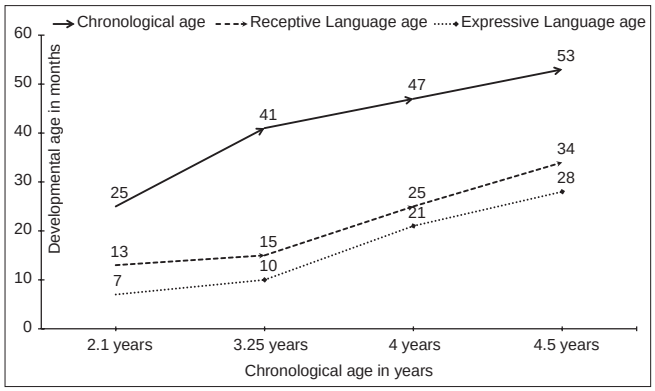

Figure 1: Changes in receptive and expressive language age with intervention

ascertainable in many cases,[8] as was seen in this boy. This narrative highlights the fact that CAS should be proactively looked for in nonverbal or minimally verbal children with ASD. It should be suspected in children in whom EL lags behind RL, despite acquiring the ability to speak a few words. The clinician can assess the quality of the oral movements involving the muscles of the mouth, jaw, tongue, lips, and cheeks which are used in actions such as blowing, whistling, or tongue movements. This can be done on demand, during imitation or observed spontaneously. The strength and coordination of all these oral structures help to create sound patterns which when combined, form meaningful words. Diagnosing CAS requires longitudinal observation and monitoring of oral motor skills (speech and nonspeech related), in addition to articulation and phonological development.[9]

The treatment of CAS needs to be intensive and individualized, requiring dynamic planning, programming, and production.[10] Some intervention goals in a child with ASD and CAS will differ from isolated ASD such as the focus on oral-motor movements and imitation of ADL on command in the former. Some goals (developing social interaction, social behaviors, nonverbal communication, prerequisites of language learning, comprehension, expression, receptive/expressive vocabulary, and socialization skills) are the same. It is imperative to focus on earlier goals before working on speech production, as premature insistence on speech production may reinforce echolalia.[11] Persistent deficits in word sound production after successful achievement of early language milestones should alert the clinician to explore the possibility of comorbid CAS.

Lessons learnt

- The intervention approach and outcomes differ in ASD with co-morbid CAS in contrast to children with isolated ASD.
- Diagnosing CAS requires regular longitudinal observation and monitoring of oral motor skills (speech and non-speech movements), in addition to articulation and phonological development.
- Intensive and individualized treatment of CAS is often necessary.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Role of Virtual Psychosocial Interventions in Coping with Mental Health Challenges of Children During the Pandemic

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Abstract

Background: The morbidity and mortality rates associated with the COVID-19 infection among children, fortunately, continue to be low; nevertheless, children are experiencing several pandemic-related mental health risks. **Clinical Description:** DK, a 9-year-old boy, was referred to the pediatrics department of a tertiary care center for compulsive oxygen saturation checking behaviors that developed a few weeks after the sudden demise of his maternal grandfather due to the COVID-19 infection. A diagnosis of adjustment disorder with emotional and behavioral problems was made as per the Diagnostic and Statistical Manual of Mental Disorder-5 criteria. **Management:** A comprehensive management plan was drawn out that focused on encouraging the parents to engage in productive and meaningful conversations regarding death being a permanent event in the life cycle. The child was asked to draw so that he could share his feelings and was also taught "belly breathing" that used a script of 4 counts in and 4 counts out by sharing child-orientated educational videos. The family was asked to chalk out a structured routine with time for creative artwork besides completing academic assignments. Follow-up after a month of therapy revealed an overall improvement in behavior, increased interactions with teachers and peers, and decline in compulsive checking of oxygen saturation levels. **Conclusions:** There is a need to expand digital treatment options for children, especially during times of public health emergencies, by using online psychoeducation resources, mental health apps, and conducting online therapy sessions.

Keywords: Adjustment disorder, artwork, cinema therapy, COVID-19, death, grief, virtual interventions

The COVID-19 pandemic and its resultant repercussions including a nationwide lockdown, physical distancing, decreased social interactions, economic hardships, and job insecurities have resulted in increased parental and family stress.[1] In addition to the high morbidity and mortality associated with the COVID-19 infections, children and adolescents are also experiencing several adverse effects associated with the mandatory stay-at-home instructions. The decision to close schools has resulted in millions of Indian children being left without access to playgrounds, extracurricular activities, and social connections with teachers and peers. Schooling their children at home has become a daunting prospect for families. Research indicates that forced confinements of families at home have increased mental tension, irritability, family conflicts, impaired parenting, and decreased subjective well-being of both parents and children.[2]

We share the story of a young boy who developed compulsive behaviors and intense irrational fears after the death of his grandfather from COVID-19. Assessment was conducted by parental and child interviews and administration of questionnaires through video conferencing. We want to highlight the fact that psychosocial interventions can be successfully implemented through the virtual platform and smartphone consultations, even in these challenging circumstances.

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Case Description

DK, a 9-year-old boy, was referred to the pediatrics department of a tertiary care center for abnormal behavior. The child had started compulsively checking his own oxygen saturation

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multiple times in a day, a behavior that developed a few weeks after the sudden demise of his maternal grandfather due to the COVID-19 infection. He had also become clingy and repeatedly sought reassurance from his parents that he was infection-free. History further revealed that the child had become withdrawn and displayed extreme agitation and distress at hearing any news related to any fatality from the coronavirus infection. The mother reported disturbed sleep, but no change in the appetite of the child. During the interviews, the child revealed his deep attachment to his grandfather, unresolved grief, and feeling of loss. Prior to this, the child was academically bright and studied in Class 4. There was no significant history of any psychosocial difficulties in the past.

The mother confided that she too was struggling to cope with the unexpected death of her father and also battling with guilt of survival. She actively avoided talking about his demise, lest it evoke sadness. Her overall negative affect and preoccupation with her own grief had impaired her ability to provide the supportive care that the child needed. Moreover, increased demands of looking after the household and working remotely from home added to her distress. Social isolation, limited social support from an extended family, and lack of structure that was usually provided by school further contributed to the child's and family's difficulties.

Management and Outcomes

All interactions and assessments were conducted through video-conferencing over several detailed sessions with the mother, child, and family. These lasted for approximately 45 min to an hour. Initially, daily sessions were conducted for a week, followed by alternate day sessions for the next week [Figure 1]. The Screen for Child Anxiety-Related Emotional Disorders (SCARED), Parent version, was used to assess anxiety problems. The child score on the somatic subdomain of the SCARED was above the cutoff score, thereby indicating elevated anxiety in these domains.[3] A diagnosis of adjustment disorder with emotional and behavioral problems was made as per the Diagnostic and Statistical Manual of Mental Disorder-5 criteria.

A management plan was drawn out that focused on encouraging the parents to engage in a productive and meaningful conversation with DK regarding death being a permanent event in a person's life cycle. Several Disney and Pixar movies (i.e., Coco, Lion King, and Big hero 6) were suggested as one way of initiating a conversation about processing death and grief, in a child-friendly way.[4] Second, since DK liked to draw and create stories, he was asked to share his feelings through the medium of line drawings. The child initially drew a boy crying copiously and it was assumed that he was projecting his feelings onto the paper and sharing his grief [Figure 2]. In order to focus on the positive and happy memories, the child was asked to draw all the activities that he had enjoyed doing with his grandfather. This time he drew and recounted an enjoyable evening that he and his grandfather had spent together fixing his bicycle [Figure 3]. DK was also taught "belly breathing" that used a script of 4 counts in and 4 counts out by sharing child orientated educational videos (available on the Homebase.org website), along with the reasons why mindful breathing was necessary.[5] The family

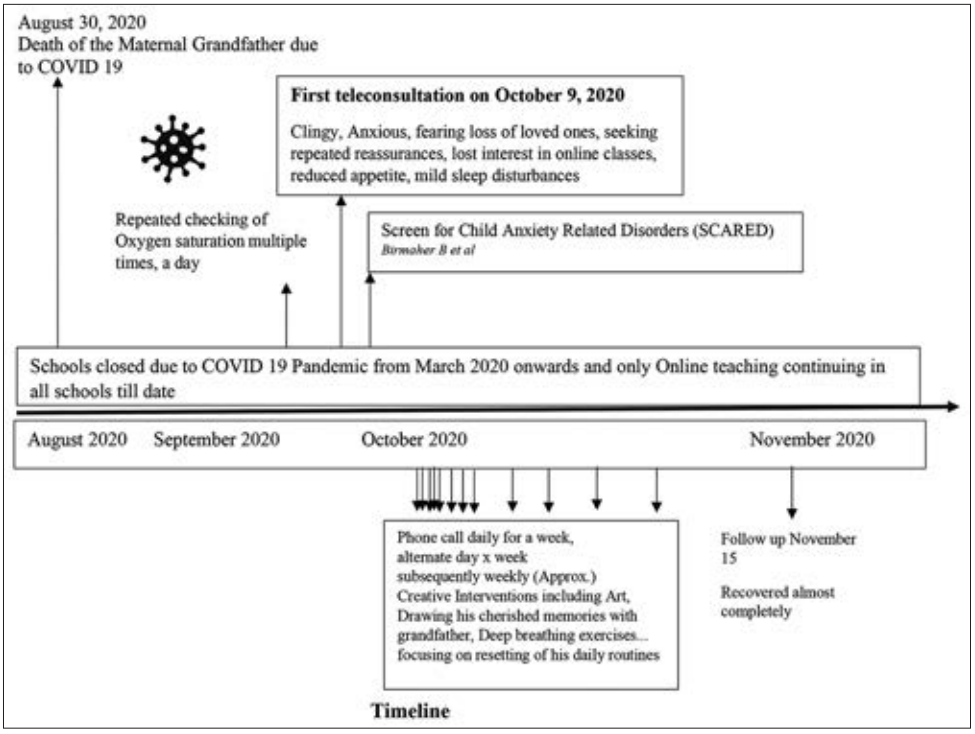

Figure 1: Timeline

Figure 2: Drawings of the child before therapy

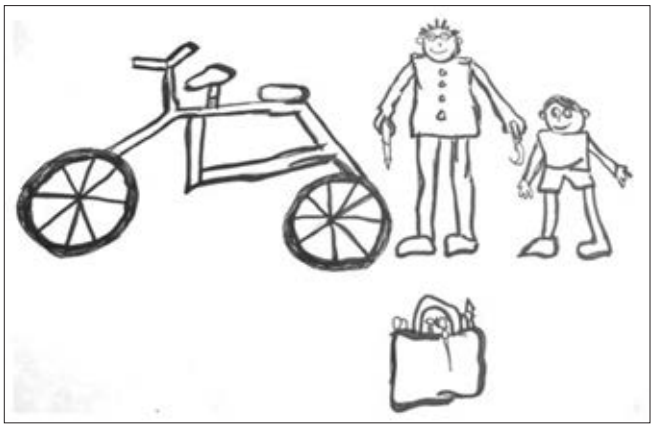

Figure 3: Drawings recalling happy memories with grandfather

was encouraged to chalk out a structured routine for the child with time for creative artwork, besides completing academic assignments. Follow-up after a month of therapy revealed an overall improvement in behavior, increased interactions with teachers and peers, a decline in the compulsive behavior, and reduced anxiety scores on SCARED.[3]

Discussion

Recent research has highlighted numerous pandemic-related mental health risks for children. A study from China found that nearly 23% and 19% of 2330 students (Grades 2–6) reported depressive and anxiety symptoms, respectively. Students who were worried about being affected by COVID-19 and not optimistic about the epidemic had significantly higher depression scores.[1] Emerging research suggests that prolonged social and physical distancing can increase feelings of loneliness among children and adolescents as it curtails their peers and social interactions. A recently published review (63 studies, n = 51,576) found a clear relationship between loneliness and future mental health problems in children and adolescents, especially depression, up to 9 years later.[6] It is possible that the social distancing measures of the COVID-19 have disproportionately affected families with preexisting mental health vulnerabilities and aggravated their psychosocial problems. Disruptions in daily routines and school closure have added to the distress of children as school routines and peer relationships are important coping mechanisms for all young people, and especially for those who are at high risk for mental health problems.

Since school reopening is still uncertain, forced isolation is likely to persist. In such a scenario there is a need for clinical services to scale up and offer intervention and preventive services. It is important to recognize that parental stress can also impact child well-being. Lee surveyed 405 American parents with at least one child (0–12 years) and found that one-third of them reported changes in their children's behavior (increased sadness and loneliness), subsequent to the pandemic. This change and increased mental health difficulties were attributed to several reasons, including disruption in daily routine and social isolation in an abusive home leading to increased maltreatment. A significant proportion of parents also confessed to feeling depressed and experiencing severe anxiety themselves due to economic uncertainty, stress, and death of close friends or relatives.[7]

Adjustment disorders are frequently diagnosed mental health disorders in children and the diagnosis is generally considered in patients who respond to a recent identifiable stressor with acute and dysfunctional emotional or behavioral response that cause significant academic and social functional impairment and are not accounted by another mental disorder. The response to the stressor varies widely and can include, but not confined to, excessive worry, repetitive and distressing thoughts, and acting out. The response needs to occur within 3 months of the onset of the stressor.[8] These disorders are amenable to the management by tele-counselling. Several intervention strategies used to enhance coping and adjust with loss include cinema therapy, artwork, and mindful breathing. Cinema education or movie therapy helps in initiating conversations about challenging events and distressful experiences, such as death, managing grief, and negative emotions. In Indian homes, death is often a taboo topic and discussing the death of animated characters in a movie may serve as a way to start difficult conversations about real-life deaths.[4] The movie "Inside-out" explicitly addresses how the emotion of sadness is needed as much as joy for growth and holistic health. Art in therapy is also used with children to share feelings, relieve distress, and acknowledge that sadness, uncertainty, and anxiety are normal emotions that are evoked during difficult and unprecedented times.[9] Clinical applications of mindful-based intervention practices such as deep breathing exercises have been shown to decrease symptoms of anxiety, depression, and maladaptive behaviors in children and adolescents in many studies.[6] The sesame street animated Muppet clips demonstrate ways in which young children can manage negative feelings such as anxiety, anger, and disappointment through various strategies.

Pediatricians need to provide anticipatory guidance to parents to help their children cope with various challenges faced during these unprecedented times. The present case illustrates how psychosocial interventions can be implemented through video conferencing using online psychoeducation resources and therapy sessions. A few randomized controlled trials have found that internet-based psychotherapeutic interventions are viable and effective options for treating depressed adolescents.[10] There is a scope to expand digital treatment for children, especially during public health emergencies. In the near future, there may be a shift in mental health-care provision toward online prevention, care, and management.

Lessons learnt

- Psychosocial interventions can be successfully implemented through video conferencing by using online psychoeducation resources and conducting online therapy sessions, especially during the challenging times
- Several intervention strategies may be used to enhance coping and adjustment among children suffering traumatic grief including cinema therapy, artwork, and mindful breathing
- Adjustment disorder is a frequently diagnosed mental health disorder among children and needs to be considered when children respond with a strong and dysfunctional response to an identifiable stressor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the parents have given his consent for images and other clinical information to be reported in the journal. The parents understand that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Desaturation during Feeding in a Term Neonate due to 20p Duplication Syndrome

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Abstract

Background: Feeding problems are common in preterm neonates of which desaturation during direct feeding is a known entity. However, term newborns have acceptable range of fall in saturation while feeding directly. Here, we report a term newborn with dysmorphic features had desaturation during feeding. **Clinical Description:** A male baby born to second-degree consanguineous parents at term who was managed for transient tachypnea of newborn had fall in saturation beyond acceptable range during feeding. He had low set ears, high-arched palate, thin upper lip, clinodactyly, and anal tag. **Management:** The baby was subjected for thorough exploration of respiratory/gastrointestinal/neurological systems which did not reveal attributable findings. Clinical exome sequencing revealed 20p duplication. He was started on orogastric feeding and could be gradually changed to direct feeding at 4 months of age. **Conclusions:** This report may improve the understanding toward approach to feeding problems in term neonates and also about phenotypic features of 20 p duplication which is less reported.

Keywords: 20p duplication, clinical exome sequencing, desaturation during feeding, dysmorphism, term neonate

A misconception that is sometimes encountered in health-care providers is that there may be a fall in oxygen saturation in newborns while they are breastfeeding. This incorrect extrapolation probably arose from the results of studies in preterm babies.[1] However, there is no concrete evidence to authenticate a similar significant fall in saturation in healthy term neonates.[2] In healthy term infants, there may be a transient drop in oxygenation in the immediate postfeed period,[1,2] but it should always be within the acceptable levels of oxygen saturation, i.e. >94%.[3]

This case report is regarding a term neonate with dysmorphic features who was evaluated for a significant drop in saturation beyond acceptable limits during feeding and detected to have underlying genetic defect (20p duplication) that has been reported to have this kind of clinical presentation. The objective of this report is to contribute to the understanding and clinical workup of infants with feeding difficulties and also to expand the clinical phenotype of 20p duplication syndrome, as features of these children are underreported.

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Clinical Description

A term baby boy, born in an extramural health facility, via a cesarean section (indication being a previous cesarean section) was transferred to the neonatal intensive care unit of our institute on the 1st day of life for respiratory distress since birth. The APGAR scores were 8 and 9 at 1 and 5 min, respectively. There was no sepsis setting. He weighed 2600 g at birth. The mother was 34 years old with an uneventful antenatal period. He was born to second-degree consanguineous parents with no significant family history. He had an elder sister with normal development.

The vitals at admission were respiratory rate of 66/min with lower intercostal retractions, and saturation maintained at 97% only with oxygen via prongs. Continuous positive airway pressure

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was started. Anthropometry (weight 2600 g, length 49 cm, and head circumference 33.5 cm) was within normal limits. It was noted that the newborn had multiple minor congenital anomalies [Table 1 and Figures 1, 2]. The septic workup and chest roentgenogram were normal. A two-dimensional echocardiogram showed a 2-mm defect in the atrial septum. The respiratory distress gradually improved, and we were able to wean him off oxygen support by 40 h of life. Given the natural course of illness and investigation profile, a diagnosis of transient tachypnea of the newborn was kept. Initially, the baby had been given orogastric (OG) tube feeding. When direct breastfeeding was started, a dramatic drop in SpO_2-45% with associated cyanosis was observed. Perfusion at that point of time was normal, the baby was normothermic, the form of the plethysmographic wave was normal and the placement of probe was correct. The hypoxia got immediately corrected on starting free-flow oxygen by nasal prongs. This event occurred on several occasions, hence we reverted to OG tube feedings.

Table 1: Minor congenital anomalies observed in the patient

Minor congenital anomalies
Cranium and face
Occipital flattening
Thick coarse straight hair
Round face with full cheeks
Laterally arched eyebrows
Upward slanting palpebral fissures
Low set ears
Partial left choanal atresia
High-arched palate
Thin upper lip
Digits
Uneven toe length with overlapping of the second toe over the great toe
Clinodactyly of the little fingers on both sides
Lower back
Sacral dimple
Perineum and genitalia
Anal tag
Left undescended testis

Management and Outcome

The baby was assessed for the presence of other concealed anomalies. We started with evaluating the upper airways for causes of obstruction. No difficulty was observed in passing a 6 French (6 Fr) suction catheter through both nares. The upper airway computed tomography (CT) scan followed by flexible nasal endoscopy confirmed partial left choanal atresia with a deviated nasal septum. Evaluation of the lower airways was done by fiber-optic bronchoscopy which revealed tracheomalacia. A CT angiogram showed a bovine type of aortic arch (left common carotid artery merges with the origin of the brachiocephalic artery, rather than arising directly from the aortic arch as a separate branch). Normal gastrointestinal (GI) tract anatomy was found on an upper GI barium contrast study, while a videofluoroscopic swallow study demonstrated efficient oral phase function with no evidence of supraglottic penetration or aspiration. Cerebral dysgenesis was ruled out by magnetic resonance imaging of the brain. However, none of these findings were a plausible explanation for the desaturation that was occurring during feeding. Ultrasonogram of the abdomen was normal. Thus, no major congenital anomaly was identified. The synthesis of all clinical data did not fit into any syndrome known to any of the treating clinicians. Neither did an online search help to establish diagnosis.

Genetic testing was simultaneously planned as per protocol of evaluation of children with multiple congenital anomalies. Clinical exome sequencing reported a likely pathogenic copy number variant with a phenotypic description; Chr 20: G.(?_407606)_(20052779_?) dup; autosomal dominant inheritance. High-resolution karyotyping confirmed additional chromosome material attached to terminal band of long arm of chromosome 20. The final diagnosis was 20p duplication syndrome. The parents were given genetic counseling regarding the nature of the genetic condition, genotypic-phenotypic correlation, and prognosis in terms of

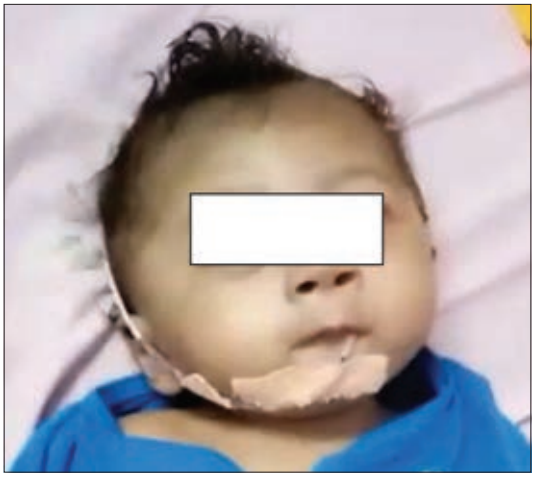

Figure 1: Facial features of the child

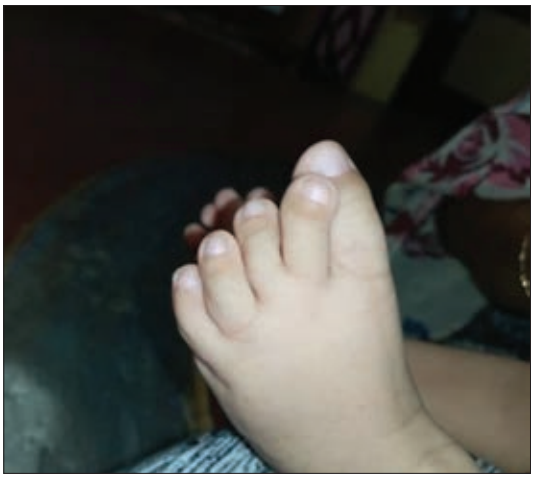

Figure 2: Left foot showing uneven toe length and overriding of the second toe over the great toe

the individual anomalies and possibility of developmental delay. OG tube feedings were continued postdischarge after ensuring that the mother had become competent to administer them without supervision. The baby was kept under close follow-up, with periodic monitoring of nutritional status and development. Trials of expressed breast milk (EBM) under saturation monitoring were also done during these visits. The baby tolerated EBM by cup and spoon feeding for the first time without desaturation at 4 months of age. This was continued, but the weight gain was not satisfactory. Upon introduction of complementary feeding, the weight gain started to increase significantly. Developmental delay was identified at 6 months (motor and mental quotient 65 and 55, respectively), for which early intervention was started.

Discussion

Our workup followed three pathways: first, looking for the cause of desaturation while feeding; second, defining the clinical phenotype; and third, looking for an underlying genetic etiology of the multiple congenital anomalies. It is very important to do a complete exploration of the upper respiratory and GI anatomy when looking for causes of feeding-related difficulties, as was done in the workup of this case. Numerical and structural abnormalities involving chromosome 20 are relatively rare. Till date, less than fifty cases have been reported. Chromosome 20p duplication is rarer than deletions. In 20p duplication, extra material from the short arm of chromosome 20 is placed on the body of the same chromosome.[4] Duplications of the long arm can also occur rarely.[5]

Infants with duplication exhibit wide variability in the clinical phenotype depending on the size of the duplicated segment. A literature search of previously reported cases revealed the following clinical phenotype;[6-8] typical facies (round face with prominent cheeks, coarse and usually straight hair, and upward slanting of eyes), developmental delay, learning difficulty, and difficulty in coordinating movement, speech delay, and malformed or fused vertebrae. Fused or irregularly shaped vertebrae have been frequently shown spinal abnormalities and develop kyphosis.[9] Minor genital anomalies are relatively common,[9] as are congenital cardiac septal defects.[10] Unusual findings are short nose with large nostrils, hypertelorism, occipital flattening, epicanthic folds, strabismus, and congenital cardiac defects.[6-8] Vision and hearing are generally unaffected, although some children display strabismus or astigmatism.[9]

Although growth is usually unaffected, there are reports of children exhibiting height >97th centile and macrocephaly. Balestrazzi *et al*. suggested that if prepubertal macroorchidism is identified in the presence of intellectual disability, trisomy 20p should be considered as a differential diagnosis.[11] Developmental delay and learning difficulties are common, but the severity is variable. Children with large duplication including parts of 20q in addition to the whole of 20p may have more severe cognitive impairment. Early assessment and intervention may help children achieve their expected potential.[4] A literature search suggests that infants with 20p duplication who have no congenital anomalies of the major organ systems can have normal growth and development with healthy survival into adulthood.

Lessons learnt

- If a significant fall in saturation occurs during feeding, possible respiratory, GI, and neurological causes need to be looked for
- Protocol of an infant with overt anomalies demands searching for internal anomalies to define the clinical phenotype in entirety
- Genetic testing should be done in children with multiple congenital anomalies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's mother has given his consent for images and other clinical information to be reported in the journal. The patient's mother understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Fatty Liver in a Child: Looking beyond Nonalcoholic Fatty Liver Disease

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Abstract

Background: Cholesteryl ester storage disease (CESD) is a rare genetic condition caused due to deficiency of the enzyme lysosomal acid lipase (LAL). The condition is characterized by poor growth, dyslipidemia, and fatty liver. There is currently no data on the prevalence of this condition in the Indian population. It can easily be confused with nonalcoholic fatty liver disease (NAFLD). **Clinical Description:** We report the case of 4-year-old boy who presented to a pediatrician with poor growth. He was born to a nonconsanguineous couple with an uneventful perinatal period. The parents felt that the child was not growing well for 2 years. At presentation, he was hemodynamically stable and anthropometrically normal. He had pallor and hepatosplenomegaly. Rest of the examination was within normal limits. Preliminary workup showed persistent transaminitis. Further evaluation revealed dyslipidemia and hepatic steatosis in the liver fibroscan. The workup for other common causes of chronic liver disease was negative, and the clinical features were suggestive of CESD. Enzyme testing is required for the confirmation of this diagnosis, which was not available at our center or any outsourcing labs. **Management:** The diagnosis of cholesteryl ester storage disease was confirmed by next-generation sequencing (NGS) with multigene panel targeting the condition. At present, this child is in process to get registered for enzyme replacement therapy. **Conclusions:** LAL deficiency is a rare and difficult to diagnose entity. It should be considered as a differential diagnosis in children presenting with chronic liver disease with dyslipidemia and in lean children with NAFLD. For rare disorders where enzyme testing is not available, NGS can be utilized for diagnosis.

Keywords: Cholesteryl ester storage disease, dyslipidemia, lysosomal acid lipase deficiency, nonalcoholic fatty liver disease

Lysosomal acid lipase (LAL) is an enzyme involved in the metabolism and breakdown of cholesteryl esters and triglycerides. Lack of LAL leads to the accumulation of these substrates in the lysosomes of different tissues.[1] The most commonly affected organs and systems in which intracellular accumulation occurs are the liver, spleen, adrenal glands, hematopoietic system, vascular endothelium, intestines, and lymph nodes.[2] Cholesteryl ester storage disease (CESD) is a progressive metabolic liver disease due to LAL deficiency (LAL-D) caused by biallelic mutations in the lipase A, lysosomal acid type (LIPA) gene located on chromosome 10q23.2-23.3.1.[3] The inheritance is autosomal recessive. Storage of cholesteryl ester and triglycerides in hepatocytes and hepatic macrophages results in hepatomegaly, microvesicular steatosis, cirrhosis, dyslipidemia, and premature atherosclerosis.[4] The clinical phenotype depends on the type of LIPA gene mutation and the severity of enzyme deficiency.

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CESD is a rare condition. However, it is also quite likely that many Indian children with fatty liver do not get recognized or are misdiagnosed as nonalcoholic fatty liver disease (NAFLD) or cryptogenic liver disease, since getting the enzymatic assay is a challenging prospect and genetic testing is expensive. We report a child with fatty liver who was eventually diagnosed as CESD. The aim of sharing this case is to sensitize clinicians to think beyond the usual causes of fatty liver.

Clinical Description

A 4-year-old boy presented to our institute's liver clinic with parental concerns regarding poor growth and abdominal

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distension noticed for 2 years. The child was born to a nonconsanguineous couple at term, with an average birth weight. He had an uneventful perinatal period and was apparently growing well till 2 years of age. Since then, the parents felt that his growth had started faltering. They also noticed that his abdomen had gradually started to appearing increasingly distended. There was no history of abdominal pain, jaundice, swelling of the feet, blood in the vomitus or stools or from any other site, or diarrhea. The history was unremarkable; the child had not received any blood transfusion. Family history of similar illness in any other members or unexplained childhood death was absent. All developmental milestones had been attained appropriately and the child was immunized for age. His diet was adequate and diverse and intake of calories and proteins was age-appropriate. The child had undergone some baseline investigations before presentation and was detected to have persistently elevated transaminases. The diagnosis had not been ascertained which was the cause for referral.

At presentation, he was hemodynamically stable and alert. His height was 102 cm (*Z* score - 0.32) and weight was 14 kg (*Z* score - 1.23). There was no icterus or stigmata of chronic liver disease on general physical examination. The abdomen was uniformly distended. The liver was firm and palpable 4 cm below the costal margin in the midclavicular line. The spleen was firm and enlarged 2 cm below the left costal margin. There were no ascites. The rest of the systemic examination was normal. The clinical features in the setting of persistently elevated transaminases were suggestive of a chronic liver disorder (chronic persistent hepatitis). The differential diagnoses that were considered included Wilson's disease, viral hepatitis, and the possibility of storage disorders with hepatosplenomegaly, normal development, and onset in early childhood, such as nonneuronopathic Gaucher's disease, glycogen storage disorders, or LAL deficiency.

The salient laboratory investigations indicating liver involvement were elevated serum alanine transaminase (114 U/L) and aspartate transaminase (186 U/L). The lipid profile was deranged; raised serum triglyceride levels (515 mg/dl) and very low-density lipoprotein (83 mg/dl), normal total cholesterol (188 mg/dl) and low-density lipoprotein (74 mg/dl) levels and low high-density lipoprotein levels (30 mg/dl). Blood sugar levels, creatinine phosphokinase, and serum uric acid were normal. The absence of this biochemical triad and the presence of splenomegaly ruled out glycogen storage disorder. An abdominal ultrasound showed an enlarged liver (131 mm span) with increased echogenicity, splenomegaly, and a normal portal vein diameter of 6 mm. Thus, portal hypertension was also excluded. Common causes of chronic liver disease such as Wilson's disease, autoimmune hepatitis, and viral hepatitis were ruled out by the absence of abnormal serum ceruloplasmin, elevated autoimmune markers, and positive viral hepatitis markers, respectively. A Fibroscan (liver elastography) ruled out cirrhosis by detecting normal liver stiffness (4.5 kPa). However, the controlled attenuation parameter of 255 dB/m was suggestive of hepatic steatosis. The clinical phenotype of hepatosplenomegaly, dyslipidemia, and a fatty liver was indicative of a lipid storage disorder, and the possibility of CESD was considered. Confirming our suspicions was a challenge. The LAL enzyme assay is unavailable in India, and there were logistic issues in arranging transport of the sample abroad. A liver biopsy could have provided supportive evidence if lipid deposition had been detected, however, we were unable to convince the parents to give consent for a liver biopsy. Therefore, we decided to proceed with genetic testing.

Management and Outcome

Next-generation sequencing (NGS)-based multigene panel testing for the CESD-related genes was conducted. Targeted gene capture using a custom capture kit was followed by sequencing performed by the Illumina sequencing platform (Illumina Inc., San Diego, California, US). A homozygous silent variation in exon 8 of the LIPA gene (chr10:G.90982268C>T) was detected. These results in the synonymous amino acid change of glutamine at codon 298 proximal to the donor splice site (p.Gln298[=]). This observed variant lies in the alpha/beta hydrolase fold domain of the LIPA protein and has been previously reported in multiple patients affected with CESD[5,6] in the ClinVar database, 1000 Genomes, and Exome Aggregation Consortium databases. The *in silico* prediction of the variant is damaging by Mutation Taster 2. On confirmation of the diagnosis of CESD, the parents were counseled and supportive management started. At present, the child is in the process of getting registered for enzyme replacement therapy (ERT) with commercially available sebelipase alfa.

Discussion

LAL-D causes progressive liver disease. However, it is often mistaken for NAFLD due to the lipid deposition in the liver and the difficulties in establishing diagnosis due to lack of awareness among clinicians, coupled with the challenges of confirming diagnosis. The age of presentation is highly variable; some patients are diagnosed in childhood, while others remain undiagnosed until adulthood. LAL-D can have a wide spectrum of clinical presentations. The most severe form is Wolman disease which has LIPA activity <1%. Its clinical manifestations include infantile acute liver failure (usually presenting under 4 months of age), hepatosplenomegaly, failure to thrive, and ascites. Investigations reveal microvesicular steatosis and adrenal calcification.[7]

CESD presents in infancy, childhood, or adulthood, depending on the residual *in vitro* LAL activity, which typically ranges from 1% to 12% of normal. The progressive

accumulation of lysosomal cholesteryl ester and triglyceride leads to the characteristic liver pathology, fibrosis, micronodular cirrhosis, and ultimately to liver failure.[8] Affected individuals usually present with a more indolent course, poor growth (what was interesting to note in this case was that though one of the presenting complaints was the parent's perception that the child was growing poorly, his anthropometry was normal), unexplained hepatosplenomegaly, elevated transaminases, fatty liver, progressive, and/or unexplained chronic liver disease. The characteristic lipid profile is elevated serum LDL-cholesterol and triglycerides, with normal to low HDL-cholesterol concentrations. The causes of premature mortality are liver failure and/or accelerated atherosclerotic disease secondary to chronic hyperlipidemia. These phenotypic features (hepatic enlargement, transaminitis, and deranged lipid profile) of LAL-D are nonspecific and also observed in NAFLD, explaining the numbers of cases that are misdiagnosed or underdiagnosed. Liver histopathology is characterized by enlarged lipid-laden hepatocytes and vacuolated Kupffer cells, typical of microvesicular steatosis, which may also be mistaken for nonalcoholic steatohepatitis. The combination of fatty liver, elevated transaminases, and dyslipidemia can also mimic metabolic syndrome. We did not consider this as a differential in our patient as he was neither obese nor in the appropriate age range.

Confirmation of CESD is established by an enzyme-based biochemical blood test that demonstrates low or absent levels of LAL. This is available as a dried blood spot test in some countries, but not in India. NGS-based multigene panel testing identifies mutations in CESD-related genes. The most commonly inherited defect is the E8SJM (c.894G > A) mutation, which is found in more than 50% of affected children and adults with LAL-D, as in our case.[9] Although genotype/phenotype correlations are limited, E8SJM homozygotes typically have early-onset, slowly progressive disease. No therapeutic options were available until as recent as late 2015, when sebelipase alfa, a recombinant human LAL protein was approved as ERT for LAL-D.[1,10] Supportive treatment includes cholestyramine, statins, and ultimately, liver transplantation.

There is a paucity of community-based prevalence data on CESD from India and it is possible that cases are being missed. The diagnosis of CESD requires a high index of clinical suspicion. Given that there is overlap of clinical picture with NAFLD and metabolic syndrome, ERT with sebelipase alpha is now available, investigation for LAL-D should be included in second-line investigations more proactively. Awareness about this entity in Indian context combined with availability of efficient diagnostic tools should facilitate the correct diagnosis and institution of early therapy.

Lessons learnt

- Diagnoses other than NAFLD should be considered in children with fatty liver, especially in children who are very young at presentation or have a lean body habitus. LAL-D should be kept in differentials in such cases
- Easy availability of LAL-D blood spot test will help in unmasking of this entity in Indian children, till then, we can utilize NGS for diagnosing these rare cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Cecal Duplication: An Unusual Presentation

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Abstract

Background: Enteric duplication cysts are rare congenital malformations that are most commonly found in the ileum and ileocecal junction, followed by the esophagus, stomach, and duodenum. Although most present in the 1st 2 years, they are often difficult to diagnose as both presentation and radiological findings can be variable and nonspecific. **Clinical Description:** We present the case report of an 11-month-old child who presented with nonbilious vomiting and diarrhea. There was no fever, abdominal distension, blood in stools, or crying on defecation. A provisional diagnosis of acute gastroenteritis was kept and management started as per the standard protocol. **Management:** A series of investigations were carried out when the child did not improve and developed bilious vomiting. Ultrasound findings were suggestive of an ileal duplication cyst which was confirmed by magnetic resonance imaging. The child then underwent surgery where cecal duplication cyst was confirmed, which was previously missed due to a malpositioned cecum. **Conclusion:** Gastrointestinal duplication cysts are rare developmental anomalies that may present as an acute abdomen in a young child. The possibility of the duplication cyst should be kept as a differential diagnosis in a child presenting with unexplained vomiting, abdominal distension, or pain. Early suspicion, investigation, and intervention help in faster recovery with minimal complications.

Keywords: Cecal duplication, diarrhea, vomiting

Intestinal duplications are rare congenital malformations that are encountered in one out of 4000–5000 births.[1] They are found most commonly in the ileum and ileocecal junction (53%), followed by the esophagus, stomach, and duodenum.[2] Colonic duplications are infrequent, accounting for 13% of total cases.[2] These develop during the embryonic growth of the gastrointestinal tract during the 1st 6–8 weeks of the development. Only a minority are diagnosed prenatally (20%–30%), but the most common age of presentation is during infancy (70%).[3] Clinical presentation and radiological findings are variable and nonspecific, leading to delayed diagnosis. Only a quarter are diagnosed preoperatively.[3] Clinical manifestations depend on the location, size, and type.

A cecal duplication cyst usually presents with abdominal distension followed by vomiting. It is rare for a cecal duplication cyst to present with the features of acute gastroenteritis. This case offers an atypical presentation of a cecal duplication cyst due to its abnormal location that was identified intraoperatively.

Clinical Description

An 11-month-old boy presented to our emergency department with 36-h history of persistent vomiting and one episode of loose stools. Before coming to us, his parents had taken him to another health-care facility, where he had been prescribed antiemetics and oral rehydration solution (ORS) and sent home. However, the vomiting continued and the frequency of watery stools increased. The vomiting was nonbilious and nonprojectile. The child did not cry while defecating. There was the absence of blood or mucus in the stools and no bleeding per rectum. There was no history of fever or symptoms suggestive of acute intestinal obstruction such as abdominal distension, discomfort, and obstipation. The child had an adequate urine output. Child was not lethargic though the activity was reduced than normal.

On general examination, vitals were stable with no signs of dehydration. Anthropometric measures showed

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stunting with other growth parameters within normal range (weight: 8.28 kg [0–2 standard deviation (SD)], length: 68.5 cm [-2SD-3SD], and weight for length 0- +1SD). There was no pallor, icterus, or lymphadenopathy. Per abdomen examination did not reveal any abdominal distension or tenderness on palpation. Bowel sounds were normal, and no mass could be palpated per abdomen. A per rectal examination was performed to look for currant jelly stools, and the result was normal. Other systemic examinations were within normal limits.

We kept a provisional diagnosis of acute gastroenteritis with and started the child on intravenous fluid, antiemetics, zinc, and ORS along with feeding. At 18 h of admission, the child had an episode of bilious vomiting, following which further investigations were planned to rule out obstruction.

Management and Outcome

Baseline complete blood count, C-reactive protein, renal function test including serum electrolytes, and liver function test were normal (hemoglobin: 11.5 mg/dl, total leukocyte count: 12100 cells/cumm, platelet count: 5.14lakh/cumm, C-reactive protein: 3.5 mg/dl, blood urea: 21.6 mg/dl, serum creatinine: 0.36 mg/dl, serum sodium: 137 mg/dl, and serum potassium: 4.7 mg/dl), and a routine stool test to look for adenovirus and rotavirus was negative.

A radiographic examination of the abdomen revealed large, dilated bowel loops. The ultrasound of abdomen showed a thick-walled cystic lesion in the right hypochondrium [Figure 1], with a typical gut signature sign of the intestinal wall. Magnetic resonance imaging of the abdomen was done as it provides excellent soft-tissue resolution and anatomical orientation. It confirmed the presence of a well-defined lobulated cyst at the level of hepatic flexure [Figure 2]. These findings suggested an ileal duplication cyst due to its location and presentation.

Surgery was planned, and preoperative examination under anesthesia revealed a mass in the hypochondrium. We could not feel the mass on routine palpation as it was deep, and the child was not very cooperative before giving anesthesia. Intraoperatively, the cecum was noted to be enlarged, mobile, and subhepatic in position, with a spherical cyst attached to the cecal wall and filled with serous fluid. The cecal cyst was compressing the adjacent stomach and intestines, causing proximal dilatation. There was no associated malrotation. The cecum with the cyst, appendix, and terminal ileum was resected, followed by end-to-end anastomosis. Histopathological analysis confirmed the diagnosis of a cecum duplication cyst based on the presence of a common single outer muscular layer and an innermost lining of the gastrointestinal mucosa. Following an uneventful postoperative period of 10 days, the child was discharged. Other structural anomalies were not found in a more in-depth evaluation of other systems. The child has been in follow-up for a year and has remained well.

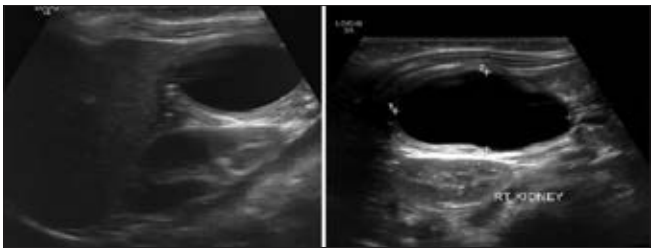

Figure 1: Ultrasonography abdomen showing a thick-walled cyst in the right hypochondrium close to the inferior margin of the liver at the level of the right kidney measuring 4.3 cm × 2.4 cm × 2.5 cm in size

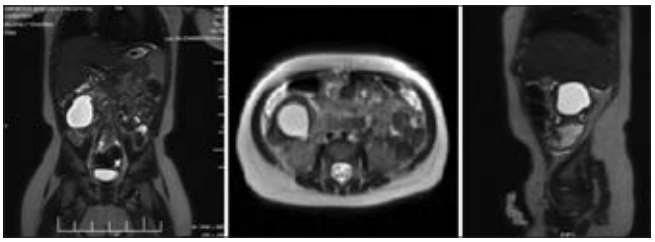

Figure 2: Coronal, axial and sagittal view of abdomen showing a well-defined lobulated cyst in the right hypochondrium, adjacent and medial to the inferior margin of liver at the level of the hepatic flexure

Discussion

The essential features of an enteric duplication cyst include a well-developed smooth muscle coat; mucosal lining found within some portion of the alimentary tract; and attachment or communication with any segment of the alimentary tract.[1] Although rare (13%), colonic duplications are primarily associated with the transverse colon and are uncommon in cecum accounting for 0.4% of all gastrointestinal duplications.[2] Only 20 such cases had been reported in the literature.[4] The etiopathogenesis of these malformations is still unknown. However, the various hypotheses include splitting of the notochord during *in utero* development, perseverance of fetal enteric diverticula, vascular occlusion in the intrauterine period, and the failure of recanalization of the intestine. Enteric duplications may be cystic, tubular, or mixed. Cystic colonic duplications are usually not associated with other anomalies, whereas tubular colorectal duplications are often associated with genitourinary, vertebral, and other structural anomalies.

Up to 80% of duplications are identified before 2 years of age. They can mimic intussusception (waxing-waning abdominal pain, vomiting, and passage of red currant stools); we found four case reports of cecal duplication mimicking intussusception[5] or malrotation/volvulus (abdominal pain and distension with vomiting and obstipation). A duplication cyst can cause recurrent episodes of abdominal pain and vomiting in infancy. Proximal intestinal lesions usually present with vomiting as an early symptom. In contrast, distal lesions present with abdominal distension and constipation. Vomiting usually does not occur. Colonic duplications tend to present later in life compared to other sites with symptoms of distal

intestinal obstruction.[6] In our case, nonbilious vomiting was the only symptom that led to further evaluation for the proximal intestinal lesions. Even the radiological investigations suggested the same. Distal intestinal involvement was identified only intraoperatively. The atypical presentation of symptoms despite being located in the large bowel was due to the cecal malposition. The cecum was mobile and subhepatic, which when distended, had led to compression of the stomach, leading to the vomiting.

A literature search revealed six cases of malrotation associated with enteric duplication. All of them were jejunal and ileal duplications that presented with the symptoms of upper intestinal obstruction in the newborn period.[7] Somuncu *et al*. reported malrotation and jejunal duplication in a 2 years old who had intermittent vomiting.[8] Although the cecum was mobile and subhepatic in this case, the duodenojejunal flexure was in the proper position that ruled out malrotation. We found only one similar case in the literature in a newborn with intestinal duplication and a malfixed right colon.[9] Kibayashi *et al*. also reported a similar case in an infant who died with complications from a duplication cyst, after being misdiagnosed as gastroenteritis.[10]

Detection and diagnosis of enteric cysts can be difficult, as their symptoms vary significantly and can reflect a broad spectrum of gastrointestinal conditions, medical and surgical. In our case, we were unable to appreciate a mass clinically, probably due to its deep location. Atypical surgical malformations can present with gastroenteritis. In this case, the character of vomitus was initially nonbilious, presumably because the cecal duplication cyst was abnormally high and compressed the stomach. It is possible that the transgressions in intestinal contraction and the increase in the intestinal content led to the obstruction of the intestine, causing bilious vomiting later. Ultrasound is the most used investigative approach for abdominal imaging in children. The classical sonographic feature is a double wall or muscular sign (innermost hyperechoic mucosa and external hypoechoic muscularis propria) called "gut signature sign." MRI provides excellent soft-tissue resolution and anatomical orientation and helps to establish the correlation between the cyst and adjacent structures before surgery.

Surgical excision is recommended even in asymptomatic cases. A classic laparotomy approach is the modality of choice, but there are reports of successful, less invasive techniques such as laparoscopy.[10] Adjacent normal bowel requires resection in addition to the cyst, as they share the same muscular wall and blood supply. In this case, we removed the terminal ilium, appendix, and cecum due to the presence of a common muscular wall and vascular supply. When the structures have an independent blood supply, they can be resected in isolation. The resection should be complete; otherwise, there is a chance of recurrence. Our case highlights a unique point of proximal intestinal obstruction secondary to a cecal duplication cyst due to the abnormal location of the cecum.

Lessons learnt

- High index of suspicion for surgical causes to be kept in a young child presenting with vomiting.
- Repeated abdominal examinations should be performed to look for a mass, as they may appear later.
- A low threshold should be kept for imaging studies in a young child presenting with gastrointestinal symptoms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Neonatal Marfan Syndrome Due to Missense Mutation in Exon 26 of FBN1 Gene

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Abstract

Background: Neonatal Marfan syndrome (MFS) lies at the most severe end of the MFS clinical spectrum, sharing some characteristics of MFS, but with a more severe clinical phenotype, slightly variable genotype, and a poor prognosis. We report a case of neonatal MFS diagnosed antenatally and in whom diagnosis was established postnatally by clinical exome sequencing. **Clinical Description:** A routine antenatal ultrasonography identified a dilated aortic root, oligohydramnios, fetal femur, and long bones length >99th percentile for the period of gestation findings in a fetus at 35 weeks of gestation. The baby was born by a cesarean section due to nonprogress of the labor. At birth, he had multiple anomalies including bilaterally cloudy cornea, bluish sclera, long slender fingers, hyperflexion of the wrist, ankle joints, and pulsatile precordium. **Management:** The patient developed severe respiratory distress immediately after birth and was intubated and initiated on positive pressure ventilation. The baby was supportive of fluid and inotropic management. The diagnosis was established based on characteristic echocardiographic findings and identification of a likely pathogenic variant disrupting the p.Cys1068 amino acid residue in FBN1, located at exon 26, which is the "neonatal" region known to be associated with neonatal MFS. The baby succumbed. **Conclusion:** Although neonatal MFS has a poor prognosis, multidisciplinary intervention is required to determine the best course of action.

Keywords: Marfan syndrome, neonate, prenatal

In 1896, Antoine Marfan described Marfan syndrome (MFS) as an autosomal dominant connective tissue disorder that exhibits characteristic musculoskeletal, ocular, and cardiac manifestations.[1] There is variability in the clinical manifestations and the life expectancy of untreated, affected individuals is reduced (~32 ± 16 years). Neonatal MFS, a related clinical condition, lies at the extreme end of the MFS clinical spectrum. In terms of severity, though it does share some characteristics of MFS, it displays unique manifestations, in terms of clinical phenotype, genotype, and prognosis. The most salient features apparent from birth include musculoskeletal (arachnodactyly, flexion deformities, hyperextensible joints, anterior chest deformity, and dolichocephaly), characteristic facies (high-arched palate, micrognathia, and crumpled ears), ocular anomalies (iridodonesis, megalocornea, and dislocated lenses), and loose skin giving a "senile" appearance.[2,3] Cardiac involvement is more severe and presents much earlier in neonatal MFS. Mitral and/or tricuspid valve insufficiency is the common causes of neonatal or infantile congestive cardiac failure in contrast to aortic and aortic root involvement in classical MFS.[1,2] Respiratory complications include infantile pulmonary emphysema in neonatal MFS.[3]

Prenatal diagnosis is often incidental and suspected based on ultrasonic findings. Since neonatal MFS is caused by a number of diverse *de novo* genetic mutations, prenatal genetic testing becomes challenging.[4] The prognosis is poor and most children do not survive without cardiovascular surgical correction of the major cardiovascular congenital anomalies. Nonetheless, multidisciplinary collaboration between the obstetrician, fetal medicine specialist, radiologist, neonatologist, cardiologist, cardiovascular surgeon, and geneticist is critical for attaining the best possible outcomes.

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We report a case of neonatal MFS that was suspected on an ultrasonogram performed in the third trimester, in whom the diagnosis was confirmed postnatally by genetic testing.

Clinical Description

A booked primigravida with a hitherto uneventful antenatal period underwent a routine third-trimester ultrasonogram in the 35th week of gestation for monitoring fetal growth parameters. Radiological findings of the length of the fetal femur and long bones >99th percentile for the gestational age and a dilated aortic root, with oligohydramnios were suggestive of MFS. The Doppler study of the umbilical artery, middle cerebral artery, ductus venosus, and uterine arteries was normal. The parents were counseled, and the mother was closely monitored by the obstetrician for the remaining pregnancy. The mother was hospitalized, and the neonatal intensive care unit (NICU) informed when she went into labor at 39 weeks of gestation. A lower segment cesarean section was performed due to nonprogress of labor. A term appropriate for age baby boy was born with a birth weight of 2675 g and Apgar scores of 6 and 9 in the 1st and 5th min, respectively. The baby had a weak cry, multiple congenital anomalies (described later), and displayed generalized hypotonia. The baby developed severe respiratory distress immediately after birth. He was transferred to the NICU suspecting congestive heart failure or congenital pulmonary emphysema, both known complications of neonatal MFS. There was no significant family history of any previous unexplained neonatal, infantile, or sudden adult death or any family member with an unusual appearance or cardiac disease.

Management and Outcome

The baby was in cold stress (temperature 36.4F) and cyanosed on being received in the NICU. He had severe respiratory distress with respiratory rates of 64/min, chest retractions, a Silverman Anderson score of 8, and oxygen saturation of 70% in room air that increased to only 82% with 100% oxygen support. The capillary refill time was >3 s, peripheral pulses were of low volume, and noninvasive blood pressure was 48/32 mmHg with a mean BP of 38 mm Hg. Anthropometry was not taken as the baby was intubated immediately and positive pressure ventilation initiated with synchronized intermittent mandatory ventilation mode. The random blood sugar was 64 mg/dl, and arterial blood gas analysis revealed metabolic acidosis, hypoxia, and hypercarbia (pH 7.14, PCO2 63.9, PO247, and HCO3 20.6). Fluid management of the peripheral circulatory failure proceeded as per the standard protocol. A detailed examination was challenging in the given circumstances. The dysmorphic features that were apparent on general physical examination are listed in Table 1 and appreciable in Figure 1. Significant systemic examination findings included a visibly pulsatile precordium with a holosystolic murmur heard at the left lower sternal border, and the absence of abdominal organomegaly. We were unable to perform an in-depth ocular evaluation. Referring to Faivre *et al*,[5] and considering the recent Ghent's criteria.

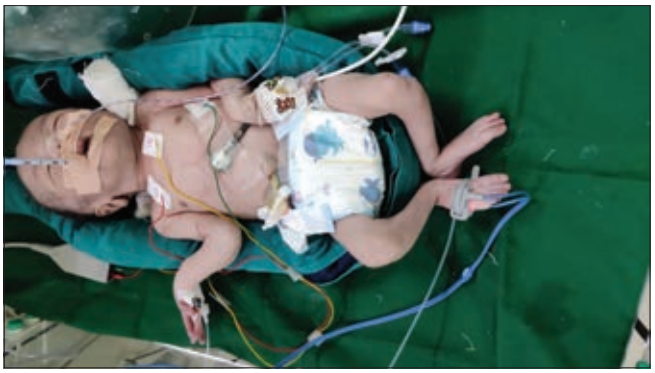

Figure 1: Long slender fingers, loose skin

Table 1: Clinical features of neonatal Marfans syndrome

Features present in the patient	Features not present/ could not be assessed
Long slender fingers hyperlaxity of the wrist and ankle joints	Pes planus
Elbow and knee joint contractures	Dolichocephaly
Redundant loose skin	Pectus excavatum
Bilaterally cloudy cornea and bluish sclera	High-arched palate
Tricuspid and mitral valve prolapse, severe tricuspid, and moderate mitral regurgitation	Scoliosis
	Iridodonesis
	Megalocornea

A chest X-ray revealed bilateral hazy lungs but no evidence of emphysema. Salient bedside 2D echocardiogram findings included severe tricuspid regurgitation, moderate mitral regurgitation (MR) due to tricuspid, and mitral valve prolapse, a moderate-sized (2.5 mm) patent ductus arteriosus (PDA) with the left to right shunting, dilation of the right atrium and right ventricle, and severe pulmonary artery hypertension. The other vascular structures (coronaries, aortic valve, arch of aorta, pulmonary valve, and pulmonary artery) were normal. Hematological and biochemical investigations were normal.

The clinical diagnosis of neonatal MFS was suspected based on the antenatal radiological phenotype, clinical phenotype, and echocardiographic findings, and a sample for clinical exome sequencing (CES) was sent for analysis. Unfortunately, the baby succumbed at 24 h of life despite escalating ventilatory and inotropic support. It had already been decided that surgical intervention would not be undertaken. CES revealed a likely pathogenic variant disrupting the p.Cys1068 amino acid residue in FBN1, located at exon 26. The patient was heterozygous for this missense mutation which causes the nucleotide thymine (located at position 3202 in exon 26 of FBN1 gene on chromosome 15), to convert to the nucleotide guanine. The final diagnosis was neonatal MFS due to the presence of the missense mutation in exon 26 of the FBN1 gene, and the parents were offered genetic counseling.

Discussion

The most (86.4%) neonatal MFS mutations are found within the exon region 24–33,[6] in contrast to that of classic and

incomplete MFS, which is only 17.4% in the same region. Neonatal MFS may rarely arise due to the mutations outside this region. A literature search revealed three case reports; twice in exon 4 and once in exon 21.[1] This newborn had a heterozygous missense mutation in exon 26 that caused the ultimate amino acid sequence to change from cysteine to glycine at codon 1068. Cysteine residues are believed to be involved in the formation of intermolecular disulfide bridges within the FBN1 protein structure. Missense substitutions affecting cysteine residues within these domains are significantly overrepresented among patients with MFS and mutations in exons 25–26 are associated with shorter survival.[6]

The clinical diagnosis of MFS can be made based on the defined parameters, the "Ghent criteria." According to this, any patient fulfilling certain combinations of aortic dilation, ectopia lentis, systemic features, family history, and FBN1 mutation can be diagnosed as MFS based on a scoring pattern.

These have been developed to facilitate recognition and improve patient management.[7] Stheneur *et al*. showed that valvular insufficiencies, diaphragmatic hernia, and mutations in exons 25 and 26 are associated with worse prognosis in infants with MFS.[8] Our patient had mitral valve prolapse, with severe tricuspid, and moderate MR and a moderate-sized PDA. PDA is rarely seen in neonatal MFS and is associated with risks of aneurysm formation, rupture, and acceleration of aortic dilation.[6]

Bender *et al*, reports that the earliest possible sonographic findings leading to a suspicion of neonatal MFS are femur length >95% at 22 weeks.[4] It may also be suspected in instances of unexplained development of dilated cardiomyopathy in the third trimester[9] Earlier diagnosis is possible in cases of familial MFS with a preidentified disease-causing allele by Chorionic Villous Sampling at 10–12 weeks of gestation, and amniocentesis at 15–18 weeks of gestation, though the disease spectrum and severity cannot be ascertained,[4] and it is not possible to establish whether the phenotype will be neonatal or classical MFS.[10] Early recognition of neonatal MFS is vital to allow for attempted multidisciplinary planning and prognosis modification, though the prognosis is usually quite grim, especially in developing countries where availability and access to tertiary level institutes with state of the art cardiothoracic-vascular surgical facilities are limited.[1] Medical therapy of congestive heart failure arising from the cardiac lesions is often unsuccessful, without surgical intervention. Heart surgery is complex and carries a high risk of mortality and morbidity. Parents must be counseled beforehand and involved in making an educated decision regarding the course of action after birth.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Lessons learnt

- The clinical phenotype, genotype, and prognosis of neonatal MFS differs greatly from classical MFS
- Incidental prenatal diagnosis of neonatal MFS can be made by finding the length of long bones exceeding >95% of the expected for the gestational age
- Management of neonatal MFS requires a multidisciplinary team.

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Conflicts of interest

There are no conflicts of interest.

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Abrupt Onset Tiny Pigmented Macules on Soles Caused by Cydnidae Bugs

A 6-year-old boy presented with the sudden appearance of multiple, small, dark brown lesions on both soles for a day. Thinking that they were due to sort of staining, the mother tried scrubbing them off with soap and water, but to no avail. They were not associated with pain, itching, abnormal sensations, discharge, or previous lesions in the same areas. There was no history of fever, joint pain, trauma, drug intake, or wearing new footwear. History of lesions elsewhere (including the mouth) or similar lesions in the past was not found. The child had a habit of roaming around inside and outside the house without footwear.

Examination revealed multiple blackish-brown macules of size ranging from 1 to 3 mm which were nonscaly and nonblanchable. The macules had sharply defined margins, irregular shapes, and no particular pattern of arrangement [Figure 1]. There was no other mucosal or skin involvement. Systemic examination was unremarkable. Complete blood counts, coagulation profile, and liver function tests were normal. Dermatitis neglecta, post-inflammatory hyperpigmentation, and lentignes were considered and disregarded due to history of daily bathing, absence of preceding lesions, and mismatch in morphological appearance. The lesions disappeared spontaneously after 4 days. Based on the characteristic onset, spontaneous resolution, absence of associated systemic features, and normal investigation reports, a diagnosis of Cydnidae pigmentation was made.

Cydnidae pigmentation is the appearance of asymptomatic discoloration overexposed parts of the body (usually palms and soles) due to contact with the "Cydnidae bug" (burrowing bug) or *Chilochoris assmuthi Breddin*, that belongs to the order Hemiptera. These winged, low flying insects are found in the soil of vegetation-rich areas adjoining human dwellings, especially during the rainy season. They release a chemical substance from their glands which result in staining of the human skin and present as pigmented macules.[1] Pigmentation can also occur when the insect is rubbed between the index finger and thumb.[2] The stains can be removed with acetone or resolve spontaneously within a few days. Only few cases have been reported till date. We are reporting this case to increase awareness among clinicians who can reassure parents and alleviate their anxiety, as well as avoid unnecessary investigations and treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parent has given his consent for images and other clinical information to be reported in the journal. The parent understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

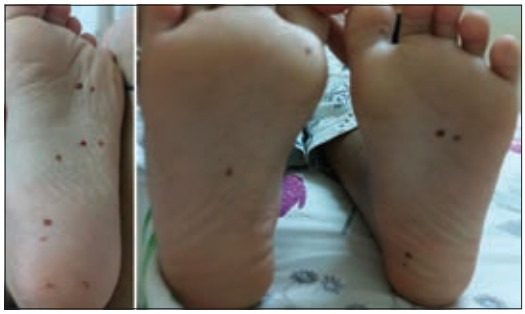

Figure 1: Freckle-like hyperpigmented macules over the sole

Conflicts of interest

There are no conflicts of interest.

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Infantile Hemangioma Treated with Systemic Propranolol

Infantile hemangiomas (IHs) are benign vascular tumors of infancy and childhood with unique clinical and histopathologic features[1]. They appear in the first weeks or months of life and display a characteristic natural history; rapid growth in the first 1–3 months followed by gradual involution. Tissue biopsies are positive for immunohistochemical staining with erythrocyte-type glucose transporter protein and other biomarkers specific for IH. The classification is according to soft-tissue depth (superficial, deep, and combined) and pattern of anatomic involvement (localized, segmental, multifocal, and indeterminate). The prevalence is reportedly 0.1% to 0.3%[2]. Most IHs are small and innocuous, resolve spontaneously, and require no treatment. However, a small proportion are considered potentially problematic. These include lesions that may result in scarring and disfigurement (e.g., facial), hepatic or airway IHs, and lesions which cause functional impairment (e.g., periorbital), ulceration, and are associated with vascular abnormalities within the cranium or in the aortic arch.

A 9-month-old healthy boy presented with a single, large (10 cm × 10 cm) vascular lesion extending over the right temporal scalp, and pre- and postauricular area [Figure 1a]. Although it had been present since birth, the parents had become concerned due to the recent episodes of bleeding and formation of raw areas on the surface of the lesion. Examination of the morphological features led us to make a diagnosis of a deep, segmented IH. The level of risk was considered high due to the presence of ulceration and disfigurement[1]. The location on the face and large size was an indication for neuroimaging. Magnetic resonance imaging of the brain revealed extracalvarial altered signal intensity lesion with few tortuous voids and a dilated tortuous feeding artery entering the lesion [Figure 2a and b].

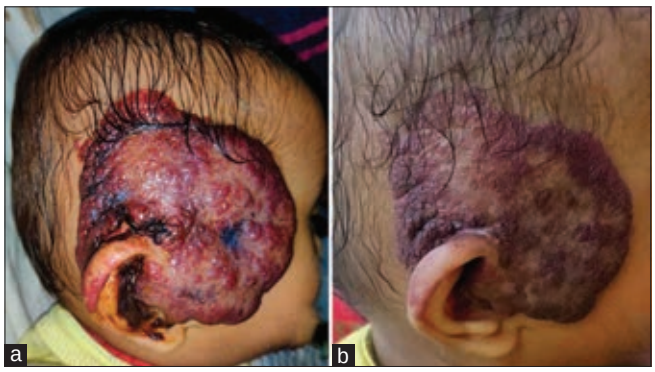

Figure 1: (a) Large infantile hemangioma with oozing, bleeding, and crusting (b) Regression of the plaque with a decrease in vascularity at 12 weeks

As per the international recommendations, and since the infant had no respiratory or cardiovascular contraindications[1], he was started on systemic propranolol. The hypothesized mechanism of action of propranolol is inhibition of vasodilation via beta-receptors. This causes vasoconstriction, reduces capillary blood flow, induces apoptosis in the endothelial cells, and results in regression of the tumor[3,4]. The infant was initially primed with Prednisolone for 2 weeks. When compared with propranolol without steroids, this strategy has been shown to demonstrate superior reduction in size in the early stages, though the ultimate resolution of size at 6 months is similar. Management is usually started in early infancy. Oral propranolol was started as per recommendations (initially 1 mg/kg/day with meals and increasing it to 2 mg/kg/day) after ensuring baseline cardiac investigations were normal. The infant was kept in close follow-up and monitored for common complications (hypoglycemia, bradycardia, hypotension, and bronchospasm). The initial plan was to continue for at least 6 months or till regression of the lesion, whichever earlier. The lesion regressed within 4 months without any complications [Figure 1b]. The child is still in follow-up for occurrence of rebound lesions. Parents have been counseled and told to seek an opinion for laser surgery for the residual lesion by 5 years of age if the residual lesion still persists.

Declaration of patient consent

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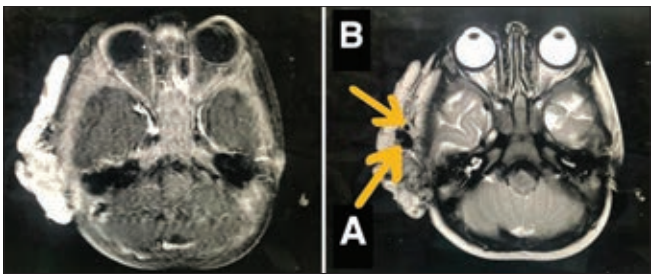

Figure 2: Magnetic resonance imaging brain (T2+ contrast and fluid-attenuated inversion recovery sequence) showing a few tortuous voids (A) and a dilated tortuous feeding artery (B) entering the lesion

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Cerebrospinal Fluid Rhinorrhea in a Child with Recurrent Pyogenic Meningitis

A 9-year-old female child was brought with complaints of fever, headache, and vomiting for the past 2 days and altered sensorium for the past 1 day with history of previous hospitalization for fever, persistent headache and persistent nasal discharge for 3 months [Figure 1]. She was diagnosed to have acute bacterial sinusitis secondary to allergic rhinitis. The child had no h/o trauma or previous surgeries. On examination, she had low Glasgow Coma Scale (GCS) (12/15) and had signs of meningeal irritation. Laboratory parameters showed neutrophilic leukocytosis and raised a C reactive protein (CRP) of 226.7 mg/dL suggestive of bacterial infection. Cerebrospinal fluid (CSF) analysis showed a turbid fluid with laboratory features, suggestive of pyogenic meningitis. During the hospital stay, the child was observed to have a continuous watery nasal discharge from right nostril suggesting CSF rhinorrhea (Video 1 (video available from: *https://www.ipcares.org/articles/2021/1/3/images/IndianPediatrCaseRep_2021_1_3_205_325088_sm2.mp4*)). Contrast-enhanced magnetic resonance imaging brain showed nasal meningoencephalocoele in the anterior cranial fossa.

CSF leaks are extracranial egress of CSF into the adjacent paranasal sinuses or tympanomastoid cavity due to an osteodural defect involving skull base. It may be due to many causes such as iatrogenic (endoscopic sinus surgeries, neurosurgical procedures), accidental trauma, and congenital malformations such as basal cephaloceles.[1] Most of the times, it is misdiagnosed as allergic rhinitis.[2] Patients with CSF rhinorrhea are at risk of developing recurrent meningitis due to spread of infection from the sinonasal cavity. There are many tests to confirm CSF rhinorrhea and to differentiate from nasal discharge such as handkerchief test showing halo sign, reservoir sign, and biochemical analysis of the nasal fluid. Neuroimaging confirms the site of leak.[3]

Figure 1: Clear, watery discharge (CSF) draining from the right side of the nose on sitting upright tilting the head forward

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Peristaltic Waves: A Clinical Clue of Infantile Hypertrophic Pyloric Stenosis

A 6-week-old male child was admitted with recurrent episodes of vomiting after breastfeeding for 10 days. Initially, the vomiting was nonbilious but had recently become projectile. There was no history of fever, diarrhea, jaundice, or lethargy. Despite being always hungry and vigorously suckling when breastfed, there was a significant history of loss of weight since birth (weight 3270 g). Urine output was normal. At admission, weight was 2515 g. The baby was severely dehydrated. Peristaltic waves moving from the left to the right side of the upper abdomen were observed [Figure 1 and Video 1 (video available from: *https://www.ipcares.org/articles/2021/1/3/images/IndianPediatrCaseRep_2021_1_3_206_325087_sm2.mp4*)]. However, an olive-shaped mass was not palpable in the abdominal midline. Hypochloremic, hyponatremic, hypokalemic metabolic alkalosis was found, with elevated urea and creatinine levels. Dehydration correction was started. Infantile hypertrophic pyloric stenosis (IHPS) was suspected which was confirmed when an abdominal ultrasonogram detected a thickened pylorus muscle with elongated pyloric canal. The baby underwent laparoscopic pyloromyotomy successfully and has been thriving in follow-up.

IHPS is the most common cause of gastric outlet obstruction in infancy and one of the most common causes of surgery in a young infant.[1] The classic triad described in this condition is visible peristalsis, palpable pyloric mass, and projectile vomiting. However, their simultaneous occurrence is rarely seen, as in this case.[2] A palpable mass is seen in 60%–80% of cases. Peristaltic wave is because of attempted forceful movement of the gastric contents past the narrow pyloric canal and is an important clue for early diagnosis.[3]

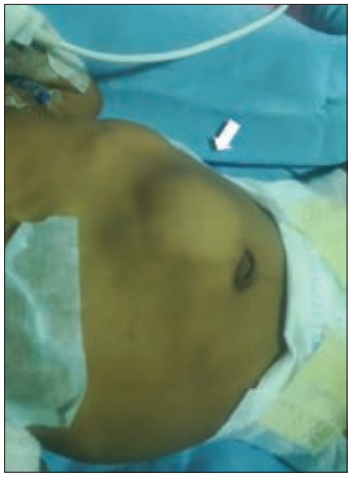

Figure 1: A wavelike elevation observed on the left upper abdomen. The peristaltic wave moved to the right side

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Managing a Child with Epilepsy: The Value of Primary Care and Three-Stage Assessment

Epilepsy is defined as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. It is estimated that, in India alone, about 10 million people suffer from epilepsy. The prevalence of epilepsy in rural areas is almost twice that seen in urban areas (1.9% vs. 0.6%).[1] However, it is estimated that almost 70%–90% of epileptic patients are either untreated, inadequately treated, or noncompliant.[1] Multiple factors contribute to this: nonrecognition that epilepsy is a medical illness, inability of families to access specialized care, challenges in managing epilepsy, and lack of coordination between primary care level and specialized health care.

In this issue, we discuss the case study of a child from a rural area, who presented to our clinic with a history of seizures. The purpose of highlighting this case is to illustrate the value of primary care and three-stage assessment in managing children with epilepsy.

Case Study

R, a 12-year-old girl, was brought to our clinic by her parents who resided in Morwal, a remote, rural village with no telephone connectivity, about 35 km from Udaipur city. Her presenting complaints were convulsions for 4 months; the episodes were associated with the loss of consciousness along with stiffening and jerky movements of the limbs, lasted for less than a minute, and occurred around 3–4 times/day. In between events, the child was alert, active, and had no difficulties in participating in her routine activities. There was no history of headaches, vomiting, fever, or ear discharge. There was no history of similar episodes, head injury, febrile illness with altered sensorium in the past, or febrile convulsions in childhood. She was born in a health center, had apparently attained all milestones at the appropriate age, and immunized. She had been living with her maternal aunt in the city for a year so that she could pursue her studies in class 6 in a school there but had been sent back to her village due to her illness. Her academic performance was average and was right-handed. Since coming home, she was spending a lot of time watching television or on the mobile. Menarche had not been attained. She was the second in birth order out of three siblings. There was no family history of epilepsy in the immediate family. Her father was an employee at the local liquor store, and her mother was a homemaker.

On examination, her height was 140 cm (−1.18 standard deviation [SD]), weight 28.9 kg (−1.52 SD), and body mass index 14.7 (−1.24 SD). Her vital parameters including blood pressure were normal. There was no overt dysmorphism or the presence of neurocutaneous markers. Her sensorium was normal and higher functions intact. There was no cranial nerve or focal neurological deficits or signs of meningeal irritation. Hearing and vision were normal.

We encouraged the family to seek a neurological consultation and to get an electroencephalogram (EEG) and magnetic resonance imaging (MRI) from a referral hospital. However, her father was unable to get leave for a few weeks. In view of these circumstances, a normal neurological examination, and the absence of history suggestive of any secondary illness, we kept a presumptive diagnosis of idiopathic generalized epilepsy and started her on sodium valproate. She was advised to limit her screen time. A few weeks later, an MRI of the brain (epilepsy protocol) revealed focal, abnormal, signal intensity in the right frontal lobe in the periventricular region that appeared hyperintense on T2-weighted and FLAIR images. An EEG showed paroxysms of generalized spike and wave, with an amplitude of 200–300 mV. The background activity was synchronous and symmetric, consisting of 8–9 Hz waves that were maximally seen over the posterior region. Hyperventilation and photic stimulation produced no significant changes. This confirmed our diagnosis, and she was asked to continue on the same dose of anticonvulsants and remain in close follow-up.

However, over the next few months, she was unable to visit regularly due to the distance, cost of travel, and inability of her father to get leave. This led to break in continuity in medication and poor seizure control. When she presented back to us 3 months later, she was still having 2–3 convulsions/day, each lasting for a few minutes. We decided to take over the prime responsibility of managing the child by ensuring the availability of antiepileptics and fortnightly follow-up visits to our clinic. With proper counseling and assurance that her antiepileptic drugs will be provided at the clinic (which was close to her home), her compliance improved, and seizure frequency decreased to one episode every 2–3 days.

A three-stage assessment was conducted to understand the family and social circumstances and determine factors that may have an impact on her condition.[2] This included the details that had been ascertained from her clinical assessment (history, examination, and established diagnosis), assessment of R (her thoughts, ideas, feelings, concerns, and fears), and contextual assessment (with respect to her family and home). R had been living away from her family, with her aunt in the city for a few months. Even after returning to the village, she was staying with her maternal grandmother and not her own family, due to a stressful environment at home. R felt that she was

neglected because she was the second consecutive girl child. This resentment emerged in the form of anger and aggression directed at her family members. Her parents complained that she did not help with the household chores and that she had to be reprimanded often.

The clinic team and visiting physician consistently counseled and sensitized the family members individually about the condition and challenges that R faced. Extra efforts were obtained to actively listen to R and support her emotionally. Gradually, we noted that this resulted in her gaining more confidence and the family members becoming more aware of her emotional needs and displaying greater empathy toward her. Her compliance with the medication became absolute. Her screen time reduced significantly with gentle but repeated counseling at each visit. She has been seizure free for 6 months. Improved compliance, family support, and improvement in the home environment, all appear to have contributed to this. Her mood appears uplifted and her attitude positive when she comes to the clinic. She has resumed her studies. Her family reports that she is much calmer and helps out at home. The image on the front cover (social pediatrics) shows the child, her grandmother and one of our team members.

Discussion

In the 21st century India, the status of children with epilepsy in rural areas is just not acceptable. In 2015, the World Health Assembly passed a resolution to address the treatment gap in epilepsy and exhorted the member states to integrate epilepsy management in primary care.[3] This case study illustrates the value of primary care that is closer to the families, affordable, responsive to their needs, and understand their circumstances, with context to the management of epilepsy in children. In this case, the primary healthcare service (our clinic), was able to diagnose, treat, and follow-up R, in conjunction with the referral hospital. If the child had been dependent only on the latter, she would have remained inadequately treated. Better coordination between two levels (e.g., appropriate back-referral from the specialist care to primary care) can definitely improve the treatment course.

A three-level assessment is the basic principle and practice of family medicine and primary care. It includes clinical assessment (all aspects needed to establish the diagnosis), individual assessment (thoughts, ideas, feelings, concerns, and fears of the concerned patient), and contextual assessment (with respect to family and the work context). In this case, the three-level assessment revealed the identification of anger of the child as well as lack of understanding and empathy of the family toward her. Supporting the child and counseling the entire family helped us address the underlying household stress and likely contributed to the improvement in compliance to treatment and improved clinical outcomes. It is well-established that stress can trigger convulsions and hamper seizure control in epileptic patients.[4]

Moving ahead, to meet the treatment gap for childhood epilepsy, there is an urgent need to equip primary care providers with skills to identify and manage, to ensure the availability of antiepileptic drugs, and to improve the coordination between specialist care and primary care. It is a moral imperative for pediatricians and neurologists to decentralize the management of epilepsy.

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Pattern Recognition of Bizarre Eye Movements: Greatly Used but Meagerly Utilized

Scene of the Crime

An 11-month-old, developmentally normal girl presented with a history of loss of attained milestones over 10 days. Premorbidly, the infant had started walking independently, had attained pincer grasp, was uttering bi-syllables, and playing lap games like "peek-a-boo." The illness had started with progressively increasing unsteadiness of gait, increased falls, and then loss of ability to walk unassisted, over 48 h. Concurrently, she lost the ability to reach for and successfully pick up her toys and stopped uttering bi-syllables. Her parents noticed that she had become very irritable, her sleep was interrupted, and she had started "startling" easily. There was no history of fever, loss of consciousness, seizures, projectile vomiting, visual or hearing impairment, facial asymmetry, or paucity of movements of any limb. There was a significant history of a febrile illness with low grade fever, cough, and coryza for a few days (sans any rash), 2 weeks before the onset of these symptoms. History of trauma, rash, or accidental ingestion of any drug was not found. There was no history of similar complaints in the past or in any close contacts. The child was the firstborn of a nonconsanguineous marriage. There was no family history of unexplained early childhood deaths, developmental delay or regression, visual/hearing impairment, or intellectual disability.

Dr. Watson: It seems like we are dealing with neuroregression. I wonder what lies in store for us in the clinical examination.

Examination revealed an extremely irritable infant with normal vitals (absence of fever and hypertension) and age appropriate for anthropometry. The anterior fontanelle was open, of normal size and at level. Pallor was seen. There was no jaundice, dysmorphic facies, neurocutaneous markers, or rash. On neurological examination, the sensorium was normal. Chaotic eye movements lasting for 1–2 s were observed [Video 1]. There were no cranial nerve deficits. The fundus was normal. Motor evaluation revealed decreased truncal and lower limb tone, power of >3/5 in the lower limbs, and preserved deep-tendon jerks. There was no apparent sensory impairment to touch or pain. Multiple cerebellar signs were noted; titubation, dysmetria, intention tremors, and truncal ataxia. She did not exhibit any signs of raised intracranial pressure or meningeal involvement. There were no palpable masses or organomegaly. The remaining systemic examination was within the normal limits.

Dr. Watson: By Jove! We are dealing with ataxia of 10 days duration! Let me review the causes of acute/sub-acute ataxia. It may even be the first episode of recurrent ataxia.

The leading causes of acute/recurrent ataxia in children include brainstem malignancies or encephalitis, postinfectious/immune phenomena, and a few select genetic disorders [Box 1]. In addition, trauma and vascular events such as cerebellar hemorrhage should be ruled out.

Dr. Watson: Hmm…I couldn't find anything! What do I need to see in "those eyes?"

The three aberrant eye movements include opsoclonus, ocular flutter, and nystagmus. Opsoclonus (also known as "dancing eyes" or saccadomania) is a form of ocular dyskinesia. It is described as sudden, repetitive, involuntary, high-amplitude, chaotic, arrhythmic, and multi-directional (i.e., upward, downward, and torsional) conjugate saccadic ocular movements. This results in oscillopsia (objects appear to jiggle or vibrate when in actuality they are still) and visual blurring. Opsoclonus is present during fixation (while looking

Box 1: Causes of acute ataxia

- Inflammatory
  - Infectious cerebellitis
  - Postinfectious cerebellitis
  - Brainstem encephalitis (Bickerstaff)
  - Acute disseminated encephalomyelitis
  - Multiple sclerosis
  - Vasculitis
  - Paraneoplastic disorders
  - Miller fisher variant of Guillain-Barré syndrome
- Drugs/toxins
  - Drugs such as anti-seizure drugs, antihistamines, lead, heavy metals, or organic chemicals
  - Brain space-occupying/mass lesions
  - Tumors
  - Abscesses
- Vascular
  - Vertebrobasilar dissection
  - Thromboembolism
- Trauma
  - Contusion
  - Hemorrhage
  - Postconcussion syndrome
- Genetic
  - Hartnup disease
  - Maple syrup urine disease
- Miscellaneous
  - Labyrinthitis
  - Basilar migraine
  - Benign paroxysmal vertigo
  - Epilepsy (nonconvulsive status and minor motor status)

at a stationary object), pursuit movements (while looking at a moving object), and convergence (while looking at an object closely). It persists during sleep or closure of the eyelids.[1] To differentiate opsoclonus from nystagmus and ocular flutter, one must appreciate the number of planes of involvement and the character of the movements. Ocular flutters are saccadic and the oscillations exist in only the horizontal plane, in contrast to opsoclonus which are multi-planar. Nystagmus, on the other hand, is a rhythmic, rapid jerk followed by a slow corrective saccade.

Dr. Watson: Very well, what are other things associated with these dancing eyes.

Opsoclonus should alert the clinician to elicit history of and look for myoclonus (of the limbs and trunk), behavioral changes (usually irritability), and sleep disturbances. One should look fortremor and hypotonia, both of which were present in this case.[2] The detection of a palpable lump on abdominal examination and hypertension is indicative of a neuroblastoma.

Dr. Watson: All right then, let us synthesize all that we have learned till now.

We have a premorbidly healthy 11-month-old girl with acute-onset regression of motor and speech milestones, excessive irritability, altered sleep pattern, easy "startling," intermittent opsoclonus, lower limb and truncal hypotonia, truncal ataxia, and cerebellar signs. Eureka! The clinical phenotype matches that of opsoclonus myoclonus ataxia (OMA). Other differentials will need to be excluded (toxic-metabolic encephalopathies, structural diseases [metastasis, inflammation, demyelination, and hemorrhage] within the pons/cerebellum).

Dr. Watson: At last, we are making some progress! Let us plan investigations.

The hematological profile and acute-phase reactants were normal. Thus, we did not feel the need to perform a lumbar puncture. The liver and kidney function tests were normal. Normal magnetic resonance imaging (MRI) of the brain excluded cerebellar lesions. The screening protocol for the detection of a neuroblastoma was followed: The 24-h urinary vanillylmandelic acid and homovanillic acid were elevated; MRI (neck, chest, abdomen, and pelvis) identified a lobulated retroperitoneal mass (2.1 cm × 2.8 cm × 3.9 cm) that was abutting the inferior vena cava and encasing the right renal vein [Figure 1]. This suggested a neuroblastoma of adrenal origin, which was confirmed by increased uptake in a 123-Iodine-meta-iodobenzylguanidine scan. A computed tomography-guided biopsy of the lesion showed the typical histopathology of a ganglioneuroblastoma. The anti-Hu antibody levels were positive on the qualitative analysis. The final diagnosis was a paraneoplastic OMA secondary to adrenal ganglioneuroblastoma.

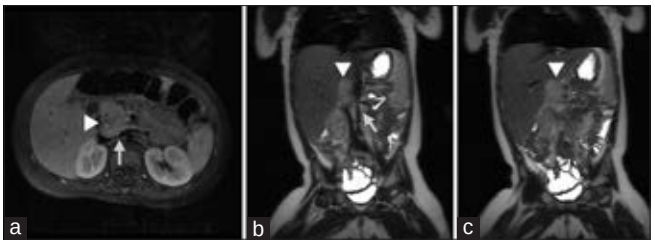

Figure 1: The image depicts a T2-weighted magnetic resonance image of the abdomen in the axial (a) and coronal planes (b and c). The images demonstrate a lesion (white arrowhead) abutting the IVC (gray arrows) and encasing the right renal vein, suggestive of right adrenal origin neuroblastoma

Dr. Watson: Great. Now let us manage her according to standard protocol.

A multi-specialty team was involved in the management. For the OMA, she was administered a single dose of intravenous immunoglobulin (IVIG) and rituximab. Adrenocorticotropic hormone (ACTH) was started. The symptoms resolved with 1 week of initiation of therapy. Specific management of the gangioneuroblastoma included neo-adjuvant chemotherapy for 2 months, surgery (total resection of the tumor and adrenalectomy with preservation of the adrenals on the unaffected side) and chemotherapy for 6 months. She was continued on ACTH for 12 months. Two years have elapsed, and till date, there has not been any recurrence of irritability, and so far, she is developing typically.

Discussion

OMA is an exceedingly rare condition (0.27–0.40/million children/year) that mainly affects young children (mean age 1.5–2 years). Although multiple underlying paraneoplastic, autoimmune, and infectious etiologies[3] are described, majority of cases are idiopathic.[4] The disease is characterized by irregular multidirectional eye movements without intersaccadic intervals, associated with myoclonus, cerebellar ataxia, and behavioral abnormalities. Early detection and management are crucial in view of its neuropsychiatric and neurological effects, as well as the risk of a possible hidden malignancy. Almost 50% children with OMA have an underlying neuroblastoma, and 2% of such children develop paraneoplastic OMA.[5] Other malignancies associated with OMA include ganglioneuroblastoma and ganglioneuroma. Postinfectious OMA is known to follow infections with Streptococcus, Epstein–Barr virus, *Mycoplasma pneumoniae*, Hepatitis C, Adenovirus C3, Rotavirus, and others. CNS autoimmunity has been demonstrated in OMA, with pathological expansion of B-cells and oligoclonal bands in the cerebrospinal fluid of children with the disease.[6]

The management of OMA encompasses multiple immunotherapeutic agents, including corticosteroids, IVIG, azathioprine, cyclophosphamide, and occasionally rituximab (supposedly decreases relapses).[7] Keeping in mind,

the long-term neurological sequelae (residual psychomotor retardation and behavioral abnormalities in 60%–80%), long-term immunosuppression may be mandated in most cases of OMA. In children with unclear etiology and an initial negative paraneoplastic workup, tumor surveillance should be aggressive during the follow-up to avoid relapses.

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Forensic Files

Mild Blunt Head Injury in Children: The Dilemma of Imaging and Nature of Injury

A mild blunt head injury (MBHI) is a head injury that is associated with a Glasgow coma scale (GCS) of 13–15 in the absence of focal neurological deficits. It is quite a common injury in childhood, constituting 15%–30% of visits to pediatric emergencies worldwide.[1] Usually, they are not associated with brain injury and long-term sequelae. However, 5% may be clinically important traumatic brain injury (ciTBI) that requires extended observation, intensive supportive care, and even neurosurgical intervention.[2] Risk stratification of the likelihood of a ciTBI (and thus, the need for neuroimaging) following an MBHI can be high (>3%), intermediate (variable), and low (<0.05%). Despite majority of children being at low risk, more than one-third of patients undergo computed tomography (CT) scan of the head, which causes unnecessary sedation, cranial irradiation exposure, and possible increased risk of future malignancy.[3]

These patients are also often present to a pediatrician as a medicolegal case. Thus, there are two main issues that a clinician faces. First, whether a neuroimaging is required or

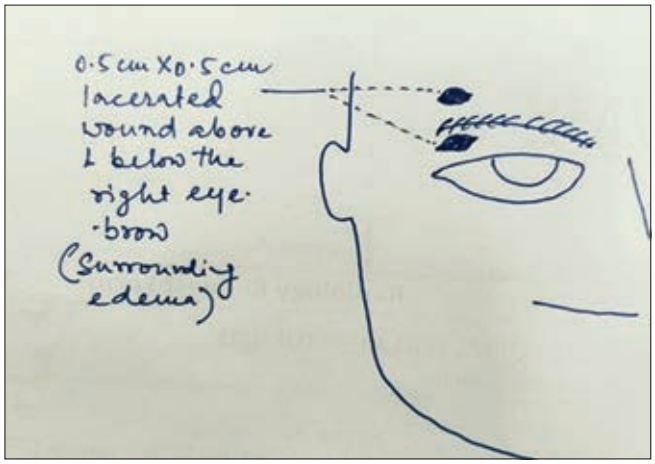

Figure 1: The medicolegal diagrammatic documentation of the injury

not; and second, whether to label the injury as grievous or simple. As practicing pediatricians, we must know how to manage such cases appropriately. The purpose of this case study is to sensitize our readers to the challenges that are faced in a child with MBHI.

Case Study

A 10-year-old boy presented to the emergency room accompanied by his father with the alleged history of being hit by a brick on his forehead by a neighbor 30 min earlier following a dispute. There were two wounds on the forehead [Figure 1]; one above and the other beneath the lateral end of the right eyebrow. Both had stopped bleeding. There was no history of severe headache, vomiting, loss of consciousness, seizures, bleeding or discharge from the ear, nose or any other site, or trauma to any other part of his body. There was no history of any sexual assault. The last immunization was at 5 years of age.

The resident on duty registered a medicolegal case, informed the institutional police post, and started examination after taking informed consent from the child and his father. The child's vitals were stable. Both wounds were lacerated, measuring 0.5 cm in width and length. There was minimal surrounding edema. There were no other injuries elsewhere on the body. No watery discharge was observed from nose or ears. Bluish discoloration was not seen in the periorbital or periauricular areas. The GCS was 14/15. Both pupils were of normal size and displayed normal reaction. There were no focal neurological deficits or signs of increased intracranial tension. Rest of the systemic examination was normal.

The wounds were sutured with nonabsorbable material after aseptic preparation and local anesthesia. A tetanus shot was given. A noncontrast CT scan of the head and base of the skull was done which revealed no abnormality. The neurosurgical opinion was that of no active intervention. The final diagnosis

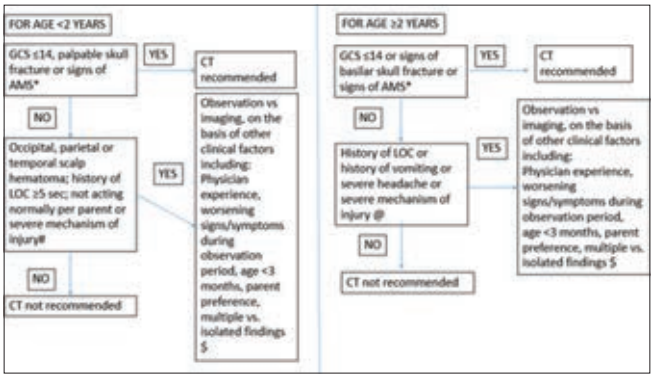

Figure 2: Pediatric Emergency Care Applied Research Network algorithm for prediction of clinically important traumatic brain injury in children.[2,5] *AMS: Altered mental status: Agitation, somnolence, repetitive questioning, or slow response to verbal communication. #: Severe mechanism: MVC with patient ejection, death of another passenger, rollover; pedestrian or bicyclist w/o helmet struck by motorized vehicle; fall from >0.9 m or 3ft; head struck by high-impact object. $: Patients with certain isolated findings (i.e., no other findings suggestive of traumatic brain injury, such as isolated LOC, isolated headache, isolated vomiting, and certain types of isolated scalp hematomas in infants >3 months. @: Motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle; falls of more than 1.5 m/5 feet; head struck by a high-impact object

was an MBHI. The decision regarding the nature of the wound was kept reserved till later. The child was discharged within 24 h after being instructed about danger signs warranting immediate return to the hospital [Box 1]. An oral antibiotic was prescribed for 5 days. The child was advised aseptic dressing of the wound and to come for suture removal after a week.

Let's Ask the Expert

What are the indications for neuroimaging a child with mild blunt head injury?

Many algorithms and clinical decision rules have been developed for identifying children with MBHI who require neuroimaging (noncontrast CT scanning or magnetic resonance imaging) and intensive monitoring. These are used in conjunction with the clinician's judgment based on the level of expertise.[4] The Pediatric Emergency Care Applied Research Network is the most commonly used tool worldwide and is based on the age of the child [Figure 2]. Children >2 years with high risk (seizure, altered mental status with GCS ≤14, or findings indicative of a skull/basilar skull fracture) require immediate imaging. Those with intermediate risk (presence of vomiting, headache, history of loss of consciousness, or an injury caused by a high-risk mechanism like a motor collision) are observed for 4–6 h and advised imaging if there is no improvement or worsening of symptoms. Those who are at low risk (absence of any of the aforementioned factors) do not require neuroimaging.[5]

Box 1: Indications for immediate return to hospital in mild traumatic brain injury

Significant drowsiness or inability to wake up
A headache that is especially severe or gets worse
Weakness, numbness, or tingling in arms or legs
Repeated vomiting
Slurred speech
Convulsions or seizures
Increasing confusion, restlessness, or agitation
Unusual behavior

Would we call the wounds sustained by this patient grievous?

A grievous hurt involves any of the following:[6] (i) emasculation; (ii) permanent privation of the sight of either eye; (iii) permanent privation of the hearing of either ear; (iv) privation of any member or joint; (v) destruction or permanent impairing of the powers of any member or joint; (vi) permanent disfiguration of the head or face; (vii) fracture or dislocation of a bone or tooth; and (viii) any hurt that endangers life or that causes the sufferer to be during the space of 20 days in severe bodily pain, or unable to follow his ordinary pursuits.

In the present case, the first five and seventh clauses are clearly not applicable. Whether the injuries would cause permanent disfigurement was uncertain at that point in time. This will only become apparent later, posthealing. However, minor lacerations on the head or face are generally not regarded as "grievous" by the Court, as they usually do not lead to permanent disfiguration. This clause is usually applicable in injuries caused by vitriol age (throwing of corrosives), which destroys identifying features on the face or head of the victim.

Let us now consider the eighth clause: endangerment of life or severe bodily pain or interference in daily activities during the following 20 days. The injury was definitely life-endangering as blunt trauma to the head can cause death. An injury is labeled as dangerous or endangering to life when the injury would be invariably fatal in the absence of medical or surgical intervention. Thus, it can be judged objectively by asking the question whether the injury would have resulted in death if the victim had not got timely medical/surgical help.

Whether an injury will be debilitating for the next few weeks is again a matter of time and an opinion that can be made only prospectively, depending upon the opinion of the treating doctor; whether the victim will be fit enough to be discharged within a few hours, a few days, or a few weeks. Hence, it is best to keep the opinion as "reserved" at admission. Once the follow-up of the victim is complete, a decision can be made regarding whether it is "grievous" or not. In this case, it was not grievous as he was discharged within a day of admission.

What are the role and responsibilities of the treating physician?

After taking history and consent for examination, the following steps should be performed:

- Assessment of the child's airway, breathing, circulation, disability, and state of consciousness and exposure status within a few seconds. Movement of the neck should be avoided while handling the patient just in case cervical spine injury is also present
- A blood sample should be collected for drug analysis (especially when intoxication or abuse is suspected). This should be packed, sealed, labeled separately, placed in a bag, and handed over to the police personnel
- Appropriate treatment of the physical and scalp injuries. Expert opinion from the surgery, neurosurgery, and/or orthopedics departments should be taken, if warranted. The treating physician decides where the patient is admitted and the time of discharge
- At discharge, indications for immediate return should be explained [Box 1].

Legislature: Hurt and Grievous Hurt

According to Section 319 of the Indian Penal Code (IPC), causing "Hurt" is defined as causing bodily pain, disease, or infirmity to any person. Pain covers only physical bodily pain. The term "infirmity" is applicable to a temporary or permanent condition in which one or more organs are unable to carry out normal bodily function. Infirmity can also be mental, i.e. if somebody is threatened with death and the victim ceases to heave home out of fear. Hurt is punishable under Section 323 of the IPC. Section 321 of the IPC is an extension of Section 319. It deals with the term "voluntarily causing hurt." This is defined as "whoever does any act with the intention of thereby causing harm to any person, or with the expertise that he's likely thereby to reason hurt to any individual, and does thereby motive harm to any person." In this case, it is essential that an element of "mens rea" (the intention or knowledge of wrongdoing that constitutes part of a crime) is proved.

Similarly, Section 320 of the IPC deals with the definition of "grievous hurt" and Section 322 defines the offense of "voluntarily causing grievous hurt." The eight specific situations that are included in the definition have been outlined earlier. The Indian Penal Code explains 'voluntarily causing grievous hurt' as when the offender not only causes grievous hurt, but had the intention of causing grievous hurt or knew that his/her actions would likely cause grievous hurt. A simple injury is conventionally defined as "any injury that

is neither extensive, nor serious, and heals rapidly without leaving any deformity or disfiguration."

It is important for a clinician to be cognizant of these definitions and the subtle differences between the two because of the following judicial implications.

- The injuries caused in Section 319 IPC (hurt) are not specified and there is no mention of risk to life, whereas in Section 320 IPC (grievous hurt), the risk of life is much graver
- Hurt is not punishable in itself. For hurt to be punishable, it must be accompanied by other offenses. However, grievous hurt is punishable in itself
- The offense of hurt is noncognizable, bailable, and triable by any Magistrate. However, the offense of grievous hurt is cognizable, bailable, and compoundable with the permission of the Court
- The punishment for hurt is given under Section 323 of the IPC which is "imprisonment of either description for a term which may extend to 1 year, or with fine which may extend to one thousand rupees, or with both." The punishment for grievous hurt is given under Section 325 of the IPC, which is "imprisonment of either description for a term which may extend to 7 years, and shall also be liable to fine."

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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IP Chronicles

Hereditary Pancreatitis: A Tale of 50 Years

Acute pancreatitis is a common cause of abdominal pain in children. Hereditary pancreatitis (HP) refers to an autosomal dominant condition (with high penetrance) in which acute and chronic pancreatitis occurs in both children and adults. The most common genetic cause is variants in the *PRSS1* gene (serine protease 1). Other causes include variants of serine protease inhibitor *Kazal type 1* (*SPINK1*), some other genes, and often multiple genetic factors. This is a brief

review of the history and evolution of genetic diagnostic tests for HP since the publication of the case report on Familial Pancreatitis by Choudhry *et al*. way back in 1996.

Clinical Case Description

The authors reported a 7-year-old child with a history of recurrent severe abdominal pain for 4 years prior to presentation. The pain was localized to the epigastric and umbilical region and had increased progressively from episodes that occurred every 4–5 months, to almost weekly. Each episode lasted for 3–4 days. There was no history of jaundice, loose stools, or any other significant abdominal complaints. The child had been assessed in many hospitals, but a diagnosis had not been established.

The patient was a moderately nourished child with a weight of 17 kg and height of 98 cm. No abnormalities were identified on examination, besides mild pallor. Salient investigations revealed anemia (hemoglobin 9 g/dL) with neutrophilic leukocytosis (total leukocyte count 17,700/mm^3 with 65% neutrophils and 35% lymphocytes). The amylase levels were raised, varying between 290 and 400 Somogyi units, with the higher values observed during the episodes of acute abdominal pain. An abdominal X-ray revealed pancreatic calcifications. A barium meal and cholecystogram were normal. When a urinary aminoacidogram was undertaken, generalized aminoaciduria was identified. Familial pancreatitis was suspected and a family survey of history and relevant investigations was undertaken.

Salient history of recurrent abdominal pain was found in the father that had started at the age of 24 years and often required hospitalization. He had also been diagnosed with diabetes mellitus that was controlled with insulin and tolbutamide and was also undergoing treatment for pulmonary tuberculosis. The mother, two brothers, and one sister were asymptomatic. Only the father was detected to have pancreatic calcifications, whereas serum amylase was raised in one of his sisters. All of them had generalized aminoaciduria. The family survey suggested some underlying genetic defects responsible for the spectrum of abnormalities in the family. At that point of time, the condition was referred to as familial pancreatitis. At the time of this case report, a diagnosis of familial/HP was made based only on a history of familial involvement and clustering. The genetic basis of pancreatitis was not established till 1996.

Review of Hereditary Pancreatitis through 50 Years

In 1952, Comfort and Steinberg,[1] reported chronic pancreatitis in six members of a single family over three generations. This was called hereditary chronic relapsing pancreatitis and assumed to be due to an autosomal dominant inheritance. Later in 1962, Gross *et al*. evaluated this condition in 38 patients from five families.[2] It was proposed that HP be defined by the following clinical and epidemiological characteristics: (1) three or more patients with pancreatitis within the same family; (2) onset at a young age; and (3) pancreatitis unrelated to excessive alcohol ingestion, gallstones, or trauma.

A relationship between a mutation in the *PRSS1* gene and HP was identified as late as 1996, almost two decades after the said case report.[3] The cystic fibrosis (CF) transmembrane conductance regulator (*CFTR*) gene, a causative gene of CF, was also reported to be associated with acute relapsing pancreatitis and chronic pancreatitis. A mutation in the serine protease inhibitor gene (*Kazal* type 1: *SPINK1*) was reported to be related to chronic idiopathic pancreatitis of unknown cause.[4] Multiple genetic causes of pancreatitis have been identified in the past 25 years. They include calcium-sensing receptor in 2003, chymotrypsin C in 2008 (*CTRC*), claudin-2 in 2012, carboxypeptidase A1 in 2013, carboxyl ester lipase in 2015, chymotrypsin B1 and B2 in 2017, pancreatic lipase in 2019, and transient receptor cation channel subfamily V member 6 gene in 2020.

When acute recurrent or chronic pancreatitis occurs due to a single-gene disorder, and Mendelian inheritance is likely, it is termed as HP. Familial pancreatitis refers to pancreatitis that occurs in a family, with an incidence that is greater than that would be expected by chance alone, given the size of the family and the standardized incidence of pancreatitis within a defined population. There are at least three different inheritance patterns for hereditary/familial pancreatitis. Autosomal dominant or "hereditary" pancreatitis is most often associated with mutations in the *PRSS1* gene on chromosome 7q35, which encodes trypsin-1 (cationic trypsinogen). Autosomal recessive or "familial" pancreatitis is usually associated with CF or mutations in the *SPINK1* gene. A complex genetic pattern has been described that is associated with a combination of genetic and environmental factors, for example, heterozygous *SPINK1* mutations, in which the mutation probably acts as a disease modifier factor.

Patients with HP have recurrent acute pancreatitis in childhood or early adolescence, chronic pancreatitis in late adolescence or early adulthood, and an increased risk for pancreatic cancer beginning in the fifth decade of life. The primary manifestations are abdominal pain and malabsorption due to pancreatic exocrine dysfunction, and diabetes mellitus due to islet cell damage. This is known as diabetes of exocrine pancreas which is usually treated with metformin and insulin therapy. This form of diabetes mellitus is different from typical type 1 diabetes in that the pancreatic alpha cells, which produce glucagon, are also affected (type 3c diabetes mellitus). This leads to a very high risk of hypoglycemia.

Major advancements have occurred in the field of diagnostics in the past 50 years. Genetic testing (*PRSS1*, *CFTR*, and *SPINK1*, plus *CTRC*) is now easily available and plays an important role in diagnosis, management,

and prognostication. It is indicated in idiopathic acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis after common causes (i.e., gallstone disease, heavy alcohol use, duct obstruction, and specific medications) have been excluded and one or more of the following criteria are satisfied: (1) an unexplained documented episode of pancreatitis as a child; (2) idiopathic chronic pancreatitis (particularly when the onset is <25 years); (3) family history of recurrent acute pancreatitis; (4) idiopathic chronic pancreatitis, or childhood pancreatitis without a known cause; and (5) relatives known to carry mutations associated with HP (i.e., *PRSS1* mutations).[5,6] These tests must be coupled with pre- and posttesting counseling. Predictive testing (that of asymptomatic individuals) can be considered in the presence of a first-degree relative with a known *PRSS1* mutation, but it must be accompanied by expert genetic counseling, and should not be done not in adolescents <16 years of age.[6] If a family carries a known mutation, a negative test eliminates the risk of HP in that individual, whereas a positive test result confers an 80% risk of developing pancreatitis. In contrast, predictive testing of *SPINK1* or *CFTR* mutations in presymptomatic individuals is of minimal value because these mutations are common and most positive patients do not develop the disease.

Future Directions

Three genes, with Mendelian genetic biology (*PRSS1*, *CFTR*, and *SPINK1*), have been recognized for over a decade to cause chronic pancreatitis, but little progress has been made since then. The availability and application of high-throughput genetic techniques, including genome-wide association studies and next-generation sequencing, will provide a large volume of new genetic variants that are associated with HP. However, the major challenge will be deciding causation in these complex genetic disorders.To understand these genetic variants and translate them into clinically useful information requires a new framework based on modeling and simulation of physiological processes. This framework involves genetic, metabolic and environmental variables at the cellular and organ levels, along with the integration of the immune system, nervous system, tissue injury and nucleic acid repair systems. This will help to identify pancreatic dysfunction in the early stages before irreversible damage occurs.

In future, genetics will be the mainstay of clinical management of many diseases including HP. The development of HP is associated with a limited number of etiologies, and there may be several years gap between the first symptoms and organ destruction. The need of the hour is to develop early and effective interventions that are based on the *etiology* rather than symptoms and complications. If the target of the etiology of pancreatic dysfunction can be recognized in the early stages of the disease, theoretically intervention can be developed to prevent the development of irreversible damage. Hope springs eternal!

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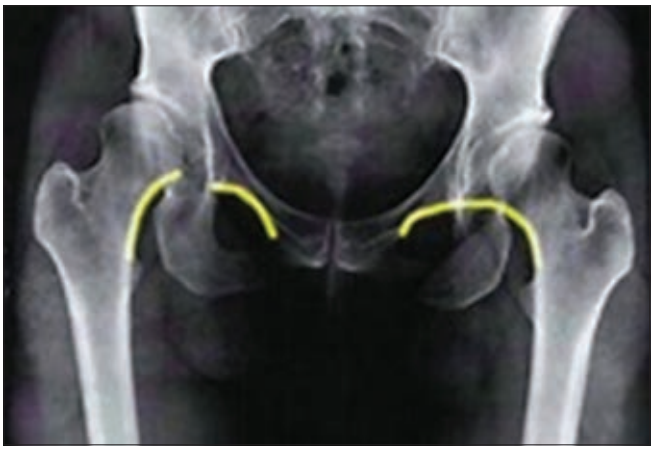
Neo-Quiz 3

1. AAP recommendation for noise levels inside Neonatal Intensive Care Units should not exceed how many decibels?
2. What does this pedigree symbol represent?

3. A term baby has Apgar scores of 3, 8 at 1 and 5 min. After being examined at 24 h by the attending doctor, it was found that the baby has segmental myoclonus, irritability with dilated pupils. Which stage to put the baby in as per Sarnat and Sarnat staging of classification of asphyxia encephalopathy?
4. Neonate is being ventilated FiO_2 of 100%, with a mean airway pressure of 28. Arterial blood gases shows a pH 7.32, PCO_2 44, PO_2 51, bicarbonate of 22 mEq/L, BE -3 calculate oxygenation index (QI)
5. Identify the line. What does it indicate?



6. Name the chart used for gestation and birth weight-specific thermoneutral zone of temperature?
7. A preterm baby born at 29 weeks is evaluated by head ultrasound on day 1 (18 h of life). The baby has severe pallor and shock on clinical examination. The ultrasound shows bilateral germinal matrix hemorrhage and no ventricular dilation. Which grade of intraventricular hemorrhage would you classify the baby into as per Volpe's classification?
8. Double-walled incubator prevents heat loss by which two mechanisms?
9. Identify the national program depicted by the logo below?

10. Name the health program launched in India which uses interactive voice response messages on mobile phones to train frontline health workers in maternal and infant care?

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Jaundice: From Physiological to Pathological

Jaundice is a common complaint encountered by pediatricians, with onset from birth and continuing till adolescence. The underlying etiology varies from benign physiological causes to severe medical/surgical illnesses. This month we focus on some uncommon causes of jaundice that have been reported recently.

Oliveira GN, Dinis I, Noruegas MJ, *et al*. A rare cause of neonatal persistent jaundice. BMJ Case Rep 2017;2017:r-223306.

A boy was born at term gestation to a 22-year-old primigravida mother with gestational diabetes and cytomegalovirus (CMV) infection detected in the first trimester. Her antenatal ultrasounds were normal. The baby cried immediately at birth and was discharged on day 2 of life. Examination was unremarkable, except for jaundice which was outside the phototherapy range. On follow-up after 48 h, the baby was lethargic, hypotonic, and deeply icteric. The vitals were normal and liver and spleen were palpable. The serum bilirubin level was 694 umol/l (indirect: 681 umol/l). Hemoglobin was 19 g/dL, hematocrit 58%, white blood cell count 11.6 × 10^9/L, and platelet count 128 × 10^9/L. Hyponatremia was noted. The glucose, urea, creatinine, and coagulation studies were normal. Although the baby responded to intensive phototherapy, he developed rebound hyperbilirubinemia whenever it was attempted to stop the phototherapy. Enteral feeds were started and oral sodium chloride was added due to persistent hyponatremia. Ultrasonography (USG) was performed. The cranial USG was normal, but the abdominal USG revealed enlarged adrenal glands, with hypoechoic heterogeneous masses, measuring 32 mm × 21 mm × 17 mm on the right and 33 mm × 23 mm × 17 mm on the left. These were suggestive of bilateral adrenal hemorrhage (AH). The neonatal thyroid function test (TFT) detected raised thyroid-stimulating hormone (TSH) levels, following which levothyroxine was started on day 14. A follow-up abdominal Doppler US on day 30 reaffirmed the bilateral AH. The hormonal profile identified raised adrenocorticotropic hormone, prolactin, aldosterone, and renin levels and low cortisol level. Together with the elevated TSH, this was indicative of hypothyroidism secondary to adrenal insufficiency. Hydrocortisone was started, and the baby exhibited improvement in hypotonia and feeding. The neurological and metabolic evaluations normalized. After 3 months, the TFT normalized and levothyroxine was stopped. At 6 months, fludrocortisone was added due to inappropriately activated renin–angiotensin–aldosterone system. Regression of the sizes and echogenicity of both adrenal masses were observed at 6 months. At 22 months, the child was asymptomatic on corticosteroid replacement therapy.

Adrenal hemorrhage occurs during neonatal period mostly in babies having difficult delivery, large for gestational age, maternal diabetes, birth asphyxia, trauma, or septicemia. It is mostly unilateral and on the right side. Bilateral adrenal hemorrhage needs replacement. The condition generally resolves in 3–6 months with a serial ultrasound monitoring.

Thornton KM, Nyp MF, Music Aplenc L, *et al*. An unusual case of rapidly progressive hyperbilirubinemia. Case Rep Pediatr 2013;2013:284029.

A 22-year-old fourth gravida mother with an uneventful antenatal period delivered a male baby at 40 weeks of gestation via vaginal delivery. The Apgar score was 7 and 8 at 1 and 5 min, respectively. He received intramuscular Vitamin K at birth. At 4 h of age, a hematoma was noted at the injection site. A few hours later, the baby developed jaundice. The serum bilirubin was 33.3 mg/dL at 29 h of age that increased to 39 mg/dl at 32 h of life. The maternal blood group was O positive. The baby was transferred to the neonatal intensive care unit and started on intensive phototherapy. On examination he was irritable, hypertonic, had intermittent opisthotonus and a high pitched cry. The baby's blood group was O positive. The direct Coombs test was negative. Salient investigation reports were a hemoglobin of 11.6 gm/dL, thrombocytopenia (platelet count: 26,000/mm^3), elevated reticulocyte count (4.9%), and increased aspartate transaminase (AST) (248 U/L). All other reports were normal, including the white blood cell count, prothrombin time, partial thromboplastin time, and fibrinogen. Double volume exchange transfusion was indicated at 35 h of life. Post exchange, the total serum bilirubin decreased to 23.3 mg/dL. This further declined over the next few days. However, the baby also developed seizures and apnea, for which mechanical ventilation was required for 2 days. On the 8th day, magnetic resonance imaging of the brain revealed a T1-weighted hyperintensity of the globus pallidus. The peripheral blood smear showed microangiopathic hemolysis, suggestive of thrombotic thrombocytopenia (TTP). The ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) enzymatic activity was measured and found to be deficient (total activity <5%). Gene sequencing analysis showed a heterozygous missense mutation in the ADAMTS13 gene (c. 304C >T [p. Arg102Cys]). Repeat testing of ADAMTS13 level at 5 months of age, reconfirmed

an enzyme activity level of <5%. On follow-up at 8 months, the child had auditory predominant kernicterus, mild truncal hypotonia, and impaired upward gaze and a severe auditory neuropathy spectrum disorder as checked on auditory testing. The patient's neurologic deficits gradually improved, but significant hearing loss persisted. The child has been on regular prophylactic fresh frozen plasma (FFP) infusions and planned for cochlear implants. Congenital TTP is a rare form caused due to mutation of the gene coding for ADAMTS13. It is inherited in an autosomal recessive pattern. Deficiency of this gene leads to decreased cleavage activity thereby causing ultra-large vWF multimers to accumulate. As a result, there is formation of platelet-rich intravascular microthrombi. This congenital deficiency is mainly corrected by regular FFP transfusions.

El Nabouch M, Rakotoharinandrasana I, Ndayikeza A, *et al*. Infantile pyknocytosis, a rare cause of hemolytic anemia in newborns: Report of two cases in twin girls and literature overview. Clin Case Rep 2015;3:535-8.

A bi-chorionic, bi-amniotic twin was delivered to a 39-year-old mother at 36 weeks of gestation. The mother had a history of multiple abortions but no family history of jaundice, blood transfusion, splenomegaly, cholelithiasis, or any similar condition. Both babies had normal Apgar scores and birth weights (twin 1 – 2840 g and twin 2 – 2800 g). Both babies developed jaundice which settled with phototherapy, and they were discharged on day 5 of life. The first twin was brought back on day 15 with jaundice, poor feeding, and poor weight gain. On examination, there was pallor but no organomegaly. Investigations showed a total bilirubin level of 15.5 mg/dL and conjugated levels of 0.47 mg/dl. Hemoglobin was 5.5 g/dL, hematocrit 18%, reticulocyte count 22.6%, and haptoglobin <0.15 g/L. The baby blood group was O positive, while the maternal blood group was A positive. Direct Coombs test was negative. Kidney function tests, liver function tests, and glucose-6-phosphate dehydrogenase (G6PD) levels were normal. The peripheral smear showed multiple pyknocytes. The second twin also developed a similar picture. Both babies developed pustular skin lesions suggestive of cutaneous staphylococcal infection. After treatment with packed cell transfusion, phototherapy, and antibiotics, they were discharged with a diagnosis of infantile pyknocytosis.

Infantile pyknocytosis is a rare neonatal condition which has two most common presentations. First is the early neonatal jaundice often resistant to phototherapy. The second presentation is hemolytic anemia noted between the second and fourth weeks of neonatal period. However, one has to be careful that pyknocytes can be physiological in nearly 5% of preterm infants during the first week of birth. These cells can also be seen in Vitamin E deficiency anemia and pyruvate kinase deficiency. Treatment of infantile pyknocytosis is mainly supportive.

Mohan P, Bavanandam S, Sunil Kumar KS. A rare cause of obstructive jaundice – Case report. Ann Clin Gastroenterol Hepatol 2017;1:1-3.

An 11-year-old boy presented with complaints of abdominal pain, fever, jaundice, and dark-colored urine for 5 days. There was no history of drug intake and family history of jaundice. Past medical records showed hospital admission at 7 years of age for prolonged fever associated with generalized lymphadenopathy and hepatosplenomegaly. The bone marrow examination done then was suggestive of eosinophilic precursors. Diagnostic laparotomy with cholecystectomy was done. Lymph node biopsy done remained inconclusive. In the present admission, examination showed icterus and tender hepatomegaly with midline surgical scar. Reevaluation of histology of the earlier resected gall bladder specimen, showed xanthogranulomatous changes with numerous eosinophils and marked fibrosis suggestive of eosinophilic cholecystitis. Blood reports showed a total count of 7300 cells/cumm, of which 13% were eosinophils. The serum bilirubin was 4.5 mg/dl, direct bilirubin 2.9 mg/dl, liver enzymes raised (alanine aminotransferase: 165 IU/L, AST: 125 IU/L, serum alkaline phosphatase: 2875 IU/L, and gamma-glutamyl transferase: 445 IU/L). Serum immunoglobulin E levels were > 1000 IU with an absolute eosinophil count of 920 cells/cumm. Kidney function tests and pancreatic enzymes were within normal limits, and markers for viral hepatitis, autoimmune liver disease, and HIV were negative. MRI abdomen showed biliary dilatation with pancreatic head mass. A diagnosis of eosinophilic cholangiopathy was made, and the child started on oral prednisolone. The patient responded well to treatment with reversal of deranged blood parameters.

Eosinophilic cholangiopathy is a condition associated with diffuse infiltration of the gallbladder wall, bile ducts, and pancreas termed as eosinophilic cholecystitis, eosinophilic cholangitis, and eosinophilic pancreatitis, respectively. The diagnosis can be made by appearance of stenosis or wall thickening of biliary system, histopathological findings of eosinophilic infiltration, and reversibility of biliary abnormalities without treatment or following steroid treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Radiology Rounds

An Infant with Hyperinflated Lungs: What's the Secret?

Sachin Singh, Joseph L. Mathew, Akshay K. Saxena[1], Prema Menon[2], Debajyoti Chatterjee[3], Meenu Singh
Departments of Pediatrics, [1]Radiodiagnosis and Imaging, [2]Pediatric Surgery and [3]Histopathology, PGIMER, Chandigarh, India

Congenital lobar emphysema (CLE) is a rare developmental abnormality of the lung, and is usually unilateral. Bilateral CLE is very rare and has been reported only in a small number of cases in the literature. CLE can result in progressive respiratory distress during the neonatal period and early infancy, and it often presents a diagnostic and therapeutic dilemma. We report a case of bilateral CLE in a 6-week male infant who presented with acute respiratory distress.

Clinical Description

A 6-week-old male infant presented to us with a history of fast breathimg since birth, and recent chest indrawing. Delivery was at term by cesarean section in a different health facility, the indication being a previous cesarean. The birth weight was 3.2 kg and Apgar scores 8 and 9, at 1 and 5 min, respectively. The infant had developed respiratory distress immediately and was admitted in the neonatal intensive care unit. Although there was no history suggesting maternal sepsis, or prolonged rupture of membranes, infectious pneumonia was presumed and he was treated with antibiotics, besides supportive management with intravenous fluids and oxygen delivered by nasal prongs. The baby was the second born of a nonconsanguineous marriage. The pregnancy was booked and supervised. No abnormalities were reported on antenatal ultrasonography. He improved and was discharged after 5 days. The discharge slip chest radiograph and reports were not available for review. Breastfeeding had been established.

At the age of 12 days, the infant developed cough and fast breathing, which worsened over the next 2 days. He also developed episodes of bluish discoloration while crying. There was no history of choking or coughing while breastfeeding, regurgitation of feeds, noisy breathing, or presence of suck-rest-suck cycles. The infant was admitted to another hospital and managed as pneumonia with antibiotics, oxygen, and fluids, for 1 week, the details of which were unavailable. Postdischarge, the baby remained well at home except for a slightly fast rate of breathing that the parents did not consider significant as he was active, alert, and breastfed well.

At 6 weeks of age, the infant developed a runny nose, worsening of the fast breathing and chest indrawing. After being admitted in another hospital for 3 days, he was referred to us for ascertaining the underlying etiology.

At admission, the temperature was 101°F, heart rate 150/min, respiratory rate 60/min with intercostal, subcostal retractions, and nasal flaring, SpO_2 86% in room air, and blood pressure 92/57 mmHg. The weight was 4.4 kg (−1.85 *Z* score), length 57 cm (−0.67 *Z* score), and head circumference 39 cm (−0.07 *Z* score). There was pallor, but no cyanosis, or significant lymphadenopathy. The throat, ear, and nasal cavity examinations were normal. No stridor was audible. The baby had a hyper-inflated chest with symmetric chest expansion, centrally positioned trachea, absence of mediastinal shift, normal percussion note in all areas, and

diminished breath sounds over the right mammary area. There were no crackles or wheeze. There was no abdominal organomegaly and the examination of the other systems was unremarkable.

Since the clinical impression was of an infant with recurrent pneumonia, the differentials that were considered included aspiration syndromes (though there was absence of feeding-related symptoms, episodic regurgitation, posturing during feeding, or cough/wheezing during or immediately after feeds); primary ciliary dyskinesia (although there was no history of ear discharge or sinusitis) and cystic fibrosis (despite absence of history of delayed meconium passage, saltiness when kissed, failure to thrive, or persistent cough). Differentials that were excluded were acyanotic congenital heart disease with left-to-right shunts (due to absence of supportive clinical findings); primary or secondary immune deficiency (not supported by multi-site infections, poor weight gain, or suggestive maternal history) and congenital TORCH infections (given the absence of low birth weight and organomegaly). A chest X-ray was done at the age of 6 weeks [Figure 1].

What are the Salient Findings in the Chest X-ray?

The rotated radiograph makes it difficult to comment on the chest symmetry, however, the thymic shadow is prominent on the right side. The lungs seem well-inflated and eight intercostal spaces can be counted bilaterally. The ninth intercostal space is just visible on the right side. There is hyperlucency of the right middle and lower zones, and also almost the entire left hemithorax [Figure 1]. The right upper lobe area is relatively hazy compared to the other lung fields, suggesting consolidation. Similarly, the right lower zone also shows haziness in the paracardial area. The cardiac silhouette seems normal, although the pulmonary bay appears to be fuller. The pleural spaces, trachea, bones, and soft tissues appear normal.

What are the Differential Diagnoses Based on the Clinical History and Radiograph?

Congenital airway or thoracic malformations, perinatal tuberculosis, and the aforementioned conditions associated with recurrent pneumonia (such as primary ciliary dyskinesia). In addition to the causes excluded before the radiograph, gastro-esophageal reflux disease was also considered less likely.

What should be the Next Line of Investigations?

This was planned according to the differentials. Hemoglobin, total and differential leukocyte count, inflammatory markers, and blood culture were all normal. Sweat chloride level was within the normal range. Gastric lavage specimens did not show acid-fast bacilli on smear examination and were negative on GeneXpert. A screening electrocardiogram and echocardiogram were normal. Since everything was still inconclusive, we planned a computed tomography (CT) scan of the thorax to rule out congenital thoracic malformations.

What are the Salient Findings in the Computed Tomography Scan?

The contrast enhanced CT scan showed hyperinflation of the right middle and left upper lobes, with mass effect on the remaining lung parenchyma [Figure 2]. There is no obvious cardiomegaly, mediastinal or hilar lymphadenopathy, or pleural or pericardial effusions. The radiological diagnosis was bilateral lobar emphysema.

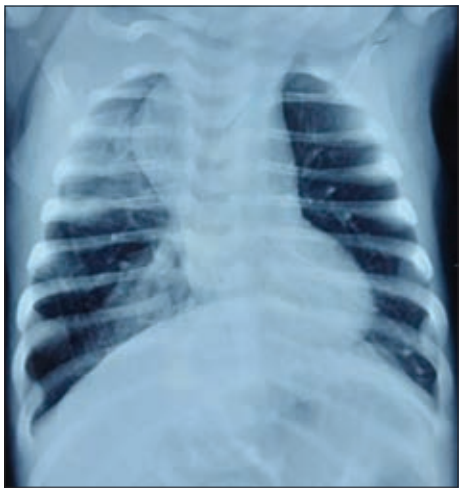

Figure 1: X-ray chest performed at the age of 6 weeks. reveals hyperlucency of the right middle and lower zones, as well as almost the entire left hemithorax

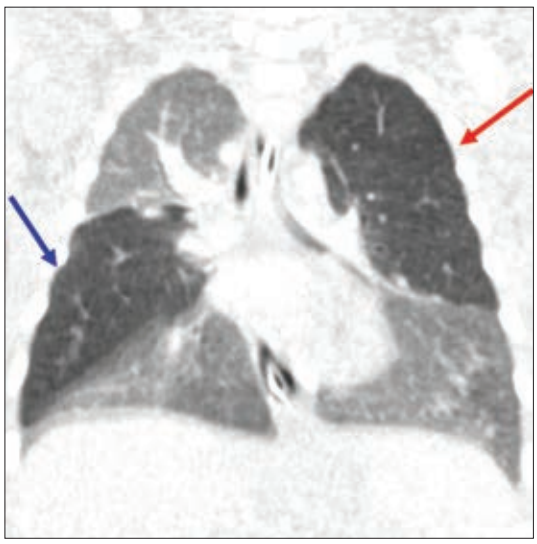

Figure 2: Coronal reconstructed image of the CECT scan shows hyperinflation of the right middle lobe (blue arrow) and left upper lobe (red arrow)

Management and Outcome

The family was counseled regarding the disease, its prognosis, potential complications, and the need for surgery. Bilateral thoracotomy was planned in a staged manner as the surgery carries high intra-operative and postoperative risk. The left upper lobe was removed through a left posterolateral thoracotomy. The infant recovered uneventfully and 3 weeks later, the procedure was repeated to remove the right middle lobe. The infant remained stable and was discharged 5 days later. Histopathological examination of both excised lobes revealed changes consistent with CLE. The infant was discharged with the absence of symptoms, normal respiratory rate, no chest indrawing and a SpO_2 of 98% in room air. The infant was followed-up regularly. At the last visit at 8 months of age, he is growing well, has had no respiratory symptoms, and is acquiring milestones appropriately. Age-appropriate immunizations were administered as per the National Immunization Schedule.

Discussion

This case highlights the fact that despite a step-wise clinical approach and relevant investigations, a clinical diagnosis may remain elusive. In the index case, the onset of symptoms since birth, the bilateral hyperinflation, and complete absence of wheezing could have led us to consider CLE. An infectious etiology was considered due to the history of the first two episodes being managed as pneumonia. It may be conjectured that had the X-rays taken during both these events been available to us, a diagnosis of CLE may have been made earlier.

CLE is a rare developmental anomaly of the lung characterized by progressive over-inflation of one or more lung lobes due to partial obstruction of the developing airway leading to ball valve obstruction and air trapping. This results in hyperinflation and consequent compression or displacement of the adjacent normal lung tissue and progressively increasing respiratory distress.[1,2] It was first reported by Gross and Lewis in 1954. The precise etiology is unknown, but a quarter of cases have deficient bronchial cartilage leading to the inappropriate airway collapse and air trapping, creating over-inflation of the lobe. Prevalence ranges from 1 in 20,000 to 30,000 infants. Males are affected more than females with a ratio of 3:1.

The designation of CLE has been revised to the following terms: congenital lobar hyperinflation, congenital lobar over-inflation, infantile lobar emphysema, congenital large hyperlucent lobe, and congenital alveolar overdistension. These names better describe the condition and to some extent overcome the limitations of the misnomer "emphysema" which is histopathologically a different entity. Infants commonly present with progressive tachypnea, respiratory distress, wheeze, recurrent respiratory infections, and failure to thrive.[1,2] However, delayed diagnosis is known in 5% cases with presentation occurring as late as 6 years of age. CLE is typically unilateral, most commonly affecting the left upper lobe (42%), followed by the right middle lobe (35%), and right upper lobe (21%). Lower lobes are affected in only about 2% cases.[1] Bilateral involvement has been reported in very few cases.[3]

The chest radiograph may show a radiolucent lobe, atelectasis of the other lobe(s), and mediastinal shift. The challenge is to determine which side of the X-ray is abnormal, as hyperinflated lobes may be misinterpreted as normal, and the focus may be on the atelectatic or consolidated portions alone. This may be the reason for the infant having been diagnosed as pneumonia twice during the first two hospital admissions. Unilateral lesions can be distinguished from radiological differentials of hyperlucency such as pneumatocele or pneumothorax by the lobar pattern, absence of cysts/cavities in the lung, and absence of pleural involvement. Bilateral lesions are more challenging. CT scans may not be required for the diagnosis, but once a diagnosis is made it helps to delineate the extent of involvement and plan the surgical approach. We strongly discourage the temptation of performing a CT scan in lieu of a meticulous clinical approach and chest radiography. Antenatal detection of CLE is possible using fetal ultrasonography or fetal magnetic resonance imaging.[4] This can help to plan delivery in an institution with facilities for neonatal intensive care and early postnatal surgery. CLE is associated with congenital heart disease in about 20% of cases, including left to right shunt defects and tetralogy of Fallot. Therefore, thorough clinical examination followed by echocardiography is essential.[5,6] Management depends upon the severity.[1-4] Severely symptomatic patients, with progressive worsening, require early lobectomy, whereas conservative approach with close follow-up may be tried in mild or asymptomatic cases. In bilateral lobar emphysema, surgery done in a staged manner can reduce the surgical complication as well as pain to infant.[7,8]

To conclude, infants who are symptomatic from birth with hyperinflated lungs in the absence of wheezing should trigger a search for a congenital malformation. Bilateral lobar over-inflation is very rare, but early diagnosis and management do yield gratifying results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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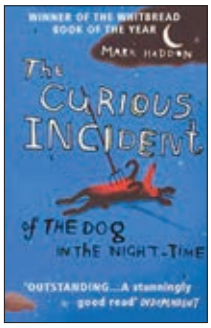
The Curious Incident of the Dog in the Nighttime

Editors comment: In this issue we continue with reviewing books that we believe are linked to the art and science of narrative medicine, by sharing details of the human perspective. This month's selection has a very curious title and is written by Mark Haddon, an acclaimed writer of children's literature, who often self-illustrates his books (do take a look at the cover!). This book was published in 2003 and was his first attempt to reach out to both children and adults. It went on to win the Whitbread Award, the Dolly Gray Children's literature Award, the Guardian Prize and the Commonwealth Writers Prize. Its literary acclaim, however is not the reason why we chose this book. We believe reading this book will help our readers learn to recognize the 'person' in an adolescent with Autism, rather than just the patient.



It was a rainy September evening in 2009. A national developmental pediatrics conference had just concluded; some of us had taken Jane McGrath, Catherine McClain, and Pat Osbourn, faculty from the University of New Mexico to dinner, and Anand Shandilya was regaling them with one lovely anecdote after another. The subject veered toward books and Anand brought up Mark Haddon's "The Curious Incident of the Dog in the Nighttime." The three were great fans of the book and an animated conversation flowed. Soon after, I bought myself a copy. Normally, I am skeptical about reading books on "conditions." Some are self-indulgent, some too specific, and rarely leave you any better learning about the subject. But to have received such exalted reviews meant this one deserved a closer look. In 2009, I had just begun to look at children with autism at our clinics. Autism enjoys the unflattering distinction of being perhaps the most misunderstood condition (un) known to mankind. No wonder then, the range of opinions, judgments, and labels can be confusing. Trying to make sense of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (then) criteria and other textbooks made me wonder if I had a disability. It was all too vague and dogmatic.

The Curious Incident begins with an interesting premise. We are introduced to 15-year-old Christopher Boone who is telling us his story in real time – he is writing it even as it unfolds! It is interesting to note that his chapters are numbered in prime numbers and that the story begins at "7 min past midnight." We are straightaway led into the plot – our protagonist finds Wellington, the neighbor's dog, lying murdered on the lawn. Christopher decides to investigate the "murder" and write a murder mystery novel which paraphrases his analytical approach to the world around him in particular and life in general.

Everything thereafter is narrated in such candid factual detail, bereft of any lacquered motifs, that we soon realize that Chirstopher sees the world differently than most of us. He sees details that we all miss, his world in neatly organized in compartments and rules, and he has no value for hyperbole. Poor Virginia Woolf gets trolled for her "I am veined with iron, with silver and with streaks of common mud. I cannot contract into the firm fist who does not depend on stimulus." He understands simile, abhors metaphors, and considers lies and metaphors to be akin. This dictates his choice of interests – maths and physics over language, machines over men, red color over brown and yellow, straight questions over rhetorical ones, puzzles over people, caring for his pet rat, Toby rather than chatting with his neighbor, Mrs. Alexander, solitude over company and outer space over the London Underground. The fact that he considers the killing of a dog as a crime akin to homicide and that it ought to be investigated with the same seriousness as that of a human, speaks volumes about his love for animals who he finds predictable, as much as his disdain for humans and their vagaries.

The title is telling – the killing of a dog by a human is actually a curious incident (a puzzle-which means it needs to be solved) pertaining to a specific "thing" (the dog) at a specific time (in the "night-time"). As we follow Christopher's emerging novel, we are fascinated by his attention to detail and to his memory for exact dates and in fact, any information he has ever come across. He can describe to the smallest detail a garden, clouds in the sky or the Milky Way as it is seen and remember dates, addresses, and entire conversations to the word. This is both a boon and a curse because sometimes the amount or kind of information to be analyzed, and especially to deal with an emotionally challenging situation, can be very overwhelming. Defense and safety mechanisms are as different-closing out the whole world in his mind, bending over and touching the forehead to the ground or throwing up are ways to deal with anxiety and panic. Touching and hugging can be near traumatic; nonverbal cues like raising an eyebrow have to be matched with mental pictures of emojis to grasp their essence. Anything that cannot be simplified has to be blocked out, in the manner of one of his role models – "Sherlock Holmes, had in a very remarkable degree, the power of detaching his mind at will."

The deeper narrative that ebbs and flows underneath, often turbulent and volcanic at times, is about Chirstopher's family and the relationship of the parents with Christopher and between themselves. The challenges that parents face when bringing up a child with special needs are many. The worst is the challenge to their own self-esteem, their social image, and their resilience and to redeem their lives and build a life which allows them to be what they are. The gulf between duty and guilt is to be bridged with white lies and compromise – a conundrum of small victories and daily setbacks which when thrown together in the cauldron of daily life is indeed a very curious incident by itself. Suffice to say, trust wins over fear, honesty over lies and the sunshine is to be found in the daily ritual called life.

The Curious Incident is a book to be read not just because its protagonist has special needs or a form of autism but because it is a saga of human emotions, and how that plays out in our relationships, our choices, our loves, and our betrayals. It helps us understand how each of us is different in so many ways, how difficult it is for us to understand others and how it is most essential for us to be accepted for who we are and not who we can be.

P. S.: A favorite quote of Christopher is Occam's razor which states "No more things should be presumed to exist than are absolutely necessary." How true!

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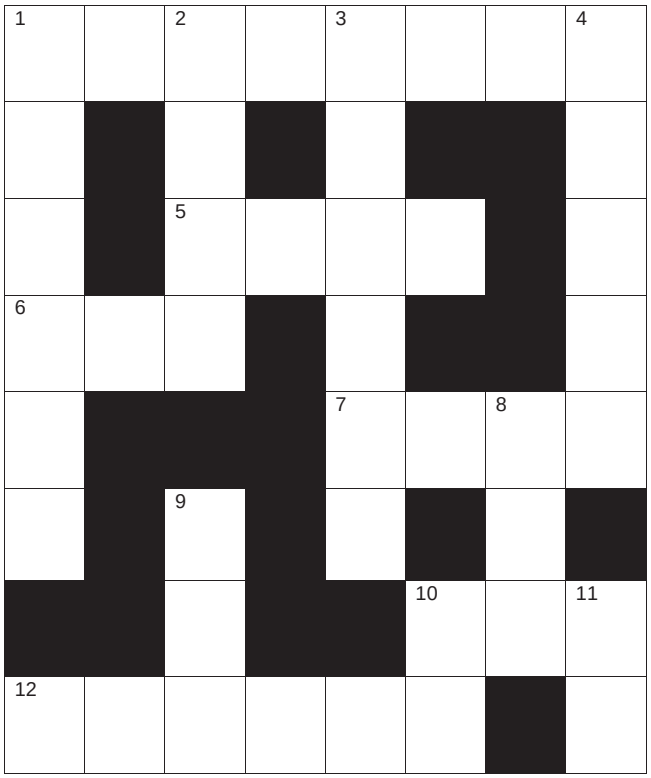
Clinical Crossword: 3 (Theme Nurturing Care)

Please send your answers to ipcares2020@gmail.com. The names of the first 10 readers with correct answers will be displayed on our website.

Across

1. A state in which one is protected from hazards resulting from deliberate human actions (8).
5. The term used to denote the number of deaths of infants per 1000 live births (4).
6. The first woman to have provided nurturing care (3).
7. An activity that if started early by parents can increase the vocabulary of pre-schoolers (4, in conjunction with 11 Down).
10. A type of enzyme that should be monitored in well child visits of children on Sodium Valproate (3, abbr.).
12. The missing word in the motto for Early Childhood Development, Survive, ____, and Transform (6).



Down

1. A state in which one is protected from hazards caused by natural forces (6).
2. Nurturing means provision of this (4).
3. A term used to promote reciprocity of child-parent interactions that is derived from racquet sports, i.e., serve and ___ (6).
4. In positive parenting caregivers are instructed not to do this in response to temper tantrums (5).
8. Universal nurturing care is meant for them (3).
9. A leading form of pollution that causes poor health in infants and children (3).
10. An example of 3 Down. When a child says 'Ae', the parent should say this (2).
11. The word used in conjunction with 7 across (2).

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