ISSN: 2772-5170

Indian Pediatrics Case Reports IPCaRes

VOLUME 2 • ISSUE 1 • JANUARY-MARCH 2022 www.ipcares.org

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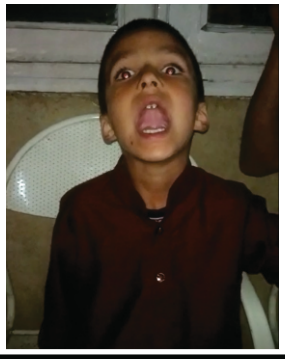

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Humanities

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An Official Publication of the Indian Academy of Pediatrics

Wolters Kluwer Medknow

Indian Pediatrics Case Reports

Volume 2 | Issue 1 | January-March 2022

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Indian Pediatrics Case Reports

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The journal's full text is available online at https://www.ipcares.org. and issues are published quarterly in February, May, August, November. The journal's full text is available online at https://www.ipcares.org. The journal publishes case reports related to pediatrics, neonatology, pediatrics surgery.

Abstracting and Indexing Information

The journal is registered with the following abstracting partners:

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  USD 300 for outside India
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Published by

Wolters Kluwer India Private Limited,
A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol,
Andheri (East), Mumbai - 400 059, India.
Phone: 91-22-66491818
Website: www.medknow.com

Printed at

Nikeda Art Prints Pvt. Ltd., Bhandup (W), Mumbai.

Indian Pediatrics Case Reports

Volume 2 | Issue 1 | January-March 2022

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Giving and Receiving Critical Appraisal: Lessons Learnt

With the release of this issue, we celebrate our first birthday. This year, the editorial board and I learnt several invaluable lessons regarding the running of a medical journal. It is an ongoing learning process, that is largely experiential.

Something that is seldom realized is that once an article is submitted for publication, the author, reviewers, editorial board, and editor are all on the same team. We share a common goal; that a well-written, unique, and scientifically meritorious clinical case is published, read and appreciated, and maybe (the icing on the cake), gets cited or triggers further research. However, sometimes during the editorial process, the partnerships sours, and instead of travelling harmoniously together, paths diverge, and players get estranged. This usually occurs when a critical appraisal is given and received. I would like to share with you a recent incident that made me realize a few important "hard truths".

The first thing we do while finalizing the contents of a forthcoming issue is to take stock of the available articles i.e., accepted or nearly ready (i.e., completed at least two cycles of reviewer-author correction and modification, have only a few creases to be ironed out, and are otherwise potentially "acceptable"). This time, since we were one short, we reviewed articles that were in mid-process (i.e., completed one cycle, has scientific merit, and may be acceptable, provided the authors satisfactorily address the issues raised, and improve the quality). After we shortlisted one, I went through the reviewers' comments, and added my own. Essentially, we highlighted: the lacunae in history, examination, and clinical reasoning; clarifications that were required; changes to be made, and (since timing was critical); explicit instructions outlining how to achieve the desired quality, within the given time frame. To expedite this process, an associate editor (X) was asked to connect with the author directly. On reviewing the letter, X diplomatically told me that it was "a bit rude" and needed to be toned down. I disagreed, believing that desperate times call for drastic measures. I also felt that a personal telephone call would soften the blow. To cut a long story short, though disheartened, the author initially agreed, then got overwhelmed when the premature deadline was crossed and requested withdrawal. Luckily, we could work out things to our mutual benefit, and we now have a very good article.

On introspection, I realized my errors in judgment and have identified strategies to avoid their recurrence. I also offer "my two cents" of advice to authors with manuscripts under review, from the perspective of someone who has also received "brutal" feedbacks, as well as an editor: (i) vent to release all pent up negative emotions, and 'forget about it' for some time (I did not give the author time to process); (ii) Tackle the appraisal only when you have calmed down; (iii) Make a list of all the points that need to be addressed, and to whom; (iv) Check and comply with the journal's system of giving a rebuttal and revision; (v) Answer the easiest ones first; (vi) Thank the reviewers for their intellectual inputs (after all, they invest their personal time without receiving any returns or incentive, and their labor is only acknowledged by the journal) and phrase your response cordially; (vii) If you disagree with any comment, provide recent scientific evidence for support, and politely decline to change; (viii) Do not leave any issue unresolved; (ix) Involve all the authors, and; (x) Show the revised draft and rebuttal to a neutral person experienced in scientific writing for their inputs, before sending it back.

Last but not the least, expect the best, but be prepared for the worst, like a request for further revision. To quote Rumi, the renowned philosopher, "If you are irritated by every rub, how will you be polished?"

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 30-Jan-2022 **Revised:** 31-Jan-2022
Accepted: 01-Feb-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_35_22

How to cite this article: Mukherjee SB. Giving and receiving critical appraisal: Lessons learnt. Indian Pediatr Case Rep 2022;2:1.

Case Series

Jatropha Curcas Poisoning in a Family from Rural Haryana

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Abstract

Background: Jatropha curcas is a flowering plant found all over the world. It has traditionally been used for medicinal purposes and as an ornamental plant. Lately, it is being promoted for biodiesel production. Since it is a commonly grown plant with seeds that are often mistaken as edible nuts, accidental ingestion is common among children. The presence of various plant toxins results in gastrointestinal, hepatic renal cardiotoxic, and hemolytic manifestations. The general public and most pediatricians are unaware of this. **Clinical Description:** We report a case series of thirteen children who presented to the emergency department with lethargy, abdominal pain, vomiting, and diarrhea after acute ingestion of seeds of an unknown plant. The presentation varied in severity of symptoms as well as degree of dehydration, which seemed to correspond to the number of seeds consumed. The parents were asked to bring parts of the plant and the seeds were identified to belong to the Jatropha curcas plant after expert botanical consultation. **Management and Outcome:** All the children were admitted. None of them had manifestations of any specific toxidrome, however, there seemed to be isolated gastrointestinal involvement, clinically. Gastric lavage was done immediately. Intravenous fluid correction was administered based on the severity of dehydration. Supportive treatment with antiemetics and antacids was provided. Baseline investigations were planned to rule out organ dysfunction. The most common derangement was neutrophilic leukocytosis. All children recovered well without any complications or sequelae. **Conclusion:** Jatropha Curcas is a noxious plant that should not be grown in areas where children play. Unknown plant poisoning should be treated with the same gravity as any other poisonous substance. All efforts should be taken to look for indicators of a specific toxidrome in case an antidote is warranted, as well as identify the concerned plant.

Keywords: Dehydration, Jatropha, ricin, shock, unknown poisoning

Acute poisoning with unknown substances is an important cause of preventable morbidity and mortality in children, if the nature of the poison can be determined and the patient managed in time. Common etiological agents include household poisons, drugs, pesticides, detergents, and even plants.[1] Plant poisoning accounts for 1.7% of all poisonous exposure in India, but most cases are accidental and consequences mild in nature.[2] There are nearly 10 known species of plants responsible for most of the accidental poisoning in India. These include *Cleistanthus collinus, Ricinus communis, Abrus precatorius, Strychnos nux-vomica, Gloriosa superba, Calotropis, Datura, Chrysanthemum*, Yellow oleander, and Papaya carica.[2] Young children are susceptible to accidental plant poisoning due to their tendency to put things in their mouths, newly acquired skills of mobility and exploration, and challenges in maintaining constant parental supervision. In contrast, older children may ingest parts of plants due to mistaken identity with edible plants, curiosity, impulsivity, and buckling to peer pressure.

Jatropha curcas, also known as biodiesel plant [Figure 1], is a noxious weed, commonly found throughout India, especially the southern parts.[3] Different parts of this plant are poisonous, like the fruit, seeds, leaf, bark, and latex. Seeds have the maximum toxicity.[4] Apart from growing wild and being cultivated for commercial purposes, it is also used for ornamental purposes in many households. Hence, it is easily accessible to children. Although cases of Jatropha poisoning are not rare, they are uncommonly reported.[5] Thus, there is limited information regarding the toxic effects of Jatropha in toxicology and medicine books,[6,7] as well as less awareness among the general public.

We report thirteen children with unknown plant poisoning that was later identified to be due to the seeds of the "Jatropha" plant. The aim is to sensitize clinicians to look for indicators of a specific toxidrome, probe into the nature of poisoning using

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Submitted: 30-Oct-2021 **Revised:** 20-Jan-2022
Accepted: 28-Jan-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_333_21

How to cite this article: Choudhary S, Gupta S, Sharma N. Jatropha curcas poisoning in a family from rural Haryana. Indian Pediatr Case Rep 2022;2:2-6.

Figure 1: Picture of Jatropha plant with flower and seeds

all possible means, make pediatricians and parents aware of the risks of Jatropha poisoning, highlight the heterogeneity of clinical features, as well as discuss the modalities of management that were used.

Clinical Description

Thirteen children between the ages of 2 and 13 years were brought to the pediatric emergency department with sudden onset of abdominal pain, vomiting, and diarrhea. The children belonged to an extended joint family residing in rural Haryana. All of them had been playing in a nearby field, and each had allegedly consumed an unknown number of black-colored seeds originating from similar looking, but unidentified plants. The children became symptomatic within 30 min to an h of ingestion. Most of them initially developed abdominal pain, which was diffuse, intermittent, and cramping in nature, with intensity varying from mild to severe. After some time, they exhibited nausea, followed by vomiting which was nonprojectile, consisting of food particles and the seeds, and without blood. Subsequently, the children developed profuse watery diarrhea, with a high purge rate. There was no blood or mucus in the stools. None of the children displayed symptoms of headache, seizures, blurred vision, excessive salivation, sweating, difficulty in breathing or tightness in chest, sudden pallor, increased urination, or difficulty in passing urine.

At admission, none of the children had clinical evidence of compromised airways, breathing or circulation, though variability in the extent of dehydration was noted. Three children had tachycardia. None displayed pallor, cyanosis, or flushed skin. Lethargy was observed in the children presenting with severe dehydration. The central nervous system examination was normal with no signs of altered sensorium, miosis/mydriasis, hypotonia/flaccidity, muscle weakness or fasciculations. There was no guarding, rigidity, tenderness, or distension on abdominal examination. The respiratory and cardiovascular systems were unremarkable. The clinical details of individual cases are described in Table 1.

Management and Outcome

The children were triaged according to their symptoms and hemodynamic status on arrival. No particular phenotype of a specific toxidrome could be identified, based on vitals and clinical signs. However, three clinical patterns were discernible, predominantly related to the severity of gastrointestinal manifestations and extent of dehydration [Table 1]. The first group included four children with severe symptoms, signs of severe dehydration, and associated lethargy. The second group included three children with moderate symptoms. They were conscious, alert but had signs of some dehydration. The third group consisted of six children with mild symptoms and no dehydration. On further probing, it became apparent that the severity of symptoms was directly related to the number of seeds consumed. The plant could not be identified by the description given by the older children, so the caretakers were immediately sent home to bring the seeds and leaves for identification.

All the children received management as per the protocol of unknown poisoning: removal or neutralization of toxins and symptomatic and supportive treatment. Each child underwent gastric lavage. Activated charcoal could not be given due to poor tolerance. Fluid resuscitation was according to standard protocol, based on degree of dehydration and age of the affected child. A 13-year-old male child in the first group presented with early signs of hypovolemic shock. He responded well to appropriate fluid resuscitation and did not require inotropic support. Antiemetics and anta-acids were also used. Oral rehydration solution was started once the oral acceptance improved. Stabilization of vitals and improvement in hydration was noted within a few hours. All children were shifted to the ward after initial stabilization.

An important aspect of the management of unknown poisoning is looking for evidence of organ or system damage/dysfunction. Hence, hemogram and biochemical workup (random blood sugar, serum electrolytes, liver and kidney function tests, and coagulation profile) were sent. The former revealed leukocytosis with neutrophilic predominance in eight children [Table 1]. Children with severe dehydration showed mildly raised urea (which normalized with fluid resuscitation) but normal creatinine levels. Urine routine microscopy and electrocardiogram were normal in all the children.

The parents brought the seeds and leaves of the plant the next morning. The expertise of a botanical laboratory was sought, and the plant was identified as Jatropha curcas. The symptoms of all the children resolved within 8–10 h of admission. They were kept under observation and discharged the next day in a stable condition.

Discussion

Jatropha curcas also known as “physic nut,” “purging nut,” and “poison nut” belong to the family Euphorbiaceae and is widely distributed in South East Asia and India.[8] Its

Table 1: Clinical phenotype and laboratory reports of affected children according to dehydration

Group	Severe symptoms with severe dehydration				Moderate symptoms with some				Moderate symptoms with some				
Serial number	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years)	13	8	6	7	10	8	5	3	11	2	6	4	7
Sex	Boy	Boy	Girl	Boy	Girl	Boy	Girl	Boy	Boy	Girl	Boy	Boy	Girl
Seeds eaten (*n*)	12	10	8	8	4	5	3	2	3	2	2	1	2
Symptoms													
Diarrhea (*n*)	20	12	10	10	7	7	5	4	3	4	5	6	2
Vomiting (*n*)	10	7	5-6	4	4	3	2	1	0	2	0	1	0
Abdominal pain (mild/moderate/severe)	Severe	Moderate	Moderate	Moderate	Moderate	Mild	Moderate	Mild	Mild	Mild	Absent	Mild	Absent
Vitals													
Temperature	Cool ext.	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Pulse (rate/vol)	116/feeble	110/good	112/good	98/good	82/good	88/good	96/good	104/good	76/good	108/good	92/good	88/good	80/good
BP (mmHg)	80/58	102/70	94/68	98/66	106/72	102/68	92/58	84/54	110/74	80/56	98/68	86/64	90/66
CRT (s)	>3	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3
S/E													
CVS	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
CNS	Lethargy	NAD	Lethargy	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
R/S	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear
G/I	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
Hb (g %)	9	10.3	8.9	9.6	9.8	10.5	10.2	8.9	12.1	10.4	11	10.7	12.3
TLC (10^3/ul)	22	18	18.6	20	18	17.7	17	11.5	12.4	5.6	9.7	7.7	10.3
DLC													
P	85	84	72	80	80	75	70	52	67	48	55	71	62
L	11	14	23	18	16	22	25	46	28	46	40	26	36
M	2	1	2	1	2	1	2	1	3	4	2	2	1
E	2	1	3	1	2	2	3	1	2	2	3	1	1
Platelets (10^5/ul)	2.7	2.3	2.4	2	2.5	2.8	2.4	2.3	3.2	4.7	1.8	1.7	2.6
Na	136	139	141	138	139	142	141	137	135	142	138	141	148
K (mEq/L)	3.6	3.8	4.3	4	4.6	4.5	4.7	3.6	4.1	3.6	4	4.5	5.3
Creatnine	0.9	0.8	0.75	0.7	0.8	0.7	0.72	0.8	0.9	0.6	0.4	0.7	0.8
Urea (mg/dL)	54	52	40	41	35	32	30	24	40	34	22	28	37
SGOT	45	40	38	42	41	42	41	41	34	37	42	38	32
SGPT (IU/L)	40	35	37	40	37	43	41	38	26	32	28	30	22

BP: Blood pressure, CRT: Capillary refill time, CVS: Cardiovascular system, CNS: Central nervous system, DLC: Differential leukocyte count, E: Eosinophil, G/I: Gastrointestinal system, Hb: Haemoglobin, K: Serum potassium, L: Lymphocytes, M: Monocytes, NAD: No abnormality detected, Na: Serum sodium, P: Polymorphs, RBS: Random blood sugar, R/S: Respiratory system, SGOT: Serum glutamate oxaloacetic transaminase, SGPT: Serum glutamate pyruvic transaminase, TLC: Total leukocyte count

Table 2: Summary of previous scientific literature on Jatropha poisoning

Author	Patients' details	Salient features
Dayasiri *et al*., 2017[1]	325, 9 months-12 years	Large multicenter study in Sri Lanka. Jatropha curcas was the most common plant ingested by children, mostly from gardens
Singhal *et al*.,2013[12]	8, 3-12 years	All children presented with lethargy, severe abdominal pain, and intense thirst. Number of seeds not specified
Singh *et al*.,2010[3]	4, 5-8 years	All patients presented with vomiting, abdominal pain. Only one had diarrhea and constricted pupils. Number of seeds not specified
Koltin *et al*.,2006[14]	4, 3-7 years	Vomiting, diarrhea, and miosis seen in all resembling organophosphorus poisoning. Number of seeds not specified
Levin *et al*.,2000[4]	2, 8.5, and 9.5 years	Both children ate 10 seeds each and presented with severe vomiting, diarrhea, and dehydration

colloquial names include "*Ratanjyot*," "*Jungle Erandi,"* and "*Bagranda*." This plant has been used in the Indian system of traditional medicine for treating ailments such as constipation, abdominal cramps/colic, skin diseases, deworming, purgative, and abortifacient. In recent years botanical research has demonstrated its potential in the production of biodiesel, a renewable biodegradable liquid fuel that is generated from vegetable oils, animal fats or recycled restaurant grease.[9,10] The Central Salt and Marine Chemical Research Institute in Bhavnager, Gujrat, is cultivating the Jatropha plant since the seeds have high amounts of oil that can be easily converted to biodiesel.[3]

Although all the parts of this plant are poisonous, the seeds are most commonly ingested form as they are often mistaken for edible nuts, as was seen in this case series. The adverse effects are primarily due to the presence of toxins such as curcin, ricin, and cyanic acid.[3] Curcin is a toxalbumin that inhibits the 60s ribosomal subunit. It is proteolytic in nature and induces hepatotoxicity and gastroenteritis.[4] Ricin is a toxic glycoprotein that causes acute cell death by inactivating ribosomal ribonucleic acid and leads to hemorrhagic necrosis of several organs.[11] The purgative effect is mostly due to diterpenoids and curcanoleic acid that is found in the in the seed oil.[5]

Three types of side effects have been observed following the ingestion of seeds are gastrointestinal, cardiotoxic, and hemolytic.[11] Abdominal pain, diarrhea, vomiting, and nausea are the most common gastrointestinal manifestations.[12] Table 2 presents available scientific literature related to children presenting with gastrointestinal manifestations. The combination of diarrhea and vomiting in the presence of pupillary constriction resembles organophosphate poisoning which is an important differential diagnosis of Jatropha poisoning. None of the children in this series presented with cholinergic signs or symptoms such as meiosis, excessive salivation, lacrimation, or sweating. The ricin toxin mainly causes cardiotoxic effects such as tachycardia, hypotension, peripheral circulatory collapse, and electrocardiographic changes.[11] Hepatic and renal dysfunction, as well hemolytic changes including agglutination of red blood cells, has been observed. None of these were noted in any of the affected children.

The treatment of Jatropha poisoning is essentially symptomatic and supportive, as there is no specific antidote. The initial steps of any acute unknown poisoning involve the assessment and stabilization of airway, breathing, and circulation. The secondary goal is to try to identify the unknown substance. Decontamination should be performed by either gastric lavage or administration of oral activated charcoal (once corrosive poisoning has been excluded) to prevent further absorption of ingested toxins. Active elimination techniques like forced diuresis, urinary alkalinization, whole bowel irrigation, and dialysis may be considered in unknown poisoning if indicated.[13] In this case series, we followed gastric decontamination with gastric lavage, fluid resuscitation and symptomatic treatment with antiemetics and antacids. A review of existing literature found mention of fluid resuscitation (including management of hypovolemic shock) and antiemetics.[11,15] We were unable to find any report requiring alkalization of urine or dialysis.

Conclusion

To conclude, poisoning with unknown substances and/or plants is common in children. There is a strong felt need to create public awareness about the detrimental effects of growing such poisonous plants in the vicinity of areas where children play. Clinicians should familiarize themselves with the protocol for unknown poisoning and recognition of various toxidromes. All attempts should be made to try to identify the plant or substance in question.

Lessons learnt

- Jatropha poisoning is a well reported poisoning in children which needs the creation of more awareness among parents and physicians for initiation of timely management
- The most common symptoms are gastrointestinal (vomiting, diarrhea and abdominal pain), which may progress to involve the liver and kidney
- The toxic effects of the plant are due to the ricin component in the seeds, and appears. to be directly proportional to the number of seeds consumed.

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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Three Indian Siblings Affected with Progressive Myoclonic Epilepsy due to Unverricht–Lundborg Disease

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Abstract

Background: Progressive myoclonus epilepsy (PME) is a group of heterogeneous genetic disorders characterized by action myoclonus, epileptic seizures, and progressive neurologic deterioration with onset of symptoms in adolescence and adulthood. Unverricht–Lundborg disease (ULD) is the most common type of PME in high-income countries; however, it is under-reported from India due to challenges in clinical recognition and establishment of diagnosis due to lack of availability of genetic studies. **Clinical Description:** We herewith report three siblings (two girls and a boy) born out of a third-degree consanguineous marriage, with onset of "difficult-to-treat" seizures since early adolescence, with concurrent action myoclonus and ataxia. All three had a waxing and waning course. Electroencephalography exhibited generalized spike-wave and polyspike-wave discharges with photosensitivity while neuroimaging was normal. **Management and Outcome:** The possibility of PME was considered in view of the clinical phenotype and strong family history. Following detailed elicitation of history, focused physical examination, and rational investigative work-up specific molecular genetic testing were planned for ULD. This showed homozygous expansion of dodecamer (set of 12 nucleotides) repeat in the cystatin B gene in all the three affected siblings. The parents were heterozygous carriers. Genetic counseling was undertaken and anticonvulsant drugs (ACDs) modified accordingly. The definitive diagnosis helped in accurate prognostication and management to improve the quality of life of all three siblings. **Conclusion:** Clinicians should consider a specific epilepsy syndrome in patients with onset of symptoms in adolescence. ULD is a type of PME with a relatively better course of illness. Establishing the diagnosis has implications on the extent of investigative workup, choice of ACD, and prognosis.

Keywords: Action myoclonus, generalized epilepsy, progressive myoclonic epilepsy, Unverricht–Lundborg disease

As a clinician, it is very important to know the difference between epilepsy and epilepsy syndrome. Epilepsy is a common neurological condition that is characterized by an enduring predisposition to generate recurrent seizures. In contrast, an epilepsy syndrome refers to a cluster of features occurring together, including age at onset, seizure type, triggers, remission (wherever applicable), and electroencephalogram (EEG) findings. These have etiologic and prognostic implications.[1] The epilepsy syndromes with onset in adolescence include genetic generalized epilepsies (GGEs) and progressive myoclonus epilepsies (PMEs).

GGE usually has their onset around adolescence, is characterized by generalized seizures (i.e., generalized tonic–clonic, myoclonic, absence, etc.), and display generalized epileptiform discharges on EEG. These include Juvenile myoclonic epilepsy (JME), Juvenile absence epilepsy, and epilepsy with generalized tonic–clonic seizures (GTCS) on awakening. On the other hand, PME is a group of rare, autosomal recessive disorders, characterized by action myoclonus (mostly drug-resistant), epileptic seizures with abnormal EEG background activity, progressive neurologic deterioration, and reduced life expectancy in most. These account for about 1% of childhood epilepsies.[2]

The PME spectrum includes heterogeneous entities; Unverricht–Lundborg disease (ULD), Lafora body disease (LBD), neuronal ceroid lipofuscinosis (NCL), myoclonic epilepsy with ragged red fibers (MERRF), Gaucher's disease, and sialidosis.[2] Understandably, individual workup is exhaustive, challenging, and expensive. A study from India on the spectrum of PME observed that an etiologic diagnosis was not reached in most cases, primarily due to the prohibitive cost of genetic studies.[3]

ULD is the most common type of PME. Typical clinical manifestations include stimulus-induced myoclonic seizures (i.e.,

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Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_205_21

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Submitted: 30-Jan-2022 **Revised:** 02-Feb-2022
Accepted: 02-Feb-2022 **Published:** 25-Feb-2022

How to cite this article: Srivastava K, Thakor BM, Roy S, Rajadhyaksha S, Datar C. Three Indian siblings affected with progressive myoclonic epilepsy due to unverricht–Lundborg disease. Indian Pediatr Case Rep 2022;2:7-11.

triggered by movement, stress, and sensory stimuli), GTCS, ataxia, and mild cognitive decline. At the onset, these symptoms may mimic GGE, resulting in misdiagnosis. ULD is endemic in several Baltic countries, the highest point prevalence being 1.91/100,000 persons in Finland.[4] An important reason for under-reporting in underdeveloped countries is unavailability of diagnostic facilities locally.

In this case series, we describe an Indian family with three siblings affected with ULD, in which the diagnosis was possible only after we collaborated with an international institute for genetic studies. At the same time, we would also like to emphasize that even in this era of sophisticated investigations, the value of a systematic clinical approach to narrow down the differential diagnoses and choose the most appropriate test for confirmation of diagnosis cannot be underscored.

Clinical Description

The index child, a 17-year-old girl, was referred to us for GTCS that was present since she was 10 years old. These occurred every 2–3 months despite having received multiple combinations of anticonvulsant drugs (ACDs) since the onset; these included valproate, oxcarbazepine, levetiracetam, clonazepam, topiramate, lamotrigine, lacosamide, and even a short course of steroids. Review of the available investigations showed generalized spike-wave and polyspike-wave discharges on her EEG and a normal magnetic resonance imaging (MRI) of the brain.

After the first GTCS, she developed unusual jerky movements of her arms and legs that occurred while attempting any movements. These worsened when performing voluntary activities such as getting up from the chair, or climbing onto the bed, and also, under emotional duress (e.g., during her examinations), or on exposure to bright light and loud sounds. The child was sure that these differed from her seizures in terms of duration (these lasted for few seconds) and nature and occurred irrespective of whichever ACD she was on. Initially, she could control or mask them to a certain extent, but they had become progressively disabling. In fact, the severity increased to such an extent that she had frequent falls, was unable to sit in the classroom, and had to drop out of school. However, she was still able to perform her activities of daily living, independently. On probing further, it became apparent that the jerks had a waxing and waning course, i.e., there were periods of worsening (lasting for weeks to months) followed by improvement. In addition, she described feeling imbalanced while walking (that we ascribed to ataxia) and tremors which also increased during voluntary movements. There was no dysphagia, dysarthria, or any visual or auditory hallucinations. Her academic performance had been satisfactory while she was still attending school. The parents did not feel that she was exhibiting any memory loss. Features of mild cognitive decline and morning drowsiness were ascribed to the multiple ACD.

The girl was born of a 3rd-degree consanguineous marriage. The antenatal and perinatal history was normal. Her development in the initial years was parallel to her peers. The detailed three-generation pedigree is presented in Figure 1. There was a significant family history of similar complaints in her younger sister and brother.

The affected sister was 5 years younger than the index child. The onset of her GTCS was at 11 years of age, occurring twice a month in the initial 2 years. She had been prescribed valproate, lamotrigine, zonisamide, and clonazepam without significant abatement till the 3rd year which lasted for a year. However, after that, the frequency increased substantially, causing her to drop out of school. The parents noted a mild cognitive decline whenever there were very frequent GTCS. She also had severe action myoclonus, bradykinesia, ataxia, and tremors.

The youngest brother (whose twin sister was unaffected) had his first GTCS at the age of 11 years, was seizure free for a year (during which period action myoclonus was noted), and currently has very frequent GTCS, for which he is on levetiracetam, clonazepam, and valproate. He does not have ataxia, tremors, or cognitive decline. The child is attending school, though he has frequent absenteeism due to the seizures. The clinical details of the three siblings, including medications and clinical course, are presented in Table 1.

On examination of the index case, her heart rate, respiratory rate, blood pressure, and body mass index were normal. There was no dysmorphism or neurocutaneous markers, but her facies appeared mask-like. She was unable to climb onto the patient bed for examination and had hesitancy in walking due to the fear of fall. Her muscle bulk, tone, power, and reflexes were normal. Myoclonus was observed which increased in amplitude and frequency on attempting movements. She also had bradykinesia, mild ataxia, and tremulousness. The respiratory, cardiovascular, and abdominal examinations were normal. The ophthalmological evaluation revealed normal vision without oculomotor apraxia (excluding Gaucher's disease). The fundus examination did not detect a cherry-red spot, retinitis pigmentosa, or optic atrophy, the presence of which would have indicated Gaucher's disease, MERRF, and NCL, respectively.

We investigated all the siblings, as per protocol. Each of them had similar EEG findings; generalized spike-wave and polyspike-wave discharges with photosensitivity [Figures 2 and 3]. The MRI (epilepsy protocol) of the index case and younger sister were normal.

Based on the clinical phenotype of the family, we considered both JME and PME. JME seemed less likely in view of the spectrum and severity of their symptoms (action myoclonus, ataxia, and tremors) and drug refractoriness. The likelihood of the PME spectrum seemed higher. We decided to review all the available clinical information and see which one seemed most suitable to avoid wasting resources and time on a battery of investigations to rule out all the other PME.

The probability of ULD was highest in view of the waxing–waning course, absence of significant cognitive decline, and a normal brain MRI. Since genetic testing was unavailable in any center in India, we collaborated with investigators based in Finland, and samples of the whole family were sent to look for expansion of

Table 1: Clinical details of three Indian siblings with Unverricht–Lundborg disease

Parameter	Index child	Younger sister	Younger brothe
Age at presentation	17 years	13 years	11 years
Age at onset of symptoms	10 years	11 years	11 years
Initial symptoms	GTCS every 2-3 months	GTCS twice a month	GTCS one per year
Other symptoms	Severe action myoclonus, tremors, ataxia	Severe action myoclonus, bradykinesia, tremors, ataxia	Mild action myoclonus
Cognition	Mild decline	Mild decline	Preserved
Scholastic performance	Dropped out of school due to myoclonus	Dropped out of school as unable to cope	Goes to school, average in studies
EEG findings	GSWD, GPSWD, PPR	GSWD, GPSWD, PPR	GSWD, GPSWD, PPR
MRI brain	Normal	Normal	Not done
Anticonvulsant therapy received	Valproate, clonazepam, levetiracetam, topiramate, lamotrigine, lacosamide, piracetam	Valproate, clonazepam, levetiracetam	Levetiracetam, clonazepam
Received elsewhere*	Oxcarbazepine* Steroids*		
Clinical progression	10-12 years - GTCS every 2-3 months 12-14 years - action myoclonus, tremors, ataxia 14-16 years - No GTCS, Mycolonus improved 16-18 years - Frequent GTCS, status epilepticus 18-23 years - Single seizure, myoclonus better controlled	11-13 years - high frequency of GTCS, severe myoclonus 13-14 years - relative improvement 14-16 years - worsening of seizures 16-17 years - quiet period, with no GTCS, myoclonus improving	12-13 years - Only single seizure 13-14 years - Very frequent GTCS requiring admission
Current status, medications	24 years, married, on levetiracetam, lamotrigine, and clonazepam	19 years, currently on valproate, clonazepam Levetiracetam	14 years, currently on

* these drugs are normally not used in generalized seizures. EEG: Electroencephalography, GPSWD: Generalized polyspike-wave discharges, GSWD: Generalized spike-wave discharges, GTCS: Generalized tonic–clonic seizures, PPR: Photoparoxysmal response (activation of generalized discharges on photic stimulation), MRI: Magnetic resonance imaging

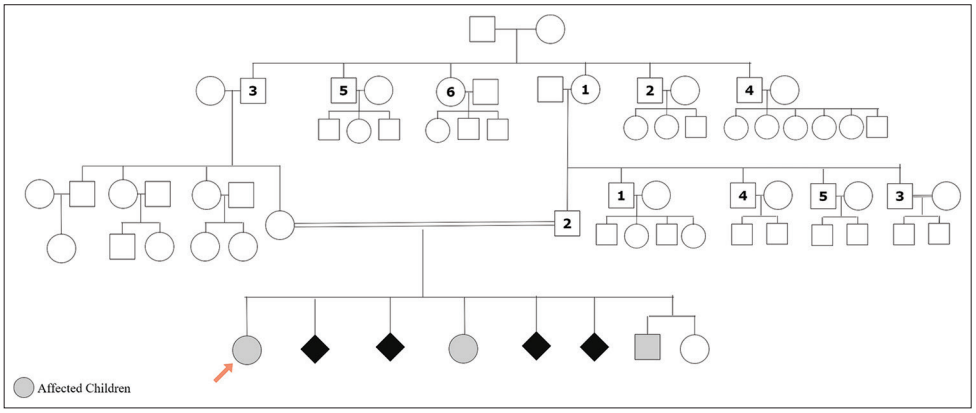

Figure 1: Three-generation pedigree chart of the family

dodecamer repeats in the cystatin B (*CSTB*) gene on polymerase chain reaction (PCR). This was detected in all the three affected siblings, and the parents were found to be heterozygous carriers of the same. The final diagnosis of all three siblings was ULD.

Management and Outcome

All the three siblings were managed on varying combinations of broad-spectrum ACD that included sodium valproate, lamotrigine, clonazepam, and topiramate. Despite medications, there was a fluctuating course wherein the myoclonus and/or GTCS worsened periodically to a degree that interfered with activities of daily living. None of the drugs were effective in controlling the action myoclonus during the "worse periods."

Formal assessment of intelligence quotient could not be done. However, the parents noted that the sisters showed mild cognitive decline. Till the last follow-up, the brother was attending school during the good periods. Both the sisters had to drop out of school due to disabling myoclonus. The index case is recently married and contemplating pregnancy. Her medications were modified and antenatal follow-up was planned with our obstetric colleagues.

The establishment of diagnosis helped in prognostication of the affected individuals and family. They were counseled regarding the relatively better prognosis in terms of possibility of disease stabilization after a few years. This is in contrast to other disorders included in PMEs, which have a uniformly fatal outcome, such as NCL and LBD.

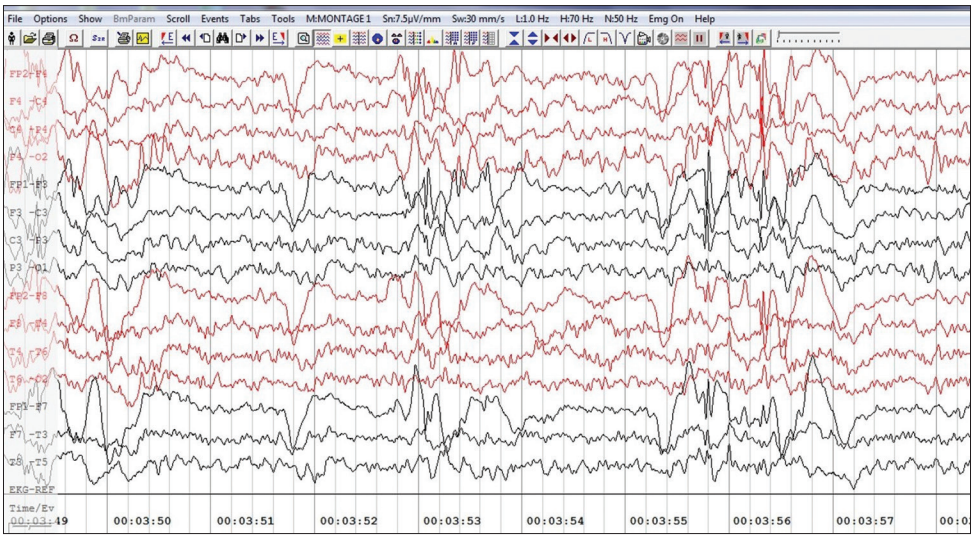

Figure 2: Electroencephalogram in awake state showing frequent multifocal and generalized spike and polyspike-wave discharges

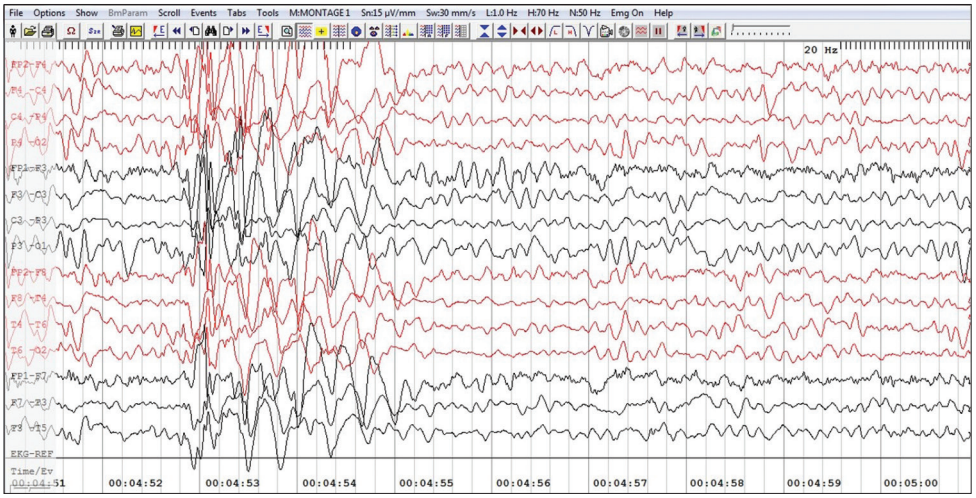

Figure 3: Electroencephalogram showing generalized high-amplitude spike-polyspike–slow-wave discharge (photoparoxysmal response) during photic stimulation at frequency of 15 Hz

Discussion

Epilepsy syndromes are distinctive syndromes that can be differentiated according to the typical age of onset (as in this case series), specific EEG characteristics, seizure semiology, and other nonseizure-related characteristics, such as cognitive affection and drug responsiveness. Classification of a specific epilepsy syndrome has implications on the extent of investigative workup, choice of ACD, and prognosis.

The two close differentials considered in this family were JME and PME. ULD shares features of both PME (refractory myoclonus, ataxia, tremors) and GGE (no evidence of progressive neurological deterioration, cognitive decline, etc.). The most characteristic feature which differentiates it from both GGE and other forms of PME is the waxing and waning periods – alternating periods of relative quiescence interspersed with periods of refractory seizures.[5] In ULD, the ataxia, tremors, and cognitive disturbances are much milder and appear later and stabilize after a few years.[6]

A step-wise approach encompassing detailed elicitation of history and examination can help reach a diagnosis and prevent unnecessary and invasive investigations, which are likely to have poor yield. Some of the PMEs have clinical indicators which can help in narrowing down the differentials: visual hallucinations (LBD); myopathy, neuropathy, and cardiomyopathy (MERRF); visual impairment, optic atrophy, or cherry-red spot (NCL/sialidosis); oculomotor apraxia or hematological manifestations (Gaucher's), etc.[7] Hence, elicitation of a detailed history and performance of a thorough examination provides direction to the planning of further investigations that include: bone marrow examination (Gaucher's disease), skin biopsy (Lafora disease), CSF lactate and muscle biopsy (MERRF), and genetic studies (NCL, ULD, etc.).

ULD is caused by mutations in the *CSTB* gene mapped to chromosome 21q22.3. This gene regulates the production of *CSTB*, a protein that reduces the activity of lysosomal cathepsins (enzymes that break down proteins). Deficiency

of CSTB predisposes neurons to oxidative stress, causing neuronal death.[8] The mutation is an unstable dodecamer repeat CCC-CGC-CCC-GCG expansion in the promoter region. Two to three dodecamer repeats are normal, 12–17 repeats are unstable without clinical manifestations, while more than 30 dodecamer repeats are pathogenic. Genetic testing is by Southern blot or PCR (as was done for this family). The mutation may be missed in exome sequencing studies.[6] Carrier testing is recommended for the spouse of affected individuals in communities with high frequency of consanguinity. Antenatal targeted testing for the dodecamer repeat expansion is available.[8]

Broad-spectrum ACDs such as valproate, levetiracetam, topiramate, zonisamide, clonazepam, and piracetam have shown variable response in seizure control.[9] Recent studies report the efficacy of brivaracetam and perampanel for both myoclonus and generalized seizures.[10,11] Narrow spectrum drugs such as phenytoin, carbamazepine, and oxcarbazepine should be avoided as they may exacerbate myoclonic seizures.

ULD is a PME with a relatively better course with respect to other PME: The myoclonus worsens for 5–10 years and then stabilizes, and epilepsy may also remit after 10–15 years with abatement of EEG changes.[12] In the past, life expectancy was only 8–15 years after the symptoms began. However, recently with newer supportive treatments, individuals with milder forms can live into their seventies.[12]

Lessons learnt

- PME and JME are the epilepsy syndromes that should be considered when the age of onset of generalized seizures is in adolescence
- PME is a group of rare and heterogeneous disorders characterized by action myoclonus, epileptic seizures, and progressive neurologic deterioration, including ataxia and cognitive decline
- Although ULD is the most common PME in high-income countries, it is under-reported from India. This may be due to challenges in clinical recognition and difficulties in establishing genetic diagnosis.

Acknowledgments

We thank Dr. Anna - Elina Lehesjoki and Dr. Tarja Joensuu of Biomedicum Helsinki, Folkhalsan Research Center, University of Helsinki, Finland, for conducting the genetic studies.

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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Biotin Supplementation in Children with Symptomatic Profound Biotinidase Deficiency and their Pregnant Mothers

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Abstract

Background: Biotin is the coenzyme of multiple carboxylases involved in gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Biotinidase (BTD) deficiency is an autosomal recessive disorder affecting the biotin cycle. It disrupts endogenous biotin recycling and results in multiple carboxylase deficiency depending upon the level of enzyme activity. Children with profound deficiency often present in infancy with neurocutaneous manifestations. Management of symptomatic children or screen-positive newborns is lifelong oral supplementation with biotin. There may be partial or complete resolution of symptoms in the former. **Clinical Description:** We describe two unrelated families diagnosed as profound BTD deficiency, with three affected children in each family. The first family had two symptomatic surviving children, a 2-year-old boy with seizures, developmental delay, and hearing loss, and a 1.5-month-old boy with seizures. Diagnosis was established while ascertaining etiology for seizures refractory to multiple anticonvulsant therapy. The second family was referred for postconceptional counseling following two infantile deaths with similar phenotype, early-onset seizures, encephalopathy, and acute metabolic decompensation. **Management:** The affected children in the first family showed a dramatic response in seizure controls with oral biotin though the other symptoms such as developmental delay and hearing loss remained unaffected. Mother was advised regarding prenatal diagnosis in the next pregnancy but was unwilling. In the second family, stored genetic material from the earlier affected infant revealed a pathogenic homozygous indel in the *BTD* gene, which was confirmed *in utero* in the subsequent pregnancy. Both women were started on oral biotin on the lines of antenatal management of holocarboxylase synthetase deficiency. After birth, therapy was continued on the confirmation of profound BTD deficiency in both babies. They have remained asymptomatic on follow-up; the first baby till a year and the second till 3 months. **Conclusion:** There is a considerable phenotypic variability in profound BTD deficiency. Early detection and prompt treatment with biotin may result in complete resolution of some symptoms and ameliorate others. Antenatal biotin supplementation in families at high risk or with prenatal diagnosis of BTD deficiency may have a favorable outcome in affected progeny.

Keywords: Alopecia, encephalopathy, hearing loss, multiple carboxylase deficiency, seizures

Biotin is a water-soluble vitamin that exists as a free form or protein bound biotinylated peptide. It is the coenzyme of multiple carboxylases involved in gluconeogenesis, fatty acid synthesis, and amino acid catabolism [Figure 1].[1] Inactive apoenzymes get converted to active holoenzymes after linkage with free biotin through reactions involving the holocarboxylase synthetase (HLCS) family of enzymes.[1] Biotinidase (BTD) is an enzyme that maintains the biotin pool by recycling bound and releasing protein bound biotin. BTD deficiency is an autosomal recessive disorder resulting from homozygous or compound heterozygous mutations in the BTD gene, which depletes the biotin pool, and results in multiple carboxylase deficiencies. Globally, the incidence is 1 per 40,000–60,000 births.[2] BTD deficiency was the most common (6.5%) inborn error of metabolism (IEM) in an Indian study of screen-positive neonates.[3]

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DOI: 10.4103/ipcares.ipcares_12_22

Classification of BTD deficiency is based on the level of mean serum activity; profound (<10% activity) and partial (10%–30% activity). There is a significant variability in clinical presentation that may not commensurate with level of activity.[1] Although the mean age of presentation of profound BTD deficiency is 3.5 months, the age at which symptoms can appear varies from as early as 1 week to as late as 10 years.[4] The clinical manifestations are

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Submitted: 15-Jan-2022 **Revised:** 01-Feb-2022
Accepted: 04-Feb-2022 **Published:** 25-Feb-2022

How to cite this article: Mishra R, Gupta MB, Mukherjee SB, Lomash A, Gupta S, Kapoor S. Biotin supplementation in children with symptomatic profound biotinidase deficiency and their pregnant mothers. Indian Pediatr Case Rep 2022;2:12-6.

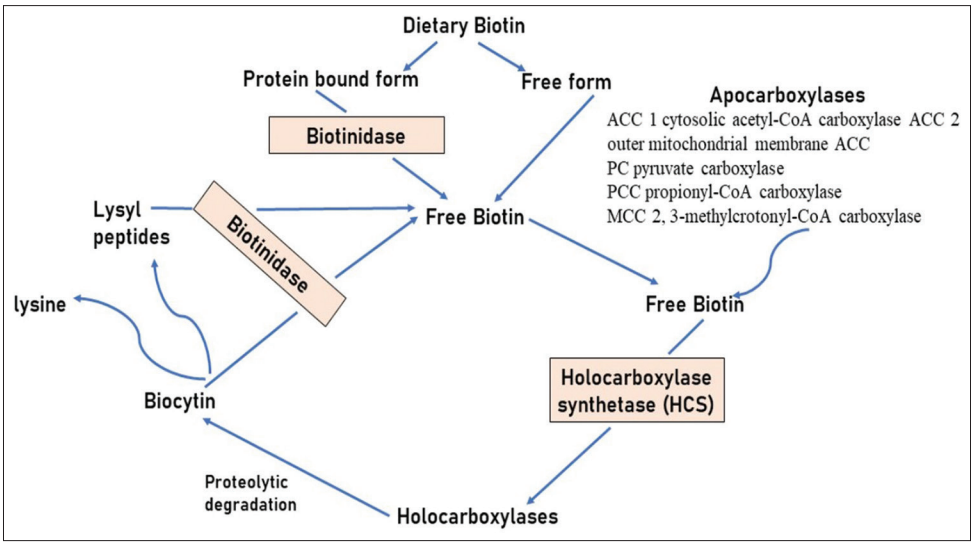

Figure 1: The biotin cycle (Adapted from Mathias R *et al*.)

usually neurocutaneous including ataxia, developmental delay, hypotonia, seizures, conjunctivitis, skin rashes, and alopecia.[4] Other manifestations include hearing loss (75%) and visual problems (50%).[4] Acute episodes of metabolic decompensation resulting in encephalopathy or death have rarely been reported.[5] Partial deficiency results in milder symptoms that are precipitated by stressful conditions such as infections.[4,5] All screen- positive newborns and symptomatic individuals should be managed with lifelong oral biotin.[1] Positive outcomes have been reported after daily biotin supplementation (10 mg) during pregnancy, in women at risk of, or with antenatally diagnosed HLCS deficiency, a disorder that also involves the biotin cycle. Although scientifically the same principle should apply in BTD deficiency, we were unable to find the reports of or studies on antenatal supplementation.

This case series highlights several interesting facets that emerged from the management of two families with profound BTD deficiency in terms of clinical presentation and the positive outcomes of antenatal and postnatal biotin supplementation.

Clinical Descriptions

Family 1

A 1.5-month-old boy was brought by his parents with complaints of multiple seizures for a week. Each episode involved stiffening and jerky movement of all his limbs and transient loss of consciousness lasting for a few seconds, and occurring 5–10 times a day. The baby was active and breastfeeding well in between each seizure. There was no history of fever, vomiting, loose stools, skin lesions, lethargy, trauma, or prior vaccination. The antenatal period was uneventful, with normal perception of quickening and fetal movements. The baby was born at term by normal delivery with birth weight 3.5 kg, normal APGAR scores and was discharged within a day.

He was the fourth issue of a third-degree consanguineous marriage [Figure 2a]. The parents were asymptomatic. The first child was a typically developing 3.5-year-old boy. The second issue was a boy born at term, with normal antenatal and perinatal periods, who developed seizures at the age of 2 months. The infant succumbed after 2 weeks without the cause of seizures being ascertained. The third child was a 2-year-old boy with developmental delay, hearing impairment, and generalized tonic–clonic seizures, which started when he was a year old. His seizures were persisting despite the use of phenytoin and sodium valproate [Table 1].

Vital parameters and anthropometry of the proband were normal. The cranium, spine, skin, and hair were normal. The infant was not dysmorphic and had no neurocutaneous markers. The only salient neurodevelopmental finding was mild generalized hypotonia. Remaining systemic examination was normal. The evaluation of the first child was normal, whereas the third was symptomatic [Table 1].

Preliminary first-line biochemical investigations excluded hypoglycemia and hypocalcemia. The biomarkers for sepsis were negative. The cranial ultrasonogram was normal, but electroencephalogram showed multifocal sharp waves. Automated brain stem response revealed profound bilateral sensorineural hearing impairment (SNHI). BTD deficiency was strongly considered in the family in view of various clinical manifestations, seizures, SNHI, and developmental delay. Enzyme assay confirmed profound deficiency in both symptomatic children with normal BTD levels in the parents and unaffected sibling. After genetic counseling, the affected individuals were started on 20 mg of daily oral biotin. Follow-up after a year of therapy showed significant improvement as depicted in Table 1.

The mother conceived again after 1.5 years. Although the parents were concerned regarding the outcome, they were unwilling for prenatal diagnosis. After a genetic consultation at 6-week gestation, they decided to start oral biotin supplementation (20 mg daily). Compliance was good and

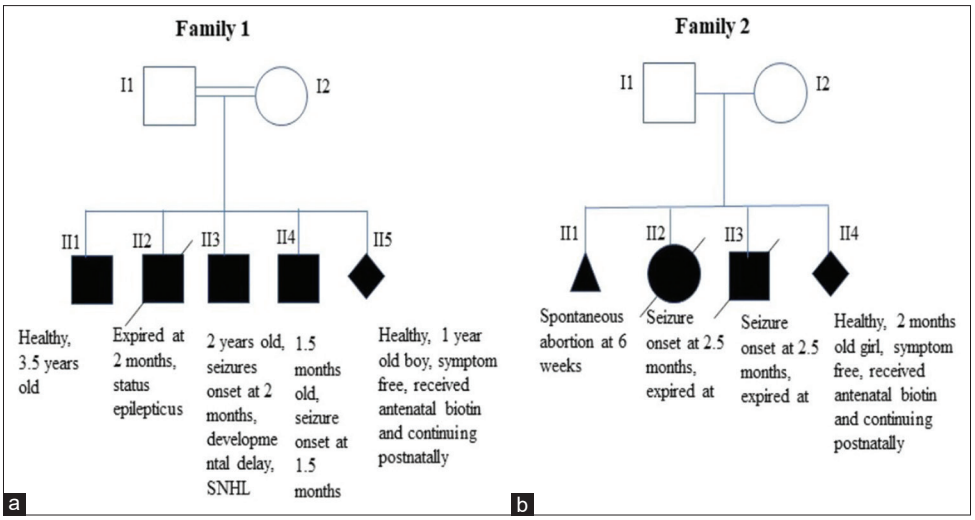

Figure 2: Three generation pedigree of family 2 (a) and family 2 (b)

Table 1: Clinical details of affected members with profound biotinidase deficiency

Details	Family 1			Family 2		
Birth order/sex	**4 boy**	**3 boy**	**5 boy**	**1 girl**	**2 boy**	**3 girl**
Age at presentation	1.5 months	3 years	3 days	2.5 months	3.5 months	At birth
Age of onset of symptoms	1.5 month Seizures	2 months Seizures	None	2.5 months Seizures	3.5 months Seizures	No symptoms
Age when biotin started	1.5 months	3 years	Antenatal and first day onwards	Not started	Not started	Antenatal and first day onwards
Developmental delay	Not apparent	+	−	+	+	−
Language delay	Not apparent	+	−	Not apparent	Not apparent	−
Seizures	Multifocal	GTCS	−	GTCS + myoclonic jerks	GTCS + myoclonic jerks	−
Hearing loss	−	+	−	−	−	−
AbN vision	−	None	−	−	−	−
Hypotonia	+	+	−	+	+	−
Spasticity	−	−	−	+	Details NA	−
Alopecia	−	−	−	+	+	−
Hearing assessment	Profound SNHI	Profound SNHI	Normal	Not done	Not done	Normal screening
Visual acuity	Normal	Normal	Normal	Not done	Not done	Normal
EEG	Multifocal sharp waves	Multi-focal sharp waves	Not done	Details NA	Not done	Not done
Neuroimaging	CECT Normal MRI normal	CECT normal MRI normal	USG cranium normal	MRI - bilateral WM hyperintensities	Not done	Not done
Biotinidase levels	Profound deficiency	Profound deficiency	Profound deficiency	Profound deficiency	Not done	Profound deficiency
Metabolic tests	Normal	Normal	Normal	Abnormal	Details NA	Normal
Genetic testing	Not done	Not done	Not done	Not done	Null indel	Null indel
Biotin	Postnatal	Postnatal	Ante and postnatal	−	−	Ante and postnatal
Status after biotin therapy	Seizure free, no hypotonia language delay	Seizure free, developmental delay and hypotonia persisting	No symptoms	Deceased	Deceased	Symptom free at 2 months

AbN: Abnormal, ACT: Anticonvulsant therapy, BERA: Brain evoked response auditory, CECT: Contrast-enhanced computed tomography, EEG: Electroencephalogram, GTCS: Generalized tonic−clonic seizures, MRI: Magnetic resonance imaging, NA: Not available, SNHL: Sensorineural hearing loss, USG: Ultrasonography, WM: White matter, +: Present, −: Absent

the pregnancy proceeded normally. A baby boy weighing 3 kg was born at term. He was started on crushed oral biotin mixed with breast milk from day 1. Enzyme assay identified profound BTD deficiency. The infant is under follow-up and remains asymptomatic at 1 year [Table 1].

Family 2

A fourth gravida 6 weeks pregnant woman presented to the genetic clinic for postconceptional counseling in view of two infantile deaths, one of which was due to profound BTD deficiency [Figure 2b]. The first pregnancy was an 8 weeks spontaneous abortion. The second pregnancy resulted in a girl delivered by cesarean section (indication being breech presentation), weighing 2500 g, and discharged on exclusive breast feeds after 4 days. She developed multiple seizures (generalized tonic–clonic seizures and flexor spasms) at 2.5 months, followed by poor feeding and lethargy within 3 days. There was no history of fever, loose motions, vomiting, or trauma. Photographs were unavailable but review of medical documents revealed the absence of social smile, hypertonicity, and exclusion of hypoglycemia, hypocalcemia, and hyper/hyponatremia. Seizures persisted despite the administration of phenobarbitone, levetiracetam, and sodium valproate. Parenteral antibiotics were started empirically. Carnitine and sodium benzoate were added suspecting an IEM. She was placed on ventilatory support within 3 days. Cranial noncontrast computed tomography revealed bilateral hyperintensities in the periventricular, frontal, and cerebellar white matter. Significant metabolic abnormalities were identified including lactic acidosis (lactate 6.0 mmol/L and pH 7.3), increased plasma ammonia (227 μg/dl), increased urinary excretion of 3-hydroxy isovaleric and 3-hydroxypropionic acids on gas chromatography–mass spectrometry (GCMS), and elevated plasma hydroxy valeryl carnitine on tandem mass spectroscopy (TMS). This metabolic profile suggested multiple carboxylase deficiency, and BTD assay revealed profound deficiency. Despite counseling, the family did not consent for genetic studies or deoxyribonucleic acid (DNA) storage. The child died after 3 days.

The third conception was a boy born at term weighing 2900 g, with no significant antenatal or perinatal history. The parents noted that he had sparse scalp hair, but normal skin (similar to the previous issue). At 3.5 months, the infant developed multiple seizures for which he was admitted in a private hospital. Clinical details were procured from history and the review of past records. It was learnt that seizures continued despite being administered phenobarbitone, valproate, levetiracetam, and clonazepam. The next day, he became unresponsive and was given ventilatory support, but he expired within 5 days. The baseline hemogram and first-line biochemistry reports were normal, and sepsis screen was negative. Plasma acylcarnitine analysis exhibited elevated nonspecific metabolites that were attributed to the critical premortem state. BTD levels were unavailable. DNA was stored for future evaluation.

Taking all clinical details into consideration [Table 1], the plan for the fourth pregnancy included genetic counseling, the need for processing the stored DNA, options for prenatal diagnosis, and administering antenatal biotin (10 mg twice a day). Clinical exome study performed on the stored DNA of the previous issue identified a pathogenic homozygous insertion and deletion (indel) in exon 4 of the BTD gene (c. 98_104delinsTCC; p. Cys33PhefsTer36).This has been reported earlier in BTD deficiency[6] and is known to cause frameshift termination 36 amino acids downstream of codon 33. After chorionic villus sampling, Sanger sequencing identified the same mutation. The couple was appraised of the likelihood of an affected fetus. Maternal risks of surgical termination of pregnancy in view of previous cesareans were discussed. An educated decision to continue the pregnancy with biotin supplementation was taken by the parents. The pregnancy proceeded uneventfully. A girl weighing 3300 g was born at term and oral biotin (5 mg) was started on the 1st day and continued after profound BTD deficiency was established on subsequent enzyme assay. The baby is under follow-up and is asymptomatic, thriving well, has normal hair and skin, bilateral pass on hearing screening by otoacoustic emission and has age-appropriate neurodevelopmental examination at 3 months.

Discussion

Biotin, also known as Vitamin B7 or Vitamin H, acts as the coenzyme of multiple carboxylases, cytosolic acetyl-CoA carboxylase (ACC) 1, outer mitochondrial membrane ACC 2, 3-methylcrotonyl-CoA carboxylase, pyruvate carboxylase, and propionyl-CoA carboxylase.[2] Since it can be administered in the free form, oral biotin can directly enter the biotin cycle and replenish the pool. Thus, any dosage greater than the recommended daily allowance (RDA), i.e., 5–10 mg/day, may resolve the multiple carboxylase dysfunction that arises from BTD deficiency.[2] The normal RDA of biotin in women (pregnant or nonpregnant) is 30 μg/day. During pregnancy, there may be increased requirement to meet growing metabolic demands, especially in a BTD deficient fetus. It is well known that the biotin content of breast milk is low (1.7–2.8 μg/L) and may not satisfy the RDA of infants under 6 months of age (5 μg/day).

Biotin supplementation results in rapid resolution of seizures and biochemical abnormalities, whereas cutaneous abnormalities and alopecia takes weeks to months to improve.[4] Some symptoms such as developmental delay, hearing loss, and optic atrophy are irreversible after becoming clinically apparent, even after initiating biotin.[4] This was evident in family 1: seizures abated in the third and fourth sons after postnatal biotin was started; developmental delay and hearing impairment remained unaltered in the third son, whereas development proceeded typically with unaffected hearing in the fourth son; and the

fifth son remained asymptomatic with combined antenatal and postnatal biotin.

The clinical phenotypes of all affected children were similar in both families: Seizures, hearing loss, the absence of skin/hair changes, and no metabolic derangement in family 1, and; sparse hair but normal skin, intractable seizures followed by acute encephalopathy, death, and metabolic derangement in family 2. However, some intrafamilial variability was also noted. Whether this was due to the oral biotin or hitherto unknown epigenetic or environmental factors affecting the biotin cycle, remains unresolved.[7]

The common metabolic derangements in untreated BTD deficiency are lactic acidosis, organic aciduria, and mild hyperammonemia.[4] Urine and plasma may reveal elevated metabolites indicative of multiple carboxylase deficiency. Routine GCMS and TMS are not recommended, as many children with profound deficiency may exhibit metabolic profiles that are normal, intermittently abnormal, or falsely negative.[8] Diagnosis is primarily by measuring BTD activity in plasma/serum by colorimetric assay. Confirmation by DNA analysis is indicated only when enzyme assay results are ambiguous,[4] and postmortem or prenatal diagnosis is required, as in the second family.

The mutation that was identified in this family has a worldwide distribution among racially and ethnically diverse population.[6] Genotype–phenotype correlations are not well defined in profound BTD deficiency. Null variants are reportedly at higher risk of hearing loss than missense variants.[9] It is noteworthy that the affected infant had normal hearing despite the null variant. One possible explanation could be the antenatal biotin that the mother was receiving from the 6th week of gestation onward. There was no indication for ascertaining genotype in the other family, despite the presence of hearing loss in symptomatic members.

Most researchers have used biotin (10 mg per day) in pregnancies at risk of HLCS deficiency.[10] We used an empirical dose of 20 mg per day in both these families affected with BTD deficiency due to nonavailability of supportive literature. Neither of the women reported any adverse effects ascribed to biotin such as skin rashes or gastrointestinal symptoms. After birth, both babies have remained asymptomatic with typical neurodevelopment, despite profound BTD deficiency.

Thus, BTD deficiency is a readily treatable disorder with oral biotin that is a safe, easily available, and economical drug. It can be given to symptomatic individuals, screen-positive neonates, and mothers at high risk of or antenatally diagnosed with BTD deficiency. We hope this case report triggers more widespread use and generates research aimed at ascertaining the optimal prenatal dosage.

Lessons learnt

- Biotin supplementation in children with profound biotinidase deficiency can result in seizure control and prevent the appearance of manifestations that are yet to develop
- Antenatal biotin supplementation can be considered in mothers at high risk of or with antenatally diagnosed biotinidase deficiency
- DNA samples of preterminal children with suspected genetic disorders should be stored after proper counseling.

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 Series

Using Innovative Narrative Therapies with Children who Witness Intimate Partner Violence

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Abstract

Background: Intimate partner violence (IPV) is a form of abuse in which one partner causes physical, psychological, or sexual harm to the other, in the relationship. Exposure of children to this kind of domestic abuse is quite common in India, though not openly discussed. The management of children who present with functional somatic symptoms (suspected to be psychogenic in nature) is extremely challenging, especially since the history of IPV is not easily forthcoming. This case series highlights the evocative power of trauma-creative narrative interventions, such as poetry writing and story-telling, that help children express their fears and distress in a safe environment. This in conjunction with other modalities of management helps in their healing. **Clinical Description:** We present three children presenting with various functional somatic symptoms belonging to dysfunctional families. Comprehensive in-depth interviews, psychological assessment, and kinetic family drawings helped us assess each case, elicit the history of IPV, and understand the nature of the individualized fears and distress being experienced. **Management and Outcome:** The primary interventions used were creative narrative interventions such as asking the children to draw, write poems, and/or tell stories about their family and the situations they were experiencing. This helped them express their feelings of helplessness and latent anger arising from witnessing these violent events. Facing their fears in a safe environment resulted in successful resolution of somatic symptoms of all the three over time. This healing was reflected in the change in expressions via the art, poems, and written/oral narrations. Other strategies like provision of psychoeducation, highlighting the connection between symptoms and the underlying trauma, referral for marital counselling, and improving social support were also used. **Conclusions:** Pediatricians should have a high index of suspicion of the possibility of psychosomatic conditions when their patients display inexplicable manifestations that do not fit into any recognizable clinical phenotype, either by description or after investigation. These children and adolescents should be referred for a psychological evaluation and further eclectic management. The use of creative narrative therapies in conjunction with other modalities can lead to successful resolution of functional somatic symptoms.

Keywords: Creative interventions, functional somatic symptoms, kinetic family drawing, psychosomatic

Population-based national-level surveys indicate that exposure of children to domestic abuse and violence is pervasive in Indian society. For example, a national study on child abuse reported that 69% of the study population had been physically abused, and among 89%, the perpetrators had been their parents.[1] Intimate partner violence (IPV) is a form of domestic abuse defined as a pattern of behavior used to gain or maintain power and control over an intimate partner that causes physical, psychological, or sexual harm to those in that relationship. Children can be exposed to IPV at home either by actually witnessing such events or even overhearing the associated sounds of discord.[2]

There is a plenty of evidence that indicates that traumatic experiences in childhood can have a long-lasting deleterious effect on the physical and psychological well-being of children and adolescents. This includes posttraumatic stress, reduced coping abilities, insecure attachment, and psychosomatic symptoms, all of which can continue into adulthood.[3,4] Creative narrative interventions, i.e., role play, drama therapy, poetry writing, story narration, and bibliotherapy-the use of books, when combined with other approaches like counseling and psychotherapy, have demonstrated considerable success with traumatized and chronically ill children.[5] The abstract medium of narrative therapies provides a healing experience by facilitating the articulation of underlying painful emotions, supporting self-expression, and validating one's emotions. Narrative therapies may also be the primary form of communication by the child with

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Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_354_21

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Submitted: 04-Dec-2021 **Revised:** 24-Jan-2022
Accepted: 24-Jan-2022 **Published:** 25-Feb-2022

How to cite this article: Malhi P, Bharti B. Using innovative narrative therapies with children who witness intimate partner violence. Indian Pediatr Case Rep 2022;2:17-20.

the therapist. Since poems and stories can be written in the third person, they provide a safe medium for disclosure of traumatic memories and sharing personal issues. This helps professionals in understanding the children's problems vicariously.[5,6]

In this case series, we highlight the evaluation of three adolescents belonging to dysfunctional families, who presented with various functional somatic complaints and the successful effect of their management using narration therapy in addition to other modalities. Our main aim is to sensitize and increase awareness of clinicians regarding the existence and importance of such services.

Clinical Description

Family 1: AS, an 11-year-old boy, was referred to the child psychology unit for symptoms of vomiting, abdominal pain, and easy fatigability for three months, on the suspicion of the treating unit that these were psychogenic in nature. Prior to the present evaluation, parents had taken multiple medical consultations, the child had undergone several investigations, and was prescribed various medications, without any symptomatic relief. The child belonged to an upper-middle-class family, was the elder of two siblings, both the parents were graduates, and the father was a professional photographer. The parents reported that AS was shy, academically bright, and enjoyed school, but the recent incapacitating symptoms had led to frequent absenteeism from school, with a subsequent decline in academic performance. The child had also become increasingly withdrawn and fearful and often talked of death.

A comprehensive psychological evaluation of the child was undertaken, comprising several psychological scales and tests. This included the Pre-adolescent Adjustment Scale that assesses a child's adjustment at home, school, with peers, and teachers, and the Kinetic Family Drawing Test. In the latter, children are instructed to draw a picture of their family, including themselves "doing something." The underlying assumption is that the addition of movement to an otherwise static drawing helps to understand the child's attitude toward other family members and the quality as well as dynamics of interpersonal relations within the family. In this particular case, it was obvious that there was a significant marital discord that was disturbing the child [Figure 1]. These drawings helped AS to open up about the situation at home, that had not been forthcoming from the parents till then. During the narration of his fears and distress at witnessing the unremitting parental conflict, he revealed that witnessing such events made him literally "sick to his stomach."

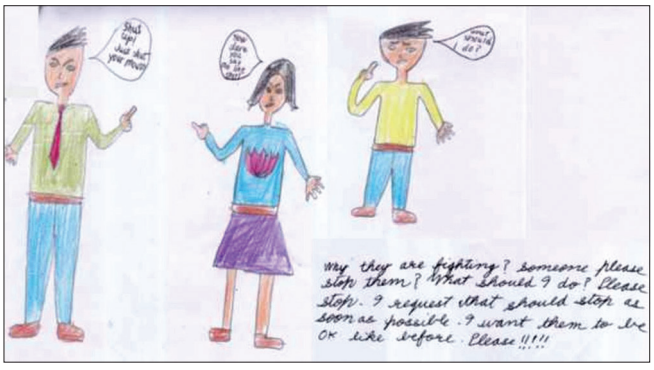

Figure 1: Kinetic family drawing made by AS with narrative

Family 2: DP, an 11-year-old boy, was referred for a psychological consultation for symptoms of non-specific pains at multiple sites including chest pain, headache, and pain in the legs for the last 6 months, for which no medical cause could be ascertained. The mother was extremely worried, especially since the child was an excellent basketball player, and the family (including the child) were keen that he should pursue a career in sports. Detailed history, elicited separately from the mother and the child, revealed frequent parental quarrels, and controlling and abusive behavior of the father. It was noted that DP harbored ambivalent feelings toward his father; though he feared him, he also had a strong desire for his love and acceptance. One of the significant thoughts that was eventually shared during the narratives was that the reason he spent hours practicing basketball was not triggered by personal motivation of becoming better, but rather an inexplicable feeling that somehow his excelling in sports would lead to decreased inter-parental hostility.

Family 3: MS, a 12-year-old boy, was referred for recurrent episodes of abnormal breathing for the past year, that was recognized as hyperventilation by the treating clinician. These episodes were brief, triggered off unexpectedly (according to his parents), occurred mainly at home in the evening, and were always in the presence of family members. The mother was concerned that the child had an underlying disease, that was being missed by the numerous doctors that they had consulted. According to her, the boy was academically bright, well-adjusted at school with several friends, and there were no complaints from the school teachers. Family history revealed that the mother had married a widower with two children from his previous marriage, who was the biological father of MS. The drawings made by MS [Figure 2] helped the team understand that there was possible alcohol abuse in the father. It emerged that there was frequent display of violent and abusive behavior after consumption of alcohol. MS would sometimes try to mediate the parental disputes by requesting his mother to leave the room or pleading with the parents to stop. This would inevitably lead to exacerbation of his symptoms. The child shared that he empathized with his mother

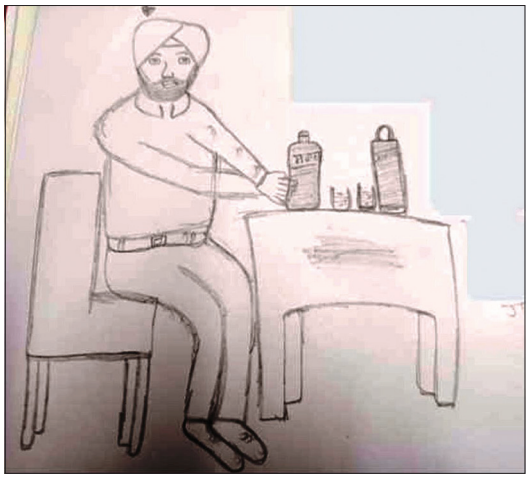

Figure 2: Kinetic family drawing of MS displaying alcohol consumption by father. This was used as a springboard for further narrative therapy

and was determined to look after her financially and emotionally when he grew up.

The compilation of additional clinical and background details of all the three cases are presented in Table 1.

Management and outcome

Comprehensive management plans were drawn for each case. It was decided that the primary treatment modalities would be art narratives that would enable the children to express their feelings in a psychologically safe environment. The drawings were used as a springboard for further discussion related to underlying family issues and interpersonal dynamics. Psychoeducation was provided to all family members and the connection between the functional symptoms and dysfunctional parental interactions in each family was underscored. In addition, the families were counseled regarding the importance of maintaining a congenial environment at home, and parents were advised to seek professional marital counseling. We provide a brief description of the individualized therapies used and their impact on the presenting complaints of each child.

Family 1: AS chose to write poetry to express his emotions and used his poems to alleviate his acute emotional distress at witnessing the endless conflicts and violent clashes of his parents. His poems touched on his dread of darkness and death. This was used as leverage for exploration and discussion of his feelings of sadness, helplessness, and anger. After three sessions spanning two months of therapy, AS reported that his physical symptoms had markedly declined. The healing was also reflected in his poetic writing wherein he wrote about the "joy of life" and "meeting his grave at hundred years" [Figure 3]. The latest follow-up done after a year of therapy revealed that AS has been asymptomatic, is attending school regularly, and excelling academically.

Family 2: DP on being asked to share his feelings through stories, narrated several tales about a boy lost in a treacherous forest infested by dangerous animals, and the struggles he had to endure to find safe passage out of those circumstances. His stories always ended with someone (a fairy or a saint), rescuing him from jaws of death at the last moment and leading him to safety. Gradually, the adolescent was also encouraged to interact more with his peers, spend time with nature, and practice deep breathing whenever he was exposed to IPV. After four months of therapy (covering three sessions), the symptoms of pain subsided. In the follow-up visit after 6 months, DP shared that he felt absolutely fine.

Family 3: The art and stories narrated by MS revolved about a boy and his current fears and struggles, as well as his aspirations of becoming a police officer who would control alcohol consumption among the public, as it was the genesis of all "evil actions." MS was also encouraged to interact with his friends, and spend time playing and exercising outdoors, away from the family in the evenings. After three weekly sessions, the symptoms resolved and no recurrence was reported at a follow-up visit three months after initiation of therapy.

Discussion

It is well established that dysfunctional parental relationships can lead to maladaptive coping and problems in parent–child attachment and negatively affect the child's psychological, behavioral, and physical well-being.[7,8] "Child affected by parental relationship distress" is a newly introduced condition in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. This entails a description of how a clinician should assess the parent and child relationship and also probe into whether it affects the course, prognosis, and treatment of mental or other medical health disorders.

With respect to IPV, the greater the child's exposure to it, the worse are the potential psychological outcomes, unless timely interventions can help change the trajectory. Identifying the context in which the child's symptoms arise, in conjunction with identifying etiologically relevant psychosocial stressors,

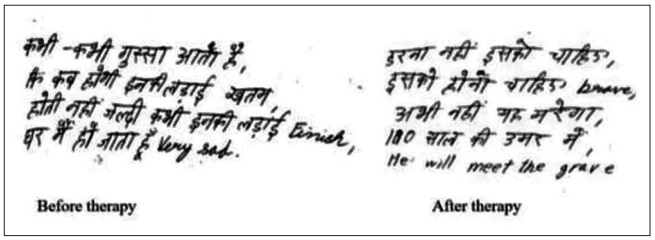

Figure 3: Poetry composed by AS before and after narrative therapy

Table 1: Clinical profile, family background, and psychosocial stressors in each case

Family	Demographic details	Presenting symptoms and duration	Parental education level and profession	Psychosocial stressors
1: AS	11 years boy, class 7 (private school); elder of 2 siblings	Vomiting, abdominal pain, easy fatigability for 3 months	Mother: Postgraduate and private school teacher Father: High school and a professional photographer	Frequent parental conflict, verbal and physical violence, mother suspects father is cheating on her
2: DP	11 years boy, class 5 (government school), elder of 2 siblings	Nonspecific aches and pains at multiple sites (chest, headache, legs) for 6 months	Both parents high school graduates, father was working abroad, but out of a job for 1 year Mother: Homemaker	Verbal and physical violence, financial stress, father demands money from his in-laws, substance abuse in father, police complaint registered against father
3: MS	12 years boy, class 6 (private school), only child	Recurrent episodes of abnormal breathing (diagnosed as hyperventilation) a year	Both parents less than high school; child's mother is second wife of father Two step siblings: Stepbrother (20 years), stepsister (22 years) married	Verbal and physical violence, substance abuse in father, financial stress, incarceration of stepbrother

helps in formulating a comprehensive management plan. Research shows that traumatized children can paradoxically long for the love and acceptance of their abusive and neglectful parents, in addition to rejecting and fearing them.[8] Children exposed to IPV may experience difficulty in forming therapeutic relationships.

It has been observed that the recommended first-line interventions for functional somatic symptoms in adults, such as distraction and relaxation techniques, may not be as successful in children.[8,9] A recent meta-analysis of 27 studies demonstrated that psychological modalities are the treatment of choice in children presenting with functional somatic symptoms.[10] Modalities like psychoeducation, relaxation, coping skills training, biofeedback, behavior therapy, and narrative therapies were found to reduce the severity of somatic symptoms and associated disability and improve school attendance.[10]

We presented this case series to highlight the fact that any early adversity including witnessing IPV can have a significant adverse impact on the physical and subjective wellbeing of children. Pediatricians should have a high index of suspicion of the possibility of psychosomatic conditions when their patients display inexplicable manifestations that do not fit into any recognizable clinical phenotype, either by description or after investigation. These children and adolescents should be referred for a psychological evaluation and further eclectic management. The use of creative narrative therapies in conjunction with other modalities can lead to successful resolution of functional somatic symptoms.

Lessons learnt

- Children presenting with functional somatic complaints need a comprehensive evaluation for stress-related causes.
- Narrative therapies may be particularly useful in children and adolescents who have difficulty in expressing and communicating their underlying painful emotions.
- Creative therapies that facilitate self-expression can help in mitigating the consequences of the trauma associated with IPV.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardians have given their consent for images and other clinical information to be reported in the journal. The guardians understand 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.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Lymphocytic Interstitial Pneumonia in an Infant with Diffuse Cystic Pulmonary Tuberculosis

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Abstract

Background: Lymphocytic interstitial pneumonia (LIP) is a rare disorder causing diffuse involvement of the lung parenchyma, including cystic changes. It is generally associated with autoimmune diseases in adults and human immunodeficiency virus infection in children. Concurrent LIP with pulmonary tuberculosis (TB) is rare and has not been reported in the pediatric population. **Clinical Description:** An 8-month-old infant who was recently diagnosed with miliary pulmonary TB and on antitubercular treatment presented with fast breathing for 2 days. Salient examination findings were tachypnea, with oxygen saturation of 84% in room air. High-resolution computed tomography of the chest showed diffuse involvement of both lungs with bilateral cystic changes. Histopathological examination of a lung biopsy specimen was consistent with LIP. **Management:** First-line antitubercular therapy was continued as per the national guideline, and methylprednisolone pulse was administered for 3 days followed by maintenance prednisolone for 8 weeks. The child responded well clinically and was kept under close follow-up. Radiological improvement became apparent at 15-month follow-up. **Conclusion:** Presence of diffuse cystic lung disease in pulmonary TB should raise suspicion for LIP. Lung biopsy is diagnostic and should be considered in such cases.

Keywords: Diffuse cystic lung disease, lymphocytic interstitial pneumonia, pulmonary tuberculosis

Lymphocytic interstitial pneumonia (LIP) is a benign lymphoproliferative disorder limited to lungs. It is characterized by inflammatory reaction of the bronchus-associated lymphoid tissue, leading to cellular infiltration of pulmonary interstitium by reactive lymphocytes, plasma cells, and histiocytes.[1] Although the exact pathogenesis is unknown, LIP is considered to be a pathological, nonspecific immunologic response to different stimuli. Table 1 depicts the various immunodeficiency, autoimmune, and infectious diseases that are associated with it.[1] The common infectious causes of LIP are human immunodeficiency virus (HIV) and Epstein–Barr virus.[1-3] Although *Mycobacterium tuberculosis* is also listed as a cause, an exhaustive literature search could not identify any reports in children.

Here, we describe an 8-month-old infant on antitubercular therapy (ATT) for a recently diagnosed miliary pulmonary tuberculosis (TB), who presented with an acute respiratory illness, displayed diffuse cystic lung disease on imaging, and histopathological evidence of LIP.

Clinical Description

An 8-month-old male child was brought to the emergency room with a history of fast breathing for 2 days. The onset was sudden, with no preceding fever, runny nose, cough, noisy breathing, loose stools, vomiting, or abdominal distension. He had a significant history of being admitted in our hospital with acute respiratory failure 6 weeks earlier (at the age of 6.5 months), severe enough to have required volume-controlled, synchronized intermittent mechanical ventilation for 7 days. The etiological diagnosis established at that admission was pulmonary TB. This had been based on bilateral miliary shadows on a chest radiograph [Figure 1a] and detection of acid-fast bacilli (AFB) on gastric aspirate (1+) that was rifampicin sensitive on GenXpert. The cerebrospinal fluid examination was normal. His weight was 6.7 kg (3rd to 15th centile for age), length 68 cm (50th to 85th centile), weight for length less than 3rd centile, and head circumference 44 cm (50th to 85th centile). He was started on four-drug ATT along with prednisolone. He was uneventfully extubated, weaned off oxygen, and discharged on day 16 of hospitalization to be followed up every 2 weeks in the outpatient

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Submitted: 06-Oct-2021 **Revised:** 12-Jan-2022
Accepted: 23-Jan-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_304_21

How to cite this article: Tsanglao WR, Miachieo N, Ao MK, Aier T, Kikon S. Lymphocytic interstitial pneumonia in an infant with diffuse cystic pulmonary tuberculosis. Indian Pediatr Case Rep 2022;2:21-4.

Table 1: Diseases associated with lymphocytic interstitial pneumonia

Autoimmune (39%)
Sjogren's syndrome
Systemic lupus erythematosus
Rheumatoid arthritis
Juvenile rheumatoid arthritis
Hashimoto thyroiditis
Myasthenia gravis
Hemolytic anemia
Pernicious anemia
Autoerythrocyte sensitization syndrome
Chronic active hepatitis
Celiac sprue
Primary biliary cirrhosis
Systemic immunodeficiency states (14%)
HIV/AIDS with and without diffuse infiltrative lymphocytosis syndrome
Common variable immunodeficiency
Agammaglobulinemia
Miscellaneous
Complication of allogeneic bone marrow transplantation
Pulmonary alveolar microlithiasis
Infections including legionella pneumonia, TB, mycoplasma, chlamydia diphenyl hydantoin use
Pulmonary alveolar proteinosis
Idiopathic

Source.[1] HIV: Human immunodeficiency virus, TB: Tuberculosis

department. The child remained well and compliant to treatment. History before the first hospitalization was unremarkable. The child was immunized and his developmental milestones were appropriate for age. He was on home-based complementary food following exclusive breastfeeding till 6 months of age. His parents had no past or current evidence of TB and were HIV negative.

At admission, he was alert with a respiratory rate of 70 per minute, subcostal recessions, heart rate of 156 per minute, blood pressure of 85/46 mmHg (50th to 90th centile), and temperature of 99°F. The oxygen saturation was 84% in room air that improved to 100% with supplemental oxygen at 2 L/min. His weight was 7.1 kg (3rd centile), length 70 cm (15th to 50th centile), weight for length less than 3rd centile, and head circumference 45 cm (50th to 85th centile). There was no clubbing, cyanosis, lymphadenopathy, or pallor on general examination. On respiratory examination, chest movement was symmetrical with no deformity; air entry was equal on both sides; and breath sounds were vesicular with no added sounds. Cardiovascular, abdominal, and central nervous system examinations were unremarkable. Based on past and present clinical presentation, a provisional diagnosis of recurrent pneumonia with failure to thrive was made and investigations were planned accordingly.

Management and Outcome

His total white cell count was elevated (19.470/mm^3) with 58% neutrophils and 37% lymphocytes. The erythrocyte

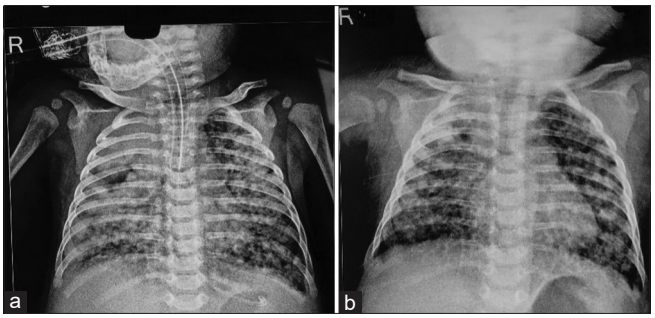

Figure 1: (a) Initial chest X-ray (first admission) showing bilateral miliary infiltrates, and right upper lobar consolidation. (b) Chest X-ray (current admission) showing persistence of radiological findings

sedimentation rate was 8 mm in the 1st h. Chest X-ray showed persistence of bilateral infiltrates compared to the previous one [Figure 1a and b]. Gastric aspirates for AFB were negative. Arterial blood gas analysis, serum electrolytes, serum lipase, and kidney and liver function tests were normal. High-resolution computed tomography (HRCT) of the chest showed extensive centrilobular nodules with tree-in- bud pattern in both lungs, multiple areas of patchy consolidation, ground-glass opacities, cavities in the right upper lobe, enlarged mediastinal lymph nodes, and well-defined cysts in the anterior and apicoposterior segments of the left upper lobe, posterior and lateral segment of the left lower lobe, and posterior segment of the right upper lobe, with few of them showing continuation with subsegmental bronchi [Figure 2]. There was no evidence of pulmonary hypertension on echocardiography. Genetic screen for cystic fibrosis done in view of recurrent pneumonia and the evidence of diffuse lung disease on HRCT was negative.

Figure 3 depicts the clinical course of the illness. The persistence of tachypnea, chest retractions, and oxygen requirement in the setting of a probable diffuse lung disease prompted us to perform an ultrasound-guided lung biopsy on the 17th day of hospitalization. The histopathological report revealed dense and diffuse infiltrates in the pulmonary interstitium, comprising lymphocytes and mononuclear cells, septal thickening, and gross architectural destruction suggestive of LIP. In addition, there was presence of caseating granulomas, Langerhans giant cell, and intra-alveolar macrophages [Figure 4]. Ziehl–Neelsen stain for AFB, and wet mount and Giemsa stain for *Pneumocystis carinii* were negative. Normal immunoglobulin (Ig) levels (IgG 680 mg/dl, IgM 96 mg/dl, and IgA 80 mg/dl) and CD4 count (918 cells/mm^3) ruled out immunodeficiency.

On the 22nd day, he was started on methylprednisolone (30 mg/kg/dose once a day) for 3 days, followed by oral prednisolone (1 mg/kg/day). Following this, there was a dramatic response in his respiratory status with tachypnea and chest retractions normalizing within 3 days. The child became oxygen independent by the 35th day of admission and was discharged on the 42nd day. Figure 3 depicts the timeline of clinical events. Prednisolone was continued for a total of 8 weeks, followed by gradual tapering. ATT was stopped on completion of 6 months in view of clinical improvement and

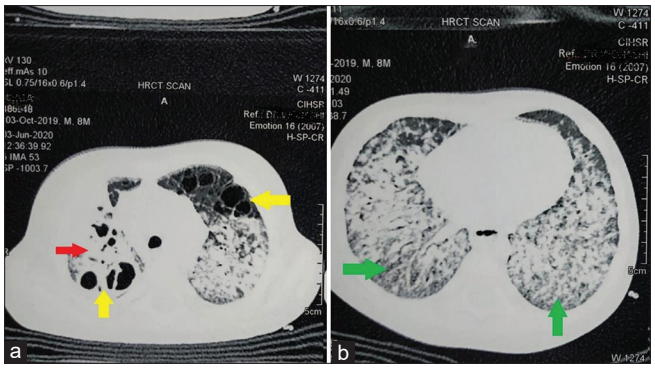

Figure 2: (a) High-resolution computed tomography chest showing well defined cysts in the anterior segment of left upper lobe and posterior segment of right upper lobe (yellow arrows), with areas of consolidation (red arrow). (b) Extensive, diffusely scattered centrilobular nodules with multiple patchy consolidation and ground glass opacities (green arrows)

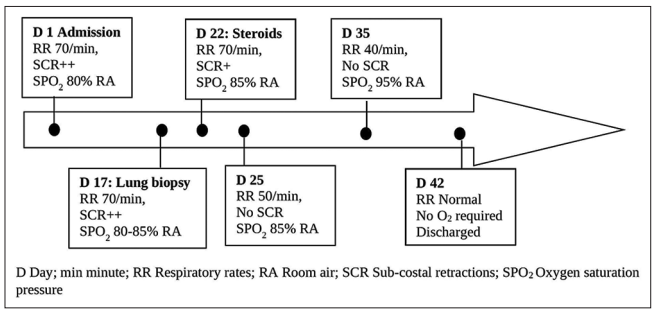

Figure 3: Clinical timeline of the patient from admission (day 1) to discharge (day 42)

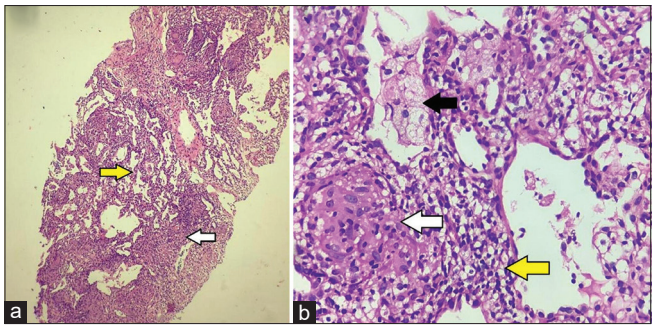

Figure 4: Lung histopathology: (a) interstitial thickening with dense mononuclear interstitial infiltrate (white arrow) and gross architectural destruction (yellow arrow). (b) Dense interstitial lymphocytic infiltrates (yellow arrow), with intra-alveolar macrophage (black arrow) and epitheloid granuloma (white arrow)

negative mycobacterial culture. At the 15-month follow-up visit, he was asymptomatic and his growth curves (weight and weight for length) demonstrated an upward trajectory. Although the chest X-ray still showed right-sided opacities, there was clearing of the cyst on the right upper and mid-zone.

Discussion

LIP is considered to be in the spectrum of benign lymphoproliferative disorders of the lung. This includes conditions such as Castleman disease, angioimmunoblastic lymphadenopathy, follicular bronchiolitis (FB), infectious mononucleosis, lymphomatoid granulomatosis, posttransplant lymphoproliferative disorder, nodular lymphoid hyperplasia, and immunoglobulin Ig4-related disease. Clinically, LIP is characterized by cough, tachypnea, wheezing, and exercise intolerance in older children. Examination generally reveals tachypnea, retractions, and bilateral crackles. In severe cases, failure to thrive, digital clubbing, and cyanosis may be seen.[4]

The finding of LIP in this patient was intriguing. Cystic lung disease is a rare presentation of pulmonary TB,[5] and only one case has been reported in infancy by Jana *et al*.[6] The exact pathogenesis of cyst formation in pulmonary TB is unclear. The proposed mechanisms of cyst formation include check-valve obstruction due to inflammation and luminal narrowing of the bronchioles, peribronchiolar fibrosis, and excavation of the necrotic material by draining bronchi.[5,7] LIP is a known cause of cystic lung disease, wherein cyst formation is postulated to result from compression of the bronchioles by lymphocytic infiltration, leading to bronchiolar stenosis and subsequent poststenotic bronchiolar ectasia.[1,8] We were unable to identify any case report of children in which there was concurrent LIP and cystic pulmonary TB. LIP has been described in a 54-year-old adult with pulmonary TB but sans the cystic changes.[9]

HRCT in LIP usually shows ground-glass opacities, centrilobular nodules, septal thickening, and cystic changes, as seen in our case.[1] In a series of HRCT findings in 22 patients (age range 24–83 years) with biopsy-proven LIP, ground-glass opacities and poorly defined diffuse centrilobular nodules were seen in all (100%); subpleural nodules in 19 cases (86%); septal thickening in 18 cases (81%); cystic changes and mediastinal lymphadenopathy in 15 cases (68%).[10] Histologically, LIP is characterized by diffuse and dense infiltrates of immature and mature lymphocytes, plasma cells, and histiocytes predominantly in the pulmonary interstitium.[1] Secondary findings include presence of proteinaceous fluid, mononuclear inflammatory cells, foamy macrophages, or giant cells within the alveolar spaces. The histopathological differential diagnosis of LIP includes *P. carinii* pneumonia in immunocompromised patients and hypersensitivity pneumonitis. In the latter, cystic changes are rarely seen on radiography, and the lymphocytic infiltrate is patchy and less dense.

Currently, there are no established guidelines for treatment of LIP.[1-3] Steroids are generally used as first line, with clinical and/or radiologic response reported in 50%–60% of cases.[1,3] Prednisolone (0.75–1.0 mg/kg/day) for 8–12 weeks or until stabilization, followed by slow taper to 0.25 mg/kg/day for another 6–12 weeks, has been recommended.[1] A case series of children with LIP and FB has also reported good response with pulse methylprednisolone and oral prednisolone.[4] Use of second-line agents, such as cyclophosphamide, hydroxychloroquine, azathioprine, and rituximab, has been described, though the level of evidence

is anecdotal.[2-4] The prognosis of LIP is unknown. An adult case series reports several outcomes; spontaneous resolution, resolution posttreatment, respiratory failure, progression to lymphoma, and a 5-year mortality rate of 33%–50%.[1,2] Data pertaining to outcomes in children with LIP after prolonged steroids are limited, though high morbidity and mortality have been reported.[4]

Lessons learnt

- Cystic lung disease is an uncommon presentation of pulmonary TB
- Lymphocytic interstitial pneumonia should be considered as a differential diagnosis in diffuse cystic pulmonary TB
- A lung biopsy should be considered in pulmonary TB with diffuse cystic lung changes on imaging.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the parents. In the form, the patient's parents have given his consent for the images and other clinical information to be reported in the journal. The patient's parents understand that the name and initials will not be published, and due efforts have been made to conceal the same, 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

Insulin Edema in an Adolescent Girl with Newly Diagnosed Type 1 Diabetes Mellitus

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Abstract

Background: Insulin edema is a rare complication that can occur following either initiation or intensification of insulin treatment in Type 1 diabetes mellitus (DM). It is an under reported condition. Awareness of this complication among physicians is important for early identification of this condition, and prompt initiation of treatment. **Clinical Description:** We present an 11-year-old girl with 2-month history of weight loss and 1-month history of polyuria and polydipsia who presented to us in moderate diabetic ketoacidosis. She developed anasarca and pulmonary edema 3 days after starting insulin. She also developed transaminitis a serum serum glutamic-oxaloacetic transaminase of 81 U/L and serum glutamic pyruvic transaminase of 83 U/L. A diagnosis of insulin edema was established after ruling out other causes like severe anemia, renal, cardiac and allergic causes. We also present a brief review of seven similar cases that we identified on a literature search. **Management and Outcome:** This included salt and fluid restriction along with diuretics. Edema resoled after 4 days of treatment, while transaminitis took 7 days to normalize. **Conclusion:** This case report highlights the importance of early recognition of the rare complication of insulin edema which can avoid unnecessary anxiety on the part of both treating physicians and parents of patients with Type 1 DM.

Keywords: Adolescent, children, insulin edema, transaminitis, type 1 diabetes mellitus

Type 1 Diabetes Mellitus (DM) is one of the most common endocrine disorders in children. It is a chronic disorder of autoimmune etiology characterized by hyperglycemia and the consequent osmotic symptoms. Prevalence of Type I DM in the Indian population is increasing with a trend of 3%–5% increase per year. The patients can present with the classical symptoms of polyuria, polydipsia and polyphagia. In many cases these symptoms do not get noticed until the child presents with diabetic ketoacidosis (DKA), a life-threatening condition. Insulin is the main stay of treatment in Type 1 DM that can on occasion lead to side effects like hypoglycemia, weight gain, and local reaction at the injection site.

An uncommon, and relatively less known complication of insulin treatment is insulin edema, which is characterized by the development of generalized or peripheral edema.[1] This can occur either following the initiation of insulin therapy, or during the intensification phase in patients already on insulin.[2,3] In the majority of cases, edema occurs within 2–4 weeks.[4,5] The first case of insulin edema was reported in 1928, however since then only a few clinical descriptions have been published in children and adolescents, worldwide [Table 1]. Though mild to moderate edema is the most common presentation, on occasion cardiopulmonary congestion can occur.[6] It can rarely also be associated with transaminitis.[2,7]

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Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_270_21

We present the case of a girl with newly diagnosed Type 1 DM who developed anasarca and transient elevation of liver enzymes on starting insulin. The aim of reporting this case is to create awareness about this rare complication among pediatricians, who frequently manage children with Type 1 DM, and sensitize them about modalities of its management.[6,7]

Clinical Description

An 11-year-old, previously asymptomatic girl, presented to us with complaints of weight loss and fatigue for 2 months, followed by increased thirst and frequency of urination for a month. The parents had also noticed a voracious increase in appetite for a few days. She did not have any history of fever, cough or breathlessness. There was no significant past history and she had no comorbid illnesses. The child was appropriately immunized for age. Her development had been normal and she was currently studying in the seventh standard

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Submitted: 30-Aug-2021 **Revised:** 26-Jan-2022
Accepted: 04-Feb-2022 **Published:** 25-Feb-2022

How to cite this article: Krishnan R, Bindu S, Riaz I, Preethi MS. Insulin edema in an adolescent girl with newly diagnosed Type 1 diabetes mellitus. Indian Pediatr Case Rep 2022;2:25-8.

Table 1: Clinical profile of 7 insulin-dependent diabetes mellitus patients with insulin edema

Reference number	Age (years)	Sex	New case	Type of edema	Weight gain (kg)	Days of onset after start of insulin	Days taken for resolution of edema	Treatment received	Elevated liver enzymes
1	14	Female	Yes	Generalized	10.2	4	14	Salt restriction	−
2	20	Female	No	Generalized and pulmonary	10	8	8	IV furosemide	+*
3	12	Male	Yes	Generalized	10	4	7	Salt and fluid restriction	−
4	12	Female	Yes	Generalised	NA	1	10	Frusemide	−
6	9.5	Female	Yes	Peripheral	1.2	8	7	Nil	−
10	14	Female	Yes	Peripheral	NA	4	10	Nil	−
10	11	Female	Yes	Peripheral	NA	5	7	Nil	−

*Serum glutamic-oxaloacetic transaminase of 99 U/L and serum glutamic pyruvic transaminase of 316 U/L. IV: Intravenous, NA: Not available

with good scholastic performance. She was the only child of nonconsanguineous parents. The only significant family history was that her paternal grandfather had been diagnosed with DM at 51 years of age and was on medication (metformin).

At presentation she was conscious and well oriented. There was no fever, and she had a pulse rate of 108 beats per minute, respiratory rate of 24 breaths per minute and blood pressure that was 106/60 mm of Hg (<50th centile for age). Anthropometric examination was normal with a weight of 25 kg (Z score-1.2), height of 142 cm (Z score-0.17), and body mass index of 12.4 kg/m^2 (Z score-1.6). The only salient general physical examination finding was the presence of some dehydration. The respiratory, cardiovascular, abdominal and central nervous system examinations were with in normal limits.

Since the clinical history was highly suggestive of DM, her blood sugar level was checked immediately, and found to be 560 mg/dl. As per standard protocol for detecting DKA, we did a venous blood gas analysis which revealed a pH of 7.29 and bicarbonate of 6.7 mEq/L. She also had ketonuria (urinary ketones 3+). Thus, a diagnosis of DM with moderate DKA was established, and standard treatment initiated with intravenous (IV) fluids and insulin infusion.[8] Her baseline investigations (blood counts, Erythrocyte Sedimentation Rate, liver and renal function tests, urine albumin and microscopy) were within normal limits at admission [Table 2]. There was no evidence of sepsis; the C reactive protein (CRP) was negative, and blood and urine cultures were sterile. The glycosylated Glycated Hemoglobin (HbA1c) was highly elevated (15%).

Management and Outcome

The metabolic acidosis got corrected within 6 h of starting treatment. After this she was started on subcutaneous insulin (1 unit per kg/day in 3 divided doses). The next day she was shifted to a split mix regimen of insulin with Neutral Protamine Hagedorn (NPH) insulin twice a day, along with regular insulin thrice daily before meals (total dose of 1U/kg/d). 2 days after starting NPH insulin facial puffiness and bilateral pitting pedal edema were noted that progressively increased and became generalized within 24 h. This was reflected in an increase in weight of 1.5 kg over the same duration. Abdominal examination detected clinical indicators of ascites. Despite these fresh clinical issues, her glycemic control continued to exhibit improvement.

All the usual causes of generalized edema were systematically excluded by history, examination and relevant tests. The child remained hemodynamically stable. There were no clinical features indicative of infection such as fever, diarrhea, abdominal pain, or tenderness. This was supported by blood counts and CRP levels that remained normal. There was no jaundice or liver enlargement, but the liver function test identified some minor abnormalities; elevation of transaminases on the day of onset of edema (serum serum glutamic-oxaloacetic transaminase of 81 U/L and serum glutamic pyruvic transaminase of 83 U/L. with normal bilirubin levels). The total protein was 6 g/dL and serum albumin 3.8 g/dL. The prothrombin time/ International normalized ratio was 1. These indicated normal hepatic synthetic function and absence of hypoproteinemia as the underlying cause of the anasarca. Also typical symptoms and signs of congestive heart failure (CHF) were absent. An underlying renal cause was also ruled out as there was no oliguria, hematuria, frothy urine or past history of renal disease. The urine microscopy was also normal, without proteinuria. Her blood urea was 25 mg/dL, and serum creatinine 0.8 mg/dL. There were no features suggestive of an acute hypersensitivity reaction like urticaria or rashes. A normal thyroid-stimulating hormone level (2.27 mIU/L) excluded hypothyroidism.

Thus, by excluding all the probable causes of edema (acute renal failure, nephrotic syndrome, CHF, liver dysfunction, allergy and hypothyroidism) a diagnosis of insulin edema was made. The child was administered Furosemide (1 mg/kg) per orally, stat. After 4 h there was sudden deterioration with tachycardia and elevation in jugular venous pressure. The oxygen saturation levels remained maintained in room air. The appearance of decreased air entry on the right side and bilateral basal crepitations, suggested acute development of pulmonary edema. IV furosemide (1 mg/kg) was given, following which there was clinical improvement within an hour. At that point, a chest X-ray, N-terminal pro–B-type natriuretic peptide, electrocardiogram, and echocardiography were done and found to be normal, confirming the absence of an underlying cardiac cause. Following oral fluid restriction (two-third maintenance),

Table 2: Lab parameters of the child at admission and at the onset of edema

Lab parameter	At admission	At the onset of edema
Hemoglobin (mg/dl)	14.4	12.4
Total count (cells/mm^3)	10,300	8600
Differential count		
Polymorphs	50	59
Lymphocytes	46	35
Monocytes	4	6
Erythrocytic sedimentation rate mm/h	25	30
Platelet count (lakhs/mm^3)	3.3	3
Blood urea (mg/dl)	32	25
Serum creatinine (mg/dl)	0.8	0.8
Serum sodium (meq/L)	125	133
Serum potassium (meq/L)	3.9	4.5
Serum bilirubin (mg/dl)	0.6	0.5
Total protein (g/dl)	7.7	6
Serum albumin (g/dl)	4.9	3.8
Serum alanine amino transferase (IU/L)	14	81
Serum aspartate amino transferase	17	83
Urine albumin	Nil	Nil
Urine sugar	Positive	Positive
Urine microscopy	Normal	Normal
HbA1c	15%	
Blood culture	Sterile	Sterile
CRP	Negative	Negative
Urine culture	Sterile	Sterile

HbA1c: Hemoglobin A1c, CRP: C reactive protein

continuation of furosemide, and salt restriction, the anasarca gradually decreased, with complete resolution within 4 days. The transaminitis normalized after 1 week.

Discussion

Insulin edema is an uncommon complication of insulin therapy. We reviewed the clinical details of 7 reported cases of insulin edema among Type 1 DM patients [Table 1]. Of these six occurred among newly diagnosed cases and one was observed following the restart of therapy in a poorly compliant 20-year-old female. Six out of the seven patients were females with a mean age group of 13.2 years (range 9.5–20 years). Female preponderance has been noted earlier; female to male ratio of 2.75 reported in a review of 15 cases.[3] Among the 7 cases we reviewed [Table 1], 3 had isolated peripheral edema and 4 generalized edema. There was one patient with additional pulmonary edema.[2] The presence of pulmonary edema (as in this case) though uncommon, has been reported previously.[9] Edema occurred 3 days after the start of insulin (2 days after starting NPH) in our patient. In our review, we noted that the occurrence of edema ranged between 1 and 8 days, after commencing/intensifying insulin. Transient elevation of transaminases that corresponded with the onset of edema was observed in 1 case. It is also an uncommon event that has been reported earlier.[2,7] In our review of 7 patients we noted that edema resolved in a span of 7–14 days, and in most cases only salt and fluid restriction was used in the management. In fact, in 3 cases oedema resolved without treatment [Table1].[6,10] In the review of 15 cases by Derya *et al*., only 5 required medical treatment.[3]

A few mechanisms have been proposed for insulin edema, but the exact pathogenesis remains unclear. The most favored explanation is the consequences of fluid resuscitation in the setting of DKA,[7] especially since the edema resolves with salt and fluid restriction and diuretics, but the reason for the late onset remains unresolved. Transient hyperaldosteronism with increase in secretion of anti-diuretic hormone resulting from the osmotic diuresis that occurs secondary to hyperglycemia is another explanation that has been suggested.[5] Insulin mediated sodium retention can occur due to the direct action of insulin on the renal tubules. Sodium absorption is increased in the proximal convoluted tubules during insulin treatment via the stimulation of Na+/K+-ATPase, as well as the expression of Na+/H + exchanger.[5] When reintroduced into the insulin-deficient state seen in DM, insulin promotes sodium retention and inhibits natriuresis by suppressing glucagon. The decreased glucagon in turn leads to decreased inhibition of aldosterone, and increased sodium retention. Arteriolar vasodilatation may have a pathogenic role,[7] as evidenced by the efficacy of ephedrine (a vasoconstrictor) in insulin edema. The transient elevation of liver enzymes has rarely been described in literature. This may be attributed to the insulin mediated increase in glycogen storage.

Despite this condition being described for almost a century, there is high probability that it is being under recognized and under-reported. International societies of clinicians dealing with DM are yet to release standardized guidelines for investigating and managing insulin edema. There is a strong felt need for this, as well as future research regarding the etiopathogenesis, and a possible genetic predisposition. This case is being reported to create awareness among physicians about early recognition of this rare complication of insulin treatment in Type 1 DM. This will avoid unnecessary anxiety of the treating team and parents, and; reduce duration of hospital stay and unnecessary investigations, thus reducing expenses. Given the female predisposition, insulin edema should be especially looked for among adolescent girls with newly detected Type 1 DM.

Lessons learnt

- Insulin edema is a rare complication that is known to occur in patients with newly diagnosed diabetes mellitus while initiating or intensifying insulin treatment
- Transaminitis can occur uncommonly along with onset of insulin edema and needs further studies for clarification
- There is a wide spectrum of presentation ranging from innocuous pedal edema to pulmonary edema. The edema usually resolves within one to 2 weeks either spontaneously or with supportive management which includes fluid restriction, diuretics and salt restriction.

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

Fetus in Fetu: A Rare Differential Diagnosis for an Antenatally Identified Ultrasonographic Intra-abdominal Mass

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Abstract

Background: Fetus in fetu (FIF) is a rare congenital anomaly in which a parasitic fetus is trapped inside the body of its twin. The incidence is 1 in 500,000 births. Initially, considered as a mature teratoma, it was later identified as a separate entity due to the presence of an axial skeleton and organized limbs. **Clinical Description:** A 48-day-old girl presented with an antenatally detected calcified intra-abdominal mass. She had a palpable retroperitoneal mass measuring 6 cm × 4 cm at the left lumbar area. Sonology showed a heteroechoic cystic mass in the left lumbar region. Serum markers were normal except for a slightly elevated serum lactate dehydrogenase. Contrast-enhanced computerized tomography of the abdomen showed a well-defined cystic lesion measuring 7.6 cm × 6.5 cm × 5.9 cm with enhancing septae, multiple calcific foci, teeth, and bones in the left suprarenal region displacing the left kidney. **Management:** Laparotomy showed a cystic appearing mass with solid components within. Cystic structure was the amniotic covering and solid component turned out to be the FIF with a face, limbs, and umbilical cord. No adjacent infiltration was seen. Pathology confirmed the finding of FIF with an identifiable vertebral column, umbilical cord, pelvis and lower limb bones, skin, and retinal and brain tissue. The infant has been under follow-up for a year and is thriving. **Conclusion:** FIF is a rare condition of infancy which can be diagnosed preoperatively by radiological examination, treated by complete excision, and confirmed by gross and histopathology. Differentiation of FIF from teratoma is mandatory as the latter can be malignant.

Keywords: Fetus in fetu, retroperitoneal calcified tumor, teratoma

Fetus in fetu (FIF) is defined as a rare congenital anomaly in which a malformed parasitic fetus is trapped inside the body of its twin.[1] The incidence is reported to be 1 in 500,000 births.[2] An early description of this condition was given by Young in 1809.[3] There are two main theories regarding the etiopathogenesis of FIF. The first, "the included twin" theory proposes that it is associated with abnormal embryogenesis in a diamniotic, monochorionic pregnancy, wherein a vertebrate fetus is enclosed within the body of another normally developing fetus.[3] The second, "the teratoma" theory suggests that the FIF mass represents a well-differentiated, highly organized teratoma.[3] The FIF complex is characterized by a fibrous membrane (representing the chorioamnion) that contains some fluids (amniotic fluid) and a fetus suspended by a cord or pedicle.[4] The growth of an FIF initially parallels that of its twin but stops abruptly due to two reasons, either the vascular dominance of the host twin or an inherent defect in the parasitic twin.[5]

We present this case to highlight the multidisciplinary collaboration that resulted in favorable outcome in an infant presenting with an antenatal radiological abnormality, the need to differentiate FIF from a teratoma, and the importance of close follow-up to ameliorate the risk of recurrence.

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Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_282_21

Clinical Description

A 48-day-old female infant was brought by her parents on a follow-up visit in relation to an antenatally detected abnormality detected on the ultrasound at 35 weeks gestation in the form of a left suprarenal calcification. The couple had been advised follow-up after delivery by the obstetrician and neonatologist team. Review of her medical records revealed that the mother had gestational diabetes mellitus, for which she was prescribed metformin. The baby was born at term gestation by cesarean section (CS), the indication being a previous CS. Her birth weight was 2.48 kg and the APGAR scores were normal. The perinatal period was uneventful, except for a single episode of asymptomatic hypoglycemia, the details of which were unavailable. She was the second child of a nonconsanguineous union. There was no family history of multiple pregnancies. At birth, the general physical and

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Submitted: 19-Sep- 2021 **Revised:** 07-Jan-2022
Accepted: 22-Jan-2022 **Published:** 25-Feb-2022

How to cite this article: Kazia AP, Mathews SJ, Vasu PP, Krishnadas S. Fetus in fetu: A rare differential diagnosis for an antenatally identified ultrasonographic intra-abdominal mass. Indian Pediatr Case Rep 2022;2:29-31.

systemic examination had been normal. There was no evidence of any palpable abdominal mass. The baby had been discharged with advice to get a postnatal abdominal ultrasound. Because of the pandemic and since the exclusively breast fed infant was thriving well, they failed to report back until 6 weeks of age. There was no history of abdominal distention, vomiting, constipation, or perception of an abdominal mass during handling.

On examination, the baby was hemodynamically stable; heart rate 108 beats per minute, blood pressure 64/48 mm of Hg, and oxygen saturation in room air 99%. The anthropometric measurements were appropriate for the age with length 52 cm, weight 4.5 kg, and head circumference 37 cm. Abdominal examination revealed a mass measuring approximately 6 cm × 4 cm involving the left hypochondrium and lumbar region. The mass was nontender with smooth surface, firm consistency, all borders palpable, except the lateral border. There was no intrinsic mobility, and the mass displayed minimal movement with respiration. There was impaired resonance on percussion, and no bruit could be heard on auscultation. Remaining systemic examination was normal. The clinical differential diagnosis considered included retroperitoneal teratoma (antenatal calcification, well-preserved child with a smooth retroperitoneal mass, and no clinical evidence of metastasis), and neuroblastoma (presentation in early infancy, antenatal calcification, and suprarenal location).

The abdominal ultrasound showed a left suprarenal hetero-echoic cystic mass measuring 7 cm × 4 cm with areas of calcification and internal vascularity. Tumor markers were planned in view of the differentials. Most were normal; serum alpha fetoprotein (AFP) 685.7 ng/ml, 24-h urinary vanillyl mandelic acid less than 1 mg/24 h, serum beta human chorionic gonadotropin less than 1.2 IU/L. The only abnormality detected was an elevated serum lactate dehydrogenase (LDH) of 654 U/L (normal values 170–580 U/L). A contrast-enhanced computed tomography (CECT) of the abdomen was performed for more refined delineation of the mass and assessment of organ of origin. This revealed a well-defined predominantly cystic lesion measuring 7.6 cm × 6.5 cm × 5.9 cm with smooth borders, enhancing septae, multiple calcific foci, teeth, bones, and irregular fat deposits in the left suprarenal region that was displacing the left kidney posteroinferiorly [Figure 1a]. The three-dimensional reconstruction showed a fetus-shaped mass in the left hypochondrium [Figure 1b]. Based on these radiological findings, our differential diagnoses narrowed down to a well-differentiated teratoma or a FIF.

Management and Outcome

We proceeded with a laparotomy with the plan to excise the mass and to send for a biopsy. Intraoperatively, the mass was located in the left lumbar area in the retroperitoneum. It was a predominantly cystic appearing mass with solid components within, having no infiltration to adjacent structures and a prominent feeding vessel to the aorta. The fluid within the amniotic covering formed the cystic part, and the FIF formed the solid part with a face, four limbs, and an umbilical cord [Figure 2]. Gross pathology showed a fetus-shaped mass with gestation age of 13 weeks, weight of 115 g, and crown rump length of 7 cm. It exhibited anencephaly, sirenomelia type 1 (Mermaid syndrome with fused lower limbs), polydactyly of the left foot, and syndactyly of both hands and feet.

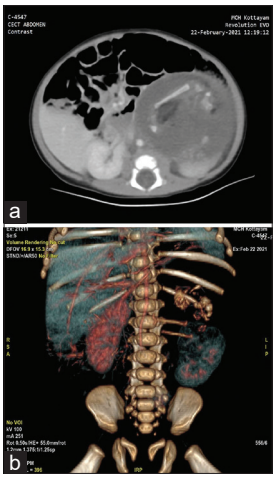

Figure 1: (a) Contrast-enhanced computed tomography of the abdomen showing a left sided mass with multiple calcifications, teeth and bones. (b) Three dimensional reconstruction of the abdominal contrast-enhanced computed tomography showing a fetus shaped mass in the left suprarenal area

The thoracic and abdominal organs, anal opening and external genitalia were not developed. The FIF showed evidence of a dorsal vertebral column [Figure 3] and umbilical cord of normal morphology, with skin, pelvic and lower limb bones (femur, tibia, and fibula) on both sides. Histopathology showed retinal tissue and parts of the brain tissue (hind brain). Section from ilium and vertebrae showed hematopoietic bone marrow as well as skeletal muscle attachment.

Based on the fetus-like shape and the presence of vertebral column, umbilical cord, and amniotic coverings, the final diagnosis of FIF was confirmed. The infant recovered well after surgery and was discharged on the 7th postoperative day. As per the standard protocol of FIF, she was kept on close follow-up with serial measurements of AFP and repeated ultrasounds of the abdomen for the detection of recurrence. At present, the patient is a 1-year-old with normal serum AFP (5 ng/ml) and LDH (155 U/L) and normal ultrasonography.

Discussion

FIF is a rare disease that usually presents before 18 months of age.[3] There are reports of later presentation in childhood or rarely in adult life. Gender predilection is uncertain; Patankar *et al*.[5] noted a 2:1 male predominance, whereas Thakral *et al*.[6] reported equal prevalence. The most common presentation of FIF is a mass, most commonly in the abdomen, and almost 80% in the retroperitoneum.[7] The FIF may be asymptomatic or produce symptoms due to a mass effect such as abdominal distention, difficulty in feeding, vomiting, jaundice, and pressure effects on the renal and/or respiratory systems.

The differential diagnosis of FIF includes causes of a neonatal intra-abdominal mass with calcification such as meconium peritonitis, neuroblastoma, adrenal hemorrhage, and a retroperitoneal teratoma. The first line of investigation is radiological. Ultrasonography shows a complex cystic mass with ill-defined solid internal components, which helps differentiate

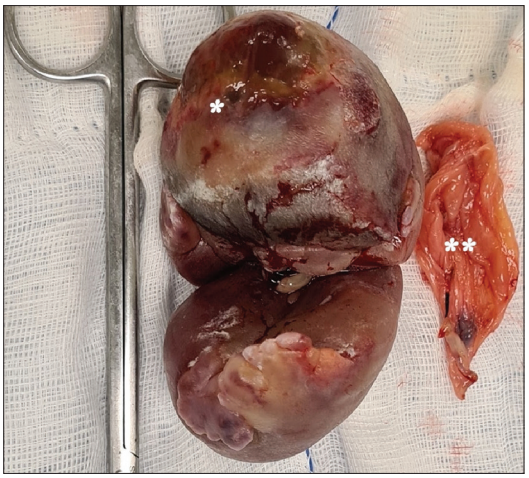

Figure 2: Postoperative image of the fetus in fetu (*) with an umbilical cord and amniotic sac (**)

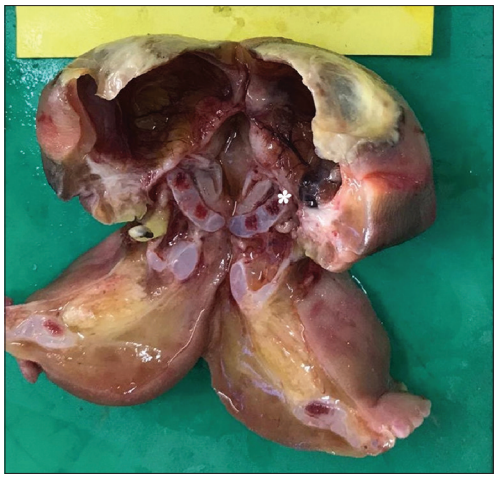

Figure 3: Internal morphology of the fetus in fetu displaying the vertebral column (*)

from meconium peritonitis, adrenal hemorrhage, and solid tumors. However, excluding a teratoma may need more sophisticated modalities such as CECT and magnetic resonance imaging by demonstration of the axial skeleton. Sometimes, it may not be possible to clearly differentiate FIF from a teratoma without histopathology.

Hence, the definitive treatment of suspected FIF is surgical excision. Since there are many similarities between FIF and teratoma at the histological level, a detailed pathological examination is imperative. An important feature that distinguishes FIF from a teratoma is the presence of a vertebral column.[6] Its presence shows that fetal development has advanced at least beyond the primitive streak stage (12–15 days of gestation) to a notochord, which is the precursor of the vertebral column.[3,6] Other characteristics of an FIF include a mass enclosed within a distinct sac, partially or completely covered by skin, grossly recognizable anatomic features such as limbs, and attached to the host by a pedicle containing relatively large blood vessels, as was seen in this case.[3,6]

FIF is almost always benign. Only one malignant case has been reported.[8] The mass recurred as a yolk sac tumor 4 months after removal which was attributed to the presence of immature tissues and remnants of the capsule of the mass. Thus, it is recommended that the FIF mass should be excised *in toto* including its coverings to prevent local recurrence.[8] Serological (AFP) as well as radiological follow-up is required[2] for early detection of immature elements, especially when a part of the sac has to be left *in situ* due to its proximity to major blood vessels.

In conclusion, FIF is considered as a benign condition whereas teratoma which is a close differential diagnosis is a potentially malignant diagnosis. In this case, close collaboration between the obstetrician, neonatologist, radiologist, surgeon, and pathologist resulted in complete workup, complete surgical excision, confirmation of diagnosis, and favorable outcome in an infant who presented with an antenatally detected radiological abnormality.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the legal guardian. In the form, 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Acute Salpingitis Presenting with Acute Abdomen in a Pre-pubertal Girl

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Abstract

Background: An acute abdomen in children is often a challenging scenario for clinicians as it is caused by various medical and surgical conditions. Although symptomatology and specific clinical findings point directly to few causes, thorough history and in-depth clinical examination help to systematically narrow down the differential diagnosis. **Clinical Description:** We report a rare case of acute salpingitis in an 8-year-old prepubertal female child presenting with acute abdominal pain and fever for 3 days. Examination revealed diffuse abdominal tenderness with guarding and rigidity along with an ill-defined, tender mass in the right iliac fossa. **Management:** Abdominal ultrasound showed a hyperechoic mass in the right iliac fossa and the appendix was not visualized. The child was kept nil oral and started on broad-spectrum antibiotics. However, the child developed abdominal distension and worsening of pain over the next 24 h. The child was taken up for emergency laparotomy, and a complex mass in the right iliac fossa adherent to small bowel and covered by omentum was noted. Histopathological examination of the excised right iliac fossa mass showed acutely inflamed right fallopian tube. Normal appendix was noted in the postoperative ultrasonogram. **Conclusion:** It is important to differentiate surgical causes from nonsurgical ones to avoid unnecessary surgery and its complications. Salpingitis may mimic acute appendicitis because of nonspecific symptomatology and radiological signs and should be considered as a differential diagnosis for acute abdomen, even in a prepubertal female child.

Keywords: Acute abdomen, appendicitis, salpingitis

Acute abdomen is a common clinical syndrome in children which can be caused by a wide spectrum of medical and surgical conditions. The exact presentation varies with etiology, severity, age, and associated symptoms. Meticulous history-taking and focused physical examinations are vital for planning rationale investigations and establishing an early diagnosis. Common medical causes of acute abdomen in a child include gastroenteritis, mesenteric lymphadenitis, worm infestation, urinary tract infection, and colitis. The common surgical causes include acute appendicitis, ischemic colitis, perforation of the bowel, intussusception, volvulus, malrotation, blunt injury abdomen, and Meckel's diverticulitis.[1] Gynecological conditions which present as acute abdomen such as a tubo-ovarian abscess, ovarian mass with torsion, rupture, and hemorrhage should be considered as differential diagnoses when investigating causes of surgical abdomen in a girl.

Acute salpingitis presenting as an acute abdomen is common in sexually active young women and is usually due to *Neisseria gonorrhoeae* or polymicrobial infection.[2] In a prepubertal child, acute salpingitis is extremely rare. It may be caused by bacteremia due to *Streptococcus pneumoniae* following acute pharyngitis, acute otitis media, and/or acute pyogenic meningitis.[3]

We report an uncommon presentation of an otherwise common condition by virtue of age-acute salpingitis in a prepubertal girl presenting as an acute surgical abdomen. It proved to be a diagnostic challenge and taught us some invaluable lessons retrospectively that we wish to share with our colleagues.

Clinical Description

An 8-year-old girl was brought to the emergency department with complaints of severe diffuse abdominal pain for 3 days and high-grade fever for 2 days. The abdominal pain was

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Submitted: 26-Sep-2021 **Revised:** 31-Oct-2021
Accepted: 22-Jan-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_294_21

How to cite this article: Babu TA, Balakrishnan P, Sharmila VA. Acute salpingitis presenting with acute abdomen in a pre-pubertal girl. Indian Pediatr Case Rep 2022;2:32-5.

diffuse in the lower abdomen and progressively increasing in severity. She also had two episodes of bilious vomiting. There was no history of preceding abdominal trauma, altered bowel habits in the form of constipation, obstipation, or loose stools, abdominal distension, or vomiting of blood. The fever was initially low grade, which became high grade within a day and was associated with chills and rigors. There was no history of any rash, ear discharge, throat pain, headache, difficulty or painful micturition, passage of red-colored or cloudy urine, or vaginal discharge. There was no history of eating food outside the home or any other family member being similarly affected. There was no history of similar complaints in the past. The child had never been hospitalized for any serious bacterial infections or undergone any operative procedure in the past. She had not attained menarche. There was no significant family history or contact with tuberculosis.

On clinical examination, the child was sick looking, febrile with a temperature of 40°C, tachycardic, had a respiratory rate of 26/min and blood pressure of 90/70 mmHg (between 5th and 50th centile for age and sex). The child's anthropometric measurements were within normal limits. The general physical examination did not reveal any pallor, icterus, palpable purpura, or edema. The abdominal examination revealed diffuse abdominal tenderness with guarding and rigidity. An ill-defined, soft, tender mass could be palpated in the right iliac fossa, which was approximately 3 cm × 3 cm in size. The cardiovascular, respiratory, and central nervous system examinations were unremarkable. In view of the examination findings present in the right iliac fossa, the differential diagnoses that were considered were acute appendicitis, appendiceal phlegmon, typhlitis, infectious colitis, and ileocecal tuberculosis. Investigations were planned accordingly.

Management and Outcome

The child was managed with intravenous fluids and broad-spectrum empirical antibiotics. Ryle's tube aspiration was started for gastric decompression. Significant results in her complete blood count were: hemoglobin 10 g/dL, total leukocyte count 21,000 cells/mm^3 with neutrophilia (80%), and a platelet count of 3 lakhs/mm^3. The erythrocyte sedimentation rate was 11 mm/h and C-reactive protein was 1.9 mg/L, both being normal**.** The X-ray of the abdomen (erect) showed gas-filled normal bowel loops with no evidence of pneumoperitoneum. Salient ultrasonographic examination findings were a hyperechoic mass in the right iliac fossa with nonlocalization of the appendix. Uterus and bilateral ovaries were normal, thus ruling out a ruptured or torsion of an ovarian cyst.

It was decided to manage the child conservatively. The fever did not subside with antibiotics, and the vomiting and abdominal pain rapidly worsened over the next 48 h of hospitalization. The child also developed mild abdominal distension. Although the vital signs, urine output, and cardiorespiratory status were stable, we decided that rather than arranging for a computed tomography (CT, which would have taken some time, as it is not available in our institute), it would be more prudent to perform an emergency exploratory laparotomy, especially since there was rapid clinical worsening and a strong clinical suspicion of a ruptured appendicular mass.

Intraoperatively, a matted mass with distorted anatomy was noted in the right iliac fossa that was adherent to the small bowel and covered by omentum. The appendix and the right fallopian tube were obscured, with the anatomy completely distorted due to the presence of adhesions. The uterus, bilateral ovaries, and left fallopian tube were grossly normal on inspection. Gross examination showed a mass (3 cm × 3 cm × 2 cm) composed of omentum (approximately 3 cm × 2 cm × 0.5 cm) and a 2-cm long congested tubal structure that appeared to be the fallopian tube. It was open on both sides, and the lumen was filled with dark-brown material. The mass was excised after releasing surrounding bowel adhesions, fixed in 10% neutral-buffered formalin, and sent for histopathological examination. This revealed features of acute salpingitis and inflamed omentum [Figures 1 and 2]. The tubal serosal exudates or its luminal contents were not sent for culture and sensitivity.

The final diagnosis was acute salpingitis. As this is a rare condition in a prepubertal child, the history and examination were revisited and further workup planned to identify the underlying cause or predisposing factors. Absence of suggestive symptoms and signs clinically excluded acute pharyngitis, acute otitis media, and meningitis. There was no history or clinical indicators suggestive of sexual abuse, and per vaginal examination was not performed in view of the patient's age. Urine microscopy was normal. Random blood glucose was normal. Blood culture and urine culture were sterile. Investigation for primary immunodeficiencies was not actively considered as there was no significant history of recurrent serious bacterial infections. Workup for tuberculosis, i.e., a chest X-ray, Mantoux test, and

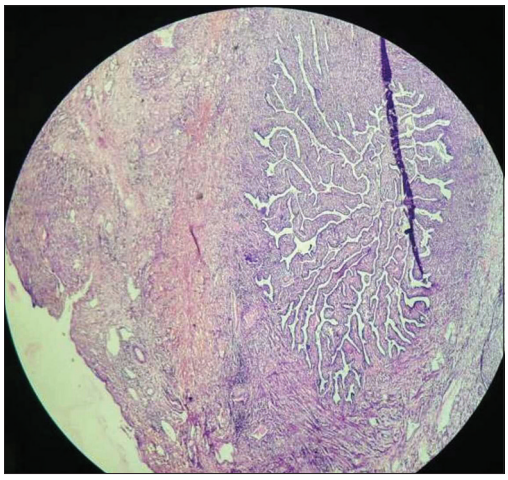

Figure 1: Microphotograph showing structure of fallopian tube with thickened wall and inflammatory cell infiltrates up to serosa (H and E stain, ×40)

cartridge-based nucleic acid amplification assay of induced sputum were negative normal. Thus, we were unable to identify any predisposing factor. The postoperative period was uneventful, and the clinical condition improved. The total and differential white blood counts normalized. Ultrasound abdomen after 1 week showed the presence of normal appendix, colon, uterus, and bilateral ovaries. Parents were counseled regarding the long-term possibility of chronic pelvic pain, chronic pelvic inflammatory disease, and infertility. The child was discharged with a final diagnosis of acute salpingitis and is on regular follow-up.

Discussion

The various causes to be considered for abdominal pain with right iliac fossa mass in a sexually inactive prepubertal female child are mentioned in Table 1. Most causes are due to infections of the intestines. Acute salpingitis is rare in prepubertal children. In older sexually active individuals, it is often due to sexually transmitted diseases secondary to *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, or nonvenereal salpingitis due to *Streptococcus pyogenes, Escherichia coli*, etc. In these cases, acute abdominal pain due to a pelvic pathology may be picked up clinically by per vaginal and/or per rectal examination. Per vaginal examination may reveal forniceal tenderness in pelvic inflammatory disease, whereas per rectal examination may reveal any adnexal mass in pelvic inflammatory disease. Given the age of the patient, these examinations were not warranted in this case. Table 2 summarizes the clinical and bacteriological details of similar case reports identified on a literature search.[3-5]

We faced certain challenges in the management of this case. One of the initial differentials was a ruptured appendicular mass. The retrocecal position of the appendix in this case could be one of the reasons for its nonvisualization in the initial ultrasound.[7] Special positioning is needed for locating a retrocecal appendix during an ultrasonogram. Often, a retrocecal appendix will be obscured by bowel gas, leading to its nonvisualization.

Table 1: Causes for acute abdomen pain with right iliac fossa mass in a female child

Appendicular abscess
Appendicular mass
Ileocecal tuberculosis
Right sided acute salpingitis
Mesenteric lymphadenitis
Crohn's disease
Torsion of right ovary
Rupture of right ovarian tumor
Cecal perforation
Intestinal lymphoma
Mesenteric cyst
Iliopsoas abscess

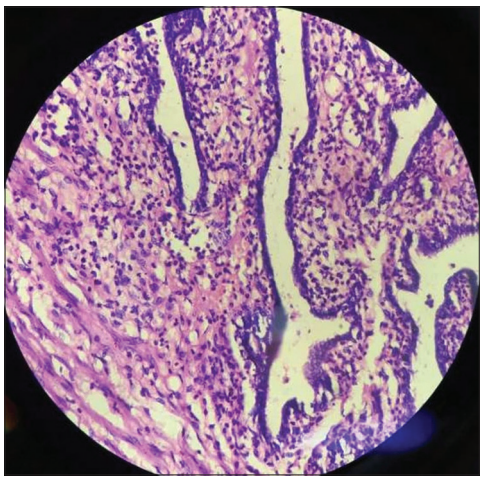

Figure 2: Microphotograph showing neutrophilic infiltrates in mucosa and wall of fallopian tube suggestive of acute salpingitis (H and E stain, ×400)

Table 2: Comparison of previous cases of acute salpingitis in prepubertal girls

Age, year, and reference	Clinical symptoms	Peroperative findings	Management	Organism identified	Risk factors
11 years, 2008[3]	Abdominal pain, fever, vaginal discharge, nausea and vomiting	Laparoscopic - Right fallopian tube coated with fibrin Appendix and bowel normal	Empirical amoxicillin-clavulanate Benzyl penicillin after culture report	*S. pneumonia*	Pneumonia
12 years, 2015[4]	Fever, acute abdominal pain, urinary symptoms, septic shock	Exploratory laparotomy - Enlarged and inflamed right and left fallopian tubes	Abdomen closed in layers without surgical intervention Cefipime, doxycycline, and metronidazole	Negative for *N. gonorrhoeae* and *C. trachomatis*	None
8 years, 1991[6]	Yellow green vaginal discharge Lower abdominal pain	Surgery not done	5 days of intravenous cefoxitin and oral erythromycin	*N. gonorrhoeae*	Positive sexual abuse history
8 years (present case)	Acute abdominal pain, fever and shock	A complex mass in right iliac fossa adherent to small bowel and covered by omentum appendix and right fallopian tube obscured by dense adhesions	Resection of right iliac fossa mass Acute salpingitis proven on histopathology	Culture not done	No known risk factors

S. pneumonia: Streptococcus pneumonia, N. gonorrhoeae: Neisseria gonorrhoeae, C. trachomatis: Chlamydia trachomatis

In this situation, the use of a three-step graded compression sonographic algorithm of sequential positioning can help to visualize retrocecal inflamed appendix when it is not visualized in the routine supine position. CT scan should be done if the appendix is still not visualized despite using this protocol, and there is a strong clinical suspicion of acute appendicitis.[8] In addition to identify retrocecal appendicitis, its extension in subhepatic or pararenal space, free gas in ruptured appendicitis, it can help in diagnosing conditions mimicking appendicitis clinically. For instance, right-sided acute salpingitis may mimic appendicitis by forming a right iliac fossa mass in children due to the shallowness of the pelvis. A CT scan is advisable before proceeding for laparotomy on clinical grounds[9] but could not be done in our case due to the rapidly worsening clinical condition and practical issues related to nonavailability of CT scanning facilities in our institute.

We planned an exploratory laparotomy in view of the rapidly worsening clinical condition of the patient and our inability to arrive at a clinical diagnosis, based on the available investigations. In this case, the right iliac fossa mass comprising the inflamed right fallopian tube and omentum with small bowel adhesions obscured the visualization of the appendix intraoperatively and would have also attributed to its nonvisualization on ultrasonography.

Usually, acute salpingitis is a nonsurgical condition which is treated conservatively with antibiotic therapy.[10] Surgical intervention is indicated in cases of pyosalpinx, rupture of the fallopian tubes, poor response to medical therapy, and when appendicitis cannot be definitely ruled out. Salpingectomy is advised when pyosalpinx leads to rupture of the fallopian tube. In this patient, the part of the right fallopian tube was removed, leaving the fimbrial end along with attached omentum. We were unable to make a bacteriological diagnosis as culture specimens from the tubal serosal exudates or its luminal contents were not sent.

Salpingitis in a prepubertal child carries a high risk of misdiagnosis, inappropriate management, and long-term sequelae-like infertility and ectopic pregnancy if delay in diagnosis leads to complications. Nonspecific symptomatology and a presentation mimicking acute abdomen secondary to supposed appendicitis contributed to the misdiagnosis in this case. The use of radiological algorithmic protocols and abdominal CT should be considered before exploratory laparotomy. Salpingitis may mimic acute appendicitis and should be always considered in the differential diagnosis of acute abdomen in a girl, even if prepubertal. All endeavors should be undertaken to establish a microbiological cause and look for predisposing causes or factors for nonsexually transmitted acute salpingitis.

Lessons learnt

- Surgical and nonsurgical causes of acute abdomen in a child can be differentiated by detailed elicitation of history, focused physical examination and rational planning of investigations
- Specific positioning of the child during an ultrasound examination is necessary for visualization of a retrocecal appendix
- Preoperative computed tomography scanning is advised to diagnose appendicitis and its mimickers, when the appendix is not visualized despite using a three-step graded compression sonography algorithm of sequential positioning
- The indications for surgery in prepubertal acute salpingitis are pyosalpinx, rupture of fallopian tubes, poor response to medical therapy, and when appendicitis cannot be ruled out.

Consent for publication

Signed informed consent was obtained from parents.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the parent. In the form, the patient's parent has given his consent for the images and other clinical information to be reported in the journal. The patient's parent 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Apparent Mineralocorticoid Excess - A Rare Cause of Endocrine Hypertension

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Abstract

Background: Endocrine causes of hypertension constitute a very small percentage of patients with secondary hypertension. Apparent mineralocorticoid excess (AME) is a rare genetic form of young-onset secondary hypertension. **Clinical Description:** We present a case of a 16-year-old boy who was diagnosed with hypertension at 5 years of age, had recurrent episodes of hypokalemic paralysis, and deranged renal function for 1 year. Hypertension was uncontrollable with multiple antihypertensive agents until an aldosterone antagonist (spironolactone) was added. Clinical history and evaluation could not identify any secondary causes of hypertension. There was no significant family history. Growth and puberty were age-appropriate. **Management and Outcome:** Endocrine workup was planned considering hypokalemia and metabolic alkalosis. This demonstrated hyporeninemic hypoaldosteronism and raised the possibility of AME and Liddle syndrome. Clinical exome sequencing revealed a probable diagnosis of AME due to a novel homozygous variant (c.911A>G) in *HSD11B2* gene. Sanger sequencing confirmed heterozygosity of the same variant in both parents. **Conclusion:** A novel homozygous variant was found in *HSD11B2* gene in a subject with early-onset hypertension associated with hypokalemic metabolic alkalosis, establishing the diagnosis of AME. The use of an algorithmic approach and individualized planning of genetic studies can help in early diagnosis. This helps clinicians to select the appropriate antihypertensive drug, attain good control, and prevent the development of end-organ damage. A high index of suspicion should be kept for AME and other hyporeninemic hypoaldosteronism conditions in the case of early-onset hypertension.

Keywords: Hypoaldosteronism, low renin, mineralocorticoid excess, pediatric, secondary hypertension

Most guidelines such as of the American Academy of Pediatrics and European Society of Hypertension recommend mandatory annual blood pressure (BP) measurement in children and adolescents for the early detection of primary as well as asymptomatic secondary hypertension.[1] Primary hypertension can be differentiated from secondary hypertension by the absence of any identifiable secondary cause. Table 1 lists various causes of secondary hypertension in children as well as their presenting features. Renal and renovascular causes are most common, constituting 34%–79% and 12%–13%, respectively, whereas endocrine disorders account for only 0.5%–6% causes of secondary hypertension.[2]

Elicitation of a detailed history, performance of a focused examination, and analysis of first-line investigation reports are invaluable steps that give direction to a clinical approach aimed at determining etiology. For instance, hypertension associated with metabolic alkalosis and hypokalemia warrants evaluation for increased mineralocorticoids. Apparent mineralocorticoid excess (AME) is a rare autosomal recessive monogenic disorder arising from deficiency of the renal isoenzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2).[3] It is characterized by severe hypertension (i.e., BP more than 95th centile + 12 mmHg, or the presence of target organ damage) that is early in onset (presenting before 40 years of age) and is due to hyporeninemic hypoaldosteronism. Normally, 11βHSD2 inactivates the glucocorticoid cortisol to a less active metabolite, cortisone. Mutations in the *11βHSD2* gene affect this step, leading to supraphysiological cortisol levels by binding and activating the mineralocorticoid receptor (MR) for aldosterone, thus behaving like an "apparent" mineralocorticoid. The spectrum of clinical phenotypes ranges from severe hypertension presenting in infancy to mild forms first seen in adulthood. Growth failure (prenatal and postnatal) may be seen in severe cases.

In AME, the renal damage that ensues from the untreated chronic hypertension makes the interpretation of biochemical and hormonal tests challenging, as well as control of hypertension difficult. The aim of presenting this case is to sensitize

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Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_312_21

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Submitted: 12-Oct-2022 **Revised:** 23-Jan-2022
Accepted: 23-Jan-2022 **Published:** 25-Feb-2022

How to cite this article: Verma S, Dabadghao P, Moirangthem A. Apparent mineralocorticoid excess - A rare cause of endocrine hypertension. Indian Pediatr Case Rep 2022;2:36-9.

Table 1: Causes of secondary hypertension with their presenting features

Disorders	Presenting features
Nonendocrine causes	
Renovascular or renal parenchymal disease	Hypertension (can be associated with conditions such as fibromuscular dysplasia, William syndrome)
Renal failure	
Glomerulonephritis	
FSGS	
Coarctation of aorta	Hypertension, headache, cold feet, cramps, congestive heart failure (infancy)
Drugs	Corticosteroids, sympathomimetics
Endocrine causes	
Pheochromocytoma and paragangliomas	Paroxysms of palpitations, headache, diaphoresis, syncope
Primary aldosteronism	Marked hypokalemia, may have muscle cramps, weakness, headache, palpitations, polyuria, polydipsia
11β-hydroxylase deficiency CAH	Hypertension, hypokalemia, precocious pseudopuberty (boys), virilisation, and hirsutism (girls)
17α-hydroxylase deficiency CAH	Genital ambiguity (46XY), primary amenorrhea (46XX)
Cushing syndrome	Central obesity, striae, easy bruisability, proximal myopathy, compressive symptoms (in pituitary=dependent Cushing disease)
AME Genetic (HSD11B2 gene)/liquorice or carbenoxolone ingestion	Hypokalemia (periodic paralysis, muscle cramps), metabolic alkalosis, hypertension
Hypothyroidism	Weight gain, pubertal arrest, weakness, sluggishness, ± goiter
Hyperthyroidism	Weight loss, palpitations, goitre, heat intolerance
Acromegaly	Hyperhidrosis, enlarging hand and feet size, compressive symptoms
Hyperparathyroidism	Bone pains, renal stones, psychosis

AME: Apparent mineralocorticoid excess, CAH: Congenital adrenal hyperplasia, FSGS: Focal segmental glomerulosclerosis

pediatricians to the clinical approach required for investigating secondary hypertension in young children.

Clinical Description

A 16-year-old boy was referred to our center for the management of hypertension with deranged renal function. The child became symptomatic for the first time at the age of 5 years when he developed bilateral lower limb weakness. At that time, he had been diagnosed with hypertension and concurrent hypokalemia and metabolic alkalosis. Over the years, the child had visited multiple experts and had been prescribed various antihypertensive drugs. His hypertension remained uncontrolled despite good compliance to beta-blockers (metoprolol), calcium channel blocker (amlodipine), and an alpha-blocker (prazosin), until a mineralocorticoid antagonist (spironolactone) was added. During this period, there was a history of multiple episodes of weakness in the bilateral lower limbs associated with muscle cramps and pain. Each episode progressed to complete weakness over hours. These were attributed to severe hypokalemia (serum potassium <2.5 mEq/L) by his treating physician, with symptomatic relief on normalization of levels after the initiation of intravenous, followed by oral potassium. There was no history of decreased micturition or the passage of red or discolored urine, swelling of any part of the body, seizures, difficulty in breathing, or growth failure. There was no history suggestive of secondary causes of hypertension, as listed in Table 1. He was born out of nonconsanguineous marriage. No other family member had a history of hypertension, coronary artery disease, or any features suggestive of thyroid, parathyroid, or abdominal neoplasia, all causes of secondary hypertension.

On examination, all peripheral pulses were palpable, the heart rate was 90 beats per minute (min), and respiratory rate was 18 per min. However, the blood pressure was elevated on multiple occasions; 159/89 mmHg (>95th +12 mmHg in both diastolic and systolic BP). There was no significant difference between the upper and lower limbs. An abdominal bruit was not heard. The child's height was 164 cm (between 50th and 75th centile on Indian population charts) and weight 58 kg (25th–50th centile). The facies and body proportions appeared normal. Pubertal development was age-appropriate with Tanner's sexual maturity rating stage 4. There was no evidence of pallor, periorbital or pedal edema, labial and lingual nodular swellings, cushingoid features, neurocutaneous markers, rashes, or skin lesions, including acne. Thyroid examination was normal. Fundus examination revealed diffuse arteriolar narrowing with no constriction indicative of grade I hypertensive retinopathy. Respiratory, cardiovascular, abdominal, and central nervous system examinations were unremarkable. Thus, the clinical phenotype was early-onset hypertension with possible renal end-organ damage and intermittent episodes of symptomatic hypokalemia.

Significant biochemical abnormalities were identified; hypokalemia (K + 2.9 mEq/L) in the presence of normal serum sodium levels (149 mEq/L) and metabolic alkalosis (venous blood gas pH 7.45, bicarbonate level 24 mEq/L). Elevated serum creatinine (2.8 mg/dL) and decreased estimated glomerular filtration rate (eGFR) of 47 mL/min/1.73 m^2 (normal >60 mL/min/1.73 m^2) confirmed chronic kidney failure. The abdominal ultrasound revealed bilateral echogenic kidneys with loss of corticomedullary differentiation and a small-sized right kidney. Renal Doppler showed normal renal vasculature. Echocardiography detected left

ventricular hypertrophy that was attributed to prolonged systemic hypertension.

The presence of hypokalemia and metabolic alkalosis suggested a hyperfunctioning mineralocorticoid axis. Thus, we decided to measure the plasma aldosterone levels and plasma renin activity. Plasma aldosterone level was 0.13 nmol/L (normal 0.19–0.83 nmol/L), while plasma renin activity was 0.2 ng/mL/h (normal 0.8–1.8 ng/mL/h). We had to stop spironolactone for 6 weeks before testing to avoid interference, and the BP was monitored strictly. During this period, there were episodes of elevation of systolic BP >160 mmHg that were managed by sublingual nicardipine (calcium channel blockers). The BP normalized as soon as spironolactone therapy was resumed. We also evaluated 17-OH-progesterone to rule out congenital adrenal hyperplasia secondary to 11 beta-hydroxylase deficiency, which was normal (10.48 nmol/L). Since the endocrinal phenotype of hyporeninemic hypoaldosteronism suggested overstimulation of the MR by cortisol or related precursors, the differential diagnoses of AME and Liddle syndrome were considered, and genetic testing was planned.

Clinical exome sequencing (ES) identified a homozygous missense variation c.911A>G in exon 5 of the *HSD11B2* (ENST00000326152.6) gene. This variant results in substitution of arginine for histidine at codon 304. Sanger sequencing confirmed that the parents were heterozygous carriers for the same variant. The c.911A>C variant has not been reported in the 1000 genomes project (https://www.internationalgenome.org), gnomAD (https://gnomad. broadinstitute.org), database of Indian exomes, and internal databases of the laboratory. It is also not reported in disease databases such as Clinvar and human gene mutation database. The *in silico* prediction of the variant was inconsistent across various tools; Functional Analysis through Hidden Markov Models predicting a deleterious effect, while MutationTaster, scale-invariant feature transform, and polyphen-2 predicting a benign effect. This was classified as a variant of uncertain significance according to the American College of Medical Genetics criteria.[4] Protein structural modeling by EasyModeller and molecular dynamic simulation for determining the possible effect of change in the amino acid residue observed no significant perturbations in interaction as well as structure between the residues and ligand at the active site of both wild and mutant structures. The superimposition of both showed negligible root mean square deviation, which suggested that the mutation did not have any effect on structure or stability of the protein.

Discussion

The differential diagnoses that need to be considered in children presenting with hypertension and hypokalemic metabolic alkalosis include heterogeneous causes; renovascular hypertension, AME, Cushing syndrome, Liddle syndrome, renal secreting tumors, 11β hydroxylase deficiency, and glucocorticoid remediable hypertension. Although the list appears daunting at first, an astute clinician can arrive at an etiological diagnosis in cases presenting with early-onset hypertension by following a stepwise algorithmic approach [Figure 1].

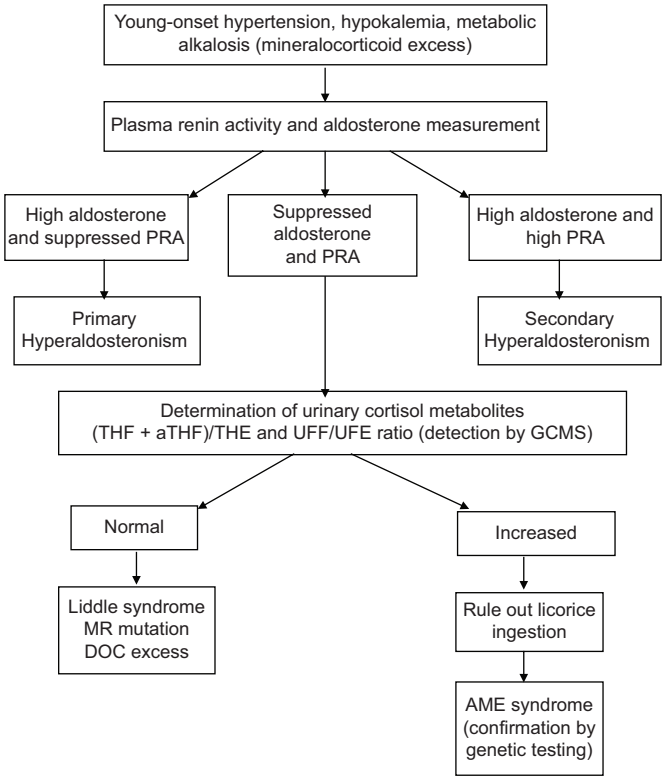

Figure 1: Algorithmic approach to early-onset hypertension. aTHF: Allo-tetrahydrocortisol; AME: Apparent mineralocorticoid excess; DOC: Deoxycortisol; MR: Mineralocorticoid receptor; PRA: Plasma renal activity; THE: Tetrahydrocortisone; THF: Tetrahydrocortisol; UFE: Urinary-free cortisone; UFF: Urinary-free cortisol

Our patient had AME, a rare cause of severe early-onset hypertension characterized by hyporeninemic hypoaldosteronism that results in excessive water and sodium retention, hypokalemia, and hypertension. The severe, chronic, and difficult to control hypertension, as well as recurrent and/or chronic hypokalemia, may have been responsible for the end organ nephropathy seen in this case, as renal parenchyma is very sensitive to the effect of cortisol. The presence of renal failure confounds the interpretation of aldosterone and plasma renin levels in hyporeninemic hypoaldosteronism conditions. Aldosterone levels increase with a decrease in eGFR, and renal failure leads to hyperreninemic hyperaldosteronism. The Framingham Offspring study demonstrated a significant association between high serum aldosterone concentrations and eGFR less than 60 mL/min per 1.73 m^2.[5] Our case showed suppressed renin and aldosterone levels even with low eGFR. The characteristic hormonal profile in AME is an increased ratio of urine-free cortisol to cortisone; 5–18 compared to <0.5 in normal individuals.[6] In this case, we were unable to test for urinary metabolites due to concurrent renal failure. The variability and overlapping nature of clinical and biochemical features with other differentials and aforementioned challenges in the interpretation of hormonal profiles highlight the importance of genetic evaluation in suspected cases of AME with end-organ renal failure.

Although the novel c.911A>G variant identified in this case is classified as a variant of uncertain significance, we believe that it is causative and offer two arguments to support this theory. First, the patient with hyporeninemic hypoaldosteronism responded very well to spironolactone, a mineralocorticoid antagonist. Second, none of the common variants usually associated with hyporeninemic hypertension (SCNN1A, SCNN1B, SCNN1G, CACNA1H, CLCN2, KCNJ5, or CYP11B1) were identified.

To conclude, a high index of suspicion for pediatric hypertension, routine and early BP monitoring, the use of an algorithmic approach, and individualized planning of genetic studies can not only help in ascertaining cause but can also guide the clinician to choose the most suitable antihypertensive drug, thereby preventing the development of end-organ damage.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the parents. In the form, the patient's elder brother has given his consent for the images and other clinical information to be reported in the journal. The patient's elder brother 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Conn's Syndrome: A Rare Cause of Acute Flaccid Paralysis in an Adolescent

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Abstract

Background: Acute flaccid paralysis is a medical emergency. Hypokalemia secondary to an aldosterone-secreting adrenal adenoma or Conn's syndrome is a rare cause of hypokalemic paralysis. There are very few case reports from the pediatric population of the same. **Clinical Description**: We report the case of a 17-year-old girl, previously asymptomatic, who presented with sudden-onset, progressive weakness of all four limbs. There was no history of altered sensorium, cranial nerve involvement, or abdominal complaints. On examination, she was found to be hypertensive. Preliminary investigations revealed severe hypokalemia and metabolic alkalosis. There was no history suggestive of gastrointestinal potassium losses. Hence, a possibility of renal losses was considered and she was found to have kaliuresis. **Management and Outcome**: In view of hypokalemia, with hypertension with increased renal potassium loss, a possibility of hyperaldosteronism was considered. Plasma aldosterone concentration was elevated with levels of 20.3 ng/dl (normal <15 ng/dl). The direct renin concentration was <0.5 µIU/l (normal 5–14 µIU/l). This confirmed a diagnosis of primary hyperaldosteronism. Contrast-enhanced CT of the abdomen showed an adrenal adenoma. She electively underwent a laparoscopic adrenalectomy after her motor power improved with potassium replacement. Currently, she remains normotensive, asymptomatic, and off medications. **Conclusion**: The case highlights that Conn's syndrome though rare is an important cause that a high index of suspicion is necessary in young hypertensive patients to make an early diagnosis of this potentially treatable condition.

Keywords: Adrenal adenoma, Conn's syndrome, hypokalemia, periodic paralysis, primary hyperaldosteronism

Periodic paralysis due to hypokalemia can be due to a primary genetic disorder resulting from autosomal dominant channelopathy.[1] This condition is characterized by transient attacks of severe flaccid paralysis of varying intensity and duration. However, hypotonia and paresis more commonly occurs due to severe hypokalemia, resulting from a variety of secondary etiologies. These include potassium wasting gastrointestinal disorders, licorice ingestion, barium poisoning, renal tubular acidosis (RTA), thyrotoxicosis, and primary hyperaldosteronism.[2] Conn's syndrome, another name for primary hyperaldosteronism, is characterized by adrenal overproduction and raised serum levels of aldosterone, which leads to arterial hypertension, hypokalemia,[3] and suppressed renin levels.[4] It is very infrequently reported: Kayal *et al*.[5] found only 1 patient (1.78%) of primary hyperaldosteronism in a study population of 56 adults with hypokalemic paralysis; and there are very few isolated case reports among children.

We report a teenager with primary hyperaldosteronism or Conn's syndrome who presented with hypokalemic paralysis, secondary to an aldosterone-secreting adrenal adenoma. The aim of presenting this case is because of the rarity of the condition in children, and also to highlight the systematic approach that was used to establish the diagnosis.

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DOI: 10.4103/ipcares.ipcares_220_21

Clinical Description

A 17-year-old, previously asymptomatic girl presented to our emergency department with complaints of intermittent fever of 5-day duration, multiple episodes of vomiting for 3 days, and weakness of both upper and lower limbs for 2 days leading to difficulty in walking and performing activities of daily living, independently. There was no history of jaundice, diarrhea, abdominal pain, or abdominal distention. She also had slurring of speech and inability to pass urine on the day of presentation. There was no history of loss of consciousness

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Submitted: 12-Jul-2021 **Revised:** 04-Feb-2022
Accepted: 06-Feb-2022 **Published:** 25-Feb-2022

How to cite this article: Sivadas S, Bhavani N, Bhaskaran P, Panicker JC, Viswanath N. Conn's syndrome: A rare cause of acute flaccid paralysis in an adolescent. Indian Pediatr Case Rep 2022;2:40-3.

or seizures. There was no history of difficulty in swallowing or drooling, or any cranial nerve involvement. There was a significant history of easy fatiguability, and weight loss of 2 kg over the past 2 months, despite normal appetite. Her menstrual cycles were normal. There was no family history of similar illness, hypertension, stroke, or renal or adrenal disease. Her immunization had been given as per schedule.

On examination, she appeared drowsy with a Glasgow Coma Scale of 14/15 (E4, V5, and M5). She had bradycardia with a pulse rate of 56 beats/min, shallow respiration respiratory rate of 18 breaths/min, and hypertension with a blood pressure (BP) of 150/100 mm Hg (>95th centile). Her weight was 34 kg (>2 standard deviations [SD] below the median), height 142 cm (>2 SD below the median), suggesting stunting and wasting but corresponding to the acceptable range of mid-parental height centiles (141 ± 8 cm), and a BMI of 17 kg/m^2 which was normal for her age and gender.

The patient exhibited signs of some dehydration. The general physical examination was unremarkable with normal spine and no evidence of cushingoid features, hyperpigmentation, edema, or virilization. Sexual maturity rating was Tanner stage IV. Throat examination was normal. The child was conscious with intact higher mental functions. There was no cranial nerve involvement. Fundus examination was normal, with no features of hypertensive retinopathy or papilledema. Severe neck muscle weakness and paresis of bilateral upper and lower limbs (grade 2/5 power in the proximal muscles and grade 3/5 in distal muscles) were present. There was generalized limb and truncal flaccidity with generalized hyporeflexia. Plantar reflexes were equivocal. The sensory system was normal. There were no signs of meningeal involvement or raised intracranial pressure. The abdomen was soft and nondistended. Bowel sounds were sluggish, and the bladder was well palpable. External genitalia were gender appropriate. Cardiovascular and respiratory examination was normal.

In view of the clinical phenotype of acute flaccid paralysis in the presence of vomiting and bradycardia, our first differential diagnoses was hypokalemic weakness (though there was no intestinal hypomotility). Other causes such as acute inflammatory demyelinating polyneuropathy and transverse myelitis were kept lower down. Rarer causes such as botulism and acute intermittent porphyria were not actively considered the other clinical features were not suggestive. The shallow as respiration, bradycardia, severe hypertension, and progressive quadriparesis warranted immediate admission in the pediatric intensive care unit.

Initial investigations confirmed our suspicions of severe hypokalemia (serum potassium 1.5 meq/L), but also identified hypernatremia (serum sodium 150 meq/L), hypophosphatemia (serum phosphorous 0.9 mg/dl), and normal serum calcium and magnesium levels. ECG showed bradycardia with PR prolongation, widened QRS complexes, and J waves. The arterial blood gas analysis showed uncompensated metabolic alkalosis; pH 7.56, pCO_2 28.1 mmHg, and bicarbonate 30 mmol/L. Her liver, renal, and thyroid function tests were normal. An echocardiogram was normal.

Management and Outcome

The child was commenced on intravenous fluids and noninvasive ventilation. Dehydration was corrected, intravenous potassium and phosphorous correction was done; hypertension was controlled with oral nifedipine. She was continued on oral potassium supplements along with oral nifedipine for hypertension. Symptomatic improvement became evident within 48–72 h with normalization of serum potassium, phosphate, and correction of metabolic alkalosis; the weakness and lethargy resolved dramatically.

The severe hypokalemia prompted us to take retrospective history to look for any known attributing cause. There was no history of preceding respiratory illness, polyuria, diarrhea, laxative or diuretic abuse, or intake of nephrotoxic medications. Since history, examination, and initial investigations ruled out the possibility of extrarenal losses, we decided to investigate for renal loss of potassium. Thus, urinary electrolyte estimation was planned. This revealed that her urine spot chloride and urine spot potassium were elevated (104 mmol and 40 mmol, respectively). The biochemical profile of hypokalemia with kaliuresis, metabolic alkalosis, and hypertension raised a strong suspicion of hyperaldosteronism. This warranted investigation to determine the levels of cortisol and renin–angiotensin–aldosterone axis to determine whether it was primary or secondary aldosteronism. Plasma aldosterone concentration (PAC) was elevated with levels of 20.3 ng/dl (normal <15 ng/dl). The direct renin concentration was <0.5 μIU/l (normal 5–14 μIU/l). Thus, the calculated aldosterone/direct renin ratio[6] was elevated at more than 40 (normal <2.4), suggestive of primary hyperaldosteronism. She was hence also started on spironolactone since it is a competitive antagonist of aldosterone and causes loss of sodium and fluid while retaining potassium. An ultrasound abdomen with Doppler was performed to look for an adrenal or extra-adrenal mass or renal artery stenosis that is known to cause secondary hyperaldosteronism and was found to be normal. An abdominal contrast-enhanced computerized tomography (CECT) revealed a normal left adrenal gland, but a hypodense nodule (26 mm × 15 mm in size) with an absolute washout of 65% in the right adrenal gland, suggestive of an adrenal adenoma [Figure 1]. A laparoscopic right adrenalectomy was performed. The histopathological findings were consistent with adrenocortical adenoma [Figure 2]. The postoperative period was uneventful. Three months later, on follow-up, she is asymptomatic, normotensive, normokalemic, and off all medications.

Discussion

We shall be focusing on the step-wise approach to hypokalemic kaliuresis. The common causes of renal

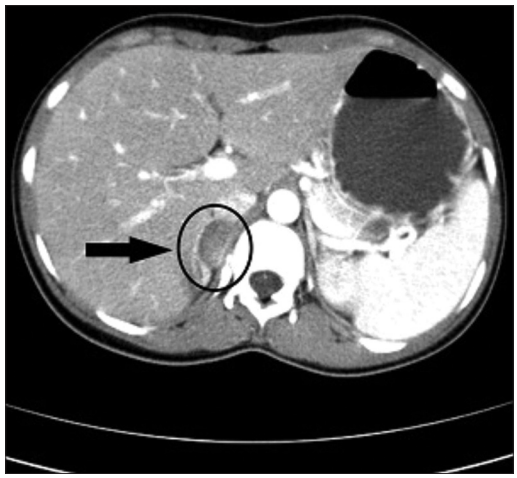

Figure 1: Abdominal contrast-enhanced computed tomography imaging showing right adrenal adenoma (arrow)

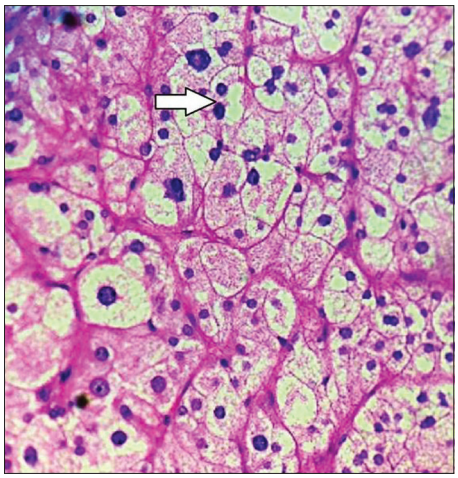

Figure 2: Histopathology showing adrenocortical adenoma with large cells with granular clear to eosinophilic cytoplasm, pleomorphic and having frequent intranuclear inclusions (arrow)

potassium losses include RTA, thiazide and loop diuretic use, Bartter and Gitelman syndromes, and mineralocorticoid excess state. In our case, the presence of metabolic alkalosis ruled out RTA. There was no history of any drug consumption, however, in view of the kaliuresis, it was important to see whether there were also accompanying chloride losses. The urinary chloride estimation detected high urinary chloride which ruled out loop or thiazide diuretic use (characterized by low urinary chloride levels). This narrowed down the differentials to Bartter and Gitelman syndromes or mineralocorticoid excess states (that include primary or secondary hyperaldosteronism, 11-beta and 17-alpha-hydroxylase deficiency, and Liddle's syndrome).[7] Both Bartter and Gitelman syndromes are characterized by normal BP, and hence they were excluded. In congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency, there is virilization, hypertension, and hypokalemia with normal aldosterone levels (as mineralocorticoids other than aldosterone are involved). This did not fit our patient's profile. Similarly, despite the presence of hypertension, 17-alpha-hydroxylase deficiency was excluded due to the absence of undervirilization. Liddle's syndrome, an autosomal dominant disorder due to mutations in the distal nephron sodium channel, is characterized by hyperaldosteronism, hypertension, hypokalemia, and alkalosis, but low serum aldosterone levels.[7]

The combination of hypertension, hypokalemia with kaliuresis, metabolic alkalosis, and high urinary chloride, in the presence of an elevated serum aldosterone-to-renin ratio clinched the diagnosis of hyperaldosteronism. Primary hyperaldosteronism is caused by adrenal adenoma, bilateral or unilateral adrenal hyperplasia, ectopic aldosterone-secreting tumors, and familial hyperaldosteronism. Renin producing tumors, renal artery stenosis, left heart failure, and cirrhosis cause secondary hyperaldosteronism due to excess renin production.[8] Both are differentiated by estimation of the renin–angiotensin–aldosterone axis. While elevated aldosterone levels are common to both, low renin with elevated aldosterone-to-renin ratio (as in this case) indicates primary hyperaldosteronism. The European society of Endocrinology recommends screening for primary aldosteronism in all subjects with the following conditions: 1) uncontrolled hypertension; 2) hypertension requiring 4 or more antihypertensives for control; 3) hypertension associated with hypokalemia; 4) hypertension and an incidental adrenal adenoma; 5) hypertension with a positive family history of early onset hypertension or young stroke or; 6) hypertension with a first degree relative with primary hyperaldosteronism.[6]

The morning angiotensin-to-renin ratio is recommended as the standard screening test; >20 suggestive of primary hyperaldosteronism. The next step is to see whether there is aldosterone suppression with any of the four following confirmatory tests: (1) oral sodium loading; (2) saline infusion; (3) fludrocortisone suppression; or (4) captopril challenge. Aldosterone suppression will be absent in PA. However, in the setting of spontaneous hypokalemia, plasma renin below detection levels, plus PAC >20 ng/dL (550 pmol/L), as seen in our patient, these confirmatory tests need not be done. Instead, one can proceed directly with adrenal imaging by CECT.[6]

Genetic testing is recommended for any of the four forms of familial hyperaldosteronism, when PA is identified in patients <20 years of age, there is a family history of PA or history of stroke in an individual <40 years of age.[9] In this case, it should have been done by virtue of the first indication, but we were unable to, because of financial constraints.

Surgery (preferably laparoscopic adrenalectomy) is the modality of choice in primary hyperaldosteronism due to unilateral disease. In contrast, medical management with mineralocorticoid receptor antagonists (spironolactone or eplerenone) is the first line of treatment in bilateral adrenal hyperplasia.[8] Thus, determining etiology is essential, as the management differs. Early diagnosis and treatment is vital, to

manage the acute crisis, as well as to prevent the long-term deleterious effects of uncontrolled hypertension on multiple organ systems.

Lessons learnt

- Hypokalemic paralysis is a life-threatening condition
- The combination of hypokalemia, hypertension, and metabolic alkalosis may indicate hyperaldosteronism
- A high clinical index of suspicion of primary hyperaldosteronism should be maintained in every young, hypertensive, and hypokalemic patient
- Early treatment of primary hyperaldosteronism with medical stabilization followed by appropriate surgical management (adrenalectomy) if warranted, can effectively resolve the hypokalemia, lower the BP, and prevent end organ damage.

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

Isolated Unilateral Palatal Palsy Secondary to COVID-19 Infection in a Child

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Abstract

Background: Unilateral acquired isolated palatal paralysis is a very rare entity seen in children. It usually occurs due to isolated involvement of the pharyngeal branch of the vagus nerve. The definite etiopathogenesis is still unclear, but postinfectious immune-associated cranial mono-neuropathy is frequently postulated as plausible cause. We report an Indian girl who presented with isolated right palatal palsy following a coronavirus disease 2019infection. To the best of our knowledge, this has never been described in the literature before. **Clinical Description:** A 7.5-year-old girl child presented with nasal twang of voice and nasal regurgitation of liquids mainly from the right side of her mouth for 7 days. There was no evidence of any other neurological or systemic involvement. There was no history suggestive of any of the common causes usually attributed to palataopharyngeal palsy. Examination revealed right palatal palsy with deviation of the uvula to the left confirming lower motor neuron weakness of the pharyngeal branch of the vagus nerve. **Management:** Routine investigations excluding usual etiological causes were normal. The severe acute respiratory syndrome–corona virus 2 (SARS-CoV-2) immunoglobulin G antibody test was positive. The final diagnosis was postinfectious immune-mediated demyelinating isolated right palatal palsy. The child responded dramatically to a short pulse of methylprednisolone for 3 days and did not display any sequelae on follow-up. **Conclusion:** In the setting of the current pandemic, we recommend including SARS-CoV-2 serology in the routine workup of children presenting with isolated palatal palsy.

Keywords: Immune mediated, isolated palatal palsy, postinfectious, severe acute respiratory syndrome coronavirus 2

Since the onset of the pandemic, many neurological manifestations have been described following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. These include a wide spectrum of disorders such as encephalopathy, encephalitis, acute necrotizing encephalopathy, seizures, stroke, anosmia, ageusia, and Guillain − Barré syndrome (GBS). Many of these are the indirect consequence of immune phenomena following the infection, rather than the direct neurotrophic effects of viral invasion.

Unilateral acquired isolated palatal paralysis is a very rare entity described in children. It usually occurs due to isolated involvement of the pharyngeal branch of the vagus nerve. The precise etio-pathogenesis is still unclear. However, postinfectious immune-associated cranial mono-neuropathy has been frequently postulated as a plausible cause. Cranial nerve involvement like isolated ophthalmoplegia or concurrently with facial nerve palsy as a part of Miller Fisher syndrome, have been reported following coronavirus disease 2019 (COVID-19) infection in adults and children.[1,2] We report a 7.5-year-old girl from India who presented with an isolated postinfectious/immune-mediated right palatal palsy after a COVID-19 infection. To the best of our knowledge, this has never been described in the scientific literature before.

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Clinical Description

A 7.5-year-old previously healthy girl presented with sudden onset, nonprogressive nasal twang of voice and nasal regurgitation of liquids (mainly from the right side of her mouth) for 7 days, without increased drooling. There was no history of seizures, altered sensorium, abnormalities in the perception of smell, blurring of vision or development of squint, facial asymmetry, difficulty in chewing, loss of hearing, abnormal position of the tongue, any sudden weakness or inability to move the limbs, sensory impairment, or neck stiffness. There has been no history of any preceding febrile illness associated with rash, sore throat associated with painful or difficulty in swallowing or speaking, facial or cranial

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Submitted: 20-Jun-2021 **Revised:** 16-Jan-2022
Accepted: 28-Jan-2022 **Published:** 25-Feb-2022

How to cite this article: Valdoriya D, Botre A, Udavant P. Isolated unilateral palatal palsy secondary to COVID-19 infection in a child. Indian Pediatr Case Rep 2022;2:44-6.

trauma, injury or operation of the throat, or joint involvement associated with swelling and painful restriction of movements. On probing further, it was revealed that two family members had been ill with COVID-19 infection 6 weeks earlier with fever and mild respiratory symptoms but had recovered uneventfully. The child herself had been asymptomatic. There was no significant history of similar complaints in the past or history of any previous hospitalization. The child was immunized. Early development was normal and she was performing adequately in school.

On examination, she had normal vitals. Her weight (23 kg) and height (120 cm) were between 25th and 50th centiles, as per age and gender. There were no abnormalities identified in the mouth or throat, presence of membrane, or significant cervical lymphadenopathy. Consciousness was preserved and her higher mental functions were normal. Salient central nervous system findings were decreased movement of the right palate with deviation of the uvula to the left on phonation. The sensation over the posterior pharyngeal wall was intact with the presence of a consensual gag reflex, indicative of a lower motor neuron (LMN) weakness of the pharyngeal branch of the vagus nerve [Figure 1]. Examination of the remaining cranial nerves did not reveal any dysfunction. There was no other motor focal deficit with normal tone, power, and deep-tendon reflexes of all four limbs. There were no cerebellar signs, involuntary movements, and signs suggestive of autonomic involvement, raised pressure, or meningeal irritation. Remaining systemic examination was unremarkable. The provisional clinical diagnosis kept was that of an isolated right LMN vagus nerve palsy. Considering the differential diagnosis of a structural lesion, or a postinfectious/immune-mediated etiology, neuroimaging, electrophysiology and blood investigations were planned.

Management and Outcome

The hemogram (hemoglobin 13.9 g/dl, total leukocyte count 7830/mm^3 and platelet count 3.28 lacs/mm^3), serum electrolytes (sodium 137 mmol/L, potassium 4.2 mmol/L, calcium 10.3 mg/dl, and phosphorus 6.6 mg/dl), Vitamin B12 levels (440 pg/ml), and inflammatory markers (high sensitive C-reactive protein <0.04 mg/dl and erythrocyte sedimentation rate 10 mm at end of 1 h) were normal. Magnetic resonance imaging of the brain (with dedicated lower cranial nerves imaging and cerebellopontine angle) revealed no focal lesion or external compression. A lumbar puncture was planned to rule out any indolent intracranial infections. The cerebrospinal fluid (CSF) analysis was normal with a total cell count of 2 leukocytes per mm^3 (100% lymphocytes), glucose level of 82 mg/dl, and protein level of 12.8 mg/dl. The nerve conduction studies for motor and sensory nerves of the upper and lower limbs showed normal conduction velocity and compound motor action potential amplitudes, thus ruling out any evidence of subclinical polyneuropathy. In the setting of the pandemic, and since there was a positive history of COVID-19 infection in the family, the child's SARS-CoV-2 immunoglobulin G (IgG) antibody test was sent. This was positive (1.53U/ml, normal <1.1U/ml).

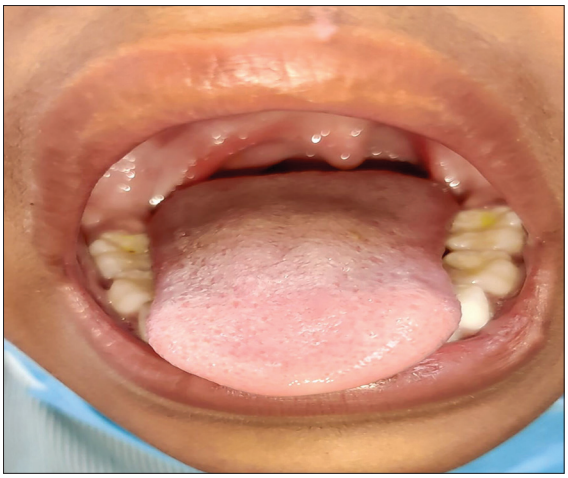

Figure 1: Isolated right palatal palsy with deviation of the uvula to the right side

Based on the history (duration between COVID infection in the household and appearance of symptoms in the child), examination, and work-up that ruled out structural brain/brainstem lesions, infectious/vascular causes, and polyneuropathy, a clinical diagnosis of postinfectious or immune-mediated demyelinating isolated right palatal palsy was established. A pulse course of intravenous methylprednisolone therapy (30 mg/kg/dose) was given for 3 days. Within 4 days, there was marked clinical improvement. The nasal twang disappeared, nasal regurgitation of liquids subsided, and the uvula became central in position; hence, the need for further oral steroids was not considered necessary. The child was discharged and kept under follow-up. At the 2-month visit, she was asymptomatic and had no residual neurological deficit.

Discussion

Isolated acquired palatal palsy is a rare clinical entity that primarily affects males in their first or the second decade of life. Clinical manifestations include hypernasal speech (97%), nasal regurgitation (73%), and dysphagia (49%), mimicking brainstem lesions.[3] There are two mechanisms that have been proposed related to etiopathogenesis. First, postinfectious cranial mononeuropathy due to an acute infection (mainly viral), as the relative immaturity of neural tissue and an increased prevalence of respiratory and gastrointestinal tract infections may lead to increased susceptibility in children. Second, ischemia results from a vascular insult to the roots of the IXth and Xth cranial nerves resulting in LM neuropathies that manifest as palatopharyngeal paralysis.[4] The preservation of normal posterior pharyngeal sensations and an intact consensual gag reflex confirms that only the pharyngeal branch of the vagal nerve is involved. Earlier, a common differential diagnosis would have been postdiphtheritic syndrome with predominant palatal palsy, but the child was completely immunized (including the 5-year booster) so the likelihood was quite low, besides the absence of other typical clinical manifestations.[5] Isolated palatal paralysis is usually idiopathic condition, but one must exclude other etiological causes like craniofacial trauma, operations (adenoidectomy), infections (herpes simplex virus, Coxsackie, Rubeola, Hepatitis

A, Varicella, and Ebstein – Barr virus attribute to 20% of cases),[6] neuromuscular disorder such as GBS, and vascular insults (i.e., an internal carotid artery aneurysm).

The fact that symptoms developed of palatopharyngeal palsy 6 weeks after her family members were symptomatic and she exhibited IgG antibodies against SARS-CoV-2 supports the typical time frame associated with postinfectious/demyelinating syndromes. We did not send CSF and serum investigations for the other viruses since there were no constitutional symptoms and the normal sepsis biomarkers and CSF reports precluded an acute central nervous system infection. A literature search of other reports of isolated cranial nerve palsies secondary to SARS-CoV-2 infection in children revealed the rare occurrence of 3rd and 7th cranial nerve either as a part of multisystem inflammatory syndrome in children, GBS or as an isolated phenomenon.[7,8] We recommend that in the setting of a pandemic, routine SARS-CoV-2 serology testing should be included in the panel of other causes that need to be ruled out before labeling isolated palatal palsy as idiopathic in children. This is especially important given that timely initiation of immunosuppression with steroids such as methylprednisolone have a definitive therapeutic role in the management.

Lessons learnt

- Isolated cranial mononeuropathy could represent an immune-mediated neurological complication of COVID-19, similar to that seen in transverse myelitis and GBS
- In the setting of the pandemic, one should consider serological testing for COVID-19 infection to routine workup before considering isolated palatal palsy as idiopathic
- Timely diagnosis and early institution of immune therapy may be instrumental in quick and complete recovery and limit development of neurological sequelae.

Declaration of patient consent

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

Implications of *CYP21A2* Gene Duplications in Carrier Screening and Prenatal Diagnosis of Congenital Adrenal Hyperplasia due to 21 Hydroxylase Deficiency

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Abstract

Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that presents as salt wasting or simple virilization (SV). It is due to biallelic mutations in the *CYP21A2* gene that encodes the 21-hydroxylase enzyme. This gene is susceptible to deletions and duplications due to the presence of a homologous pseudogene and its location in the RCCX module. This complicates the interpretation of molecular analysis of the *CYP21A2* gene. **Clinical Description:** During preconception counseling and subsequent workup of a couple, the wife (who had been diagnosed with simple virilizing CAH at the age of 14 years, based on clinical and metabolic profile) was identified with c.373C >T variant on one and a deletion on the other allele of *CYP21A2*. Her asymptomatic husband harbored a novel c. 939+5G>A variant in intron 7 of *CYP21A2*. Prenatal diagnosis by Sanger sequencing revealed the presence of both maternal (c.373C>T) and paternal (c. 939+5G>A) variants in the fetus, indicative of SV form. After genetic counseling, the parents decided to continue with the pregnancy. **Management and Outcome:** A baby boy was born who underwent investigations according to the standard protocol. However, a diagnosis of CAH could not be established conclusively. The molecular diagnosis of both baby and parents was revisited. It was found that the baby harbored a duplication of *CYP21A2* (inherited from his father) along with a novel variant. The duplication neutralized the paternal variant, and thus the baby was not affected, but a carrier. **Conclusion:** Evaluation of duplication in parents is crucial before prenatal testing, as duplications have important bearing on the carrier status.

Keywords: *CYP21A1P*, multiplex ligation-dependent probe amplification, pseudogene, RCCX, variant

The P450 enzyme 21-hydroxylase, hydroxylates progesterone, and 17-hydroxyprogesterone to yield 11-deoxycortisone (required for the synthesis of aldosterone) and 11-deoxycortisol (required for the synthesis of cortisol), respectively. Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, is a common autosomal recessive disorder, with impaired steroidogenesis resulting in the deficiency of cortisol and aldosterone, and the overproduction of adrenal androgens. The latter occurs because the excess 17-hydroxyprogesterone (which accumulates due to the enzymatic block) is diverted into the pathway for androgen biosynthesis. This results in increased levels of androstenedione, that in turn is converted to testosterone outside the adrenal gland. These derangements start by the 8^{th}–10^{th} week of gestation.

Thus, both classical forms of 21-hydroxylase deficiency (severe salt-wasting [SW] and mild simple virilizing [SV]) manifest as ambiguous genitalia in newborn females, and progressive postnatal virilization in both genders. The 21-hydroxylase enzyme is completely inactivated in the SW form resulting in severe renal salt loss, and a critical presentation that requires emergency management (vomiting, dehydration, weight loss, hypotension, hypoglycemia, hyponatremia, and hyperkalemia). In contrast, since the SV form has normal aldosterone levels and salt loss is absent. The nonclassical form is milder; affected individuals are asymptomatic at birth and present later with various degrees of hyperandrogenism.[1] Worldwide, the overall incidence of CAH ranges from 1 in 10,000 to 1 in 20,000 in the general population.[2] In India, a recent survey reported a prevalence of 1 in 5762.[3]

The *CYP21A2* gene is present in the major histocompatibility complex at chromosome locus 6p21.3, along with a highly homologous pseudogene *CYP21A1P* located 30 kb downstream.

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Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_211_21

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Submitted: 06-Jul-2021 **Revised:** 16-Dec-2021
Accepted: 04-Feb-2022 **Published:** 25-Feb-2022

How to cite this article: Dubey S, Saxena R, Puri RD, Verma IC. Implications of *CYP21A2* gene duplications in carrier screening and prenatal diagnosis of congenital adrenal hyperplasia due to 21 Hydroxylase deficiency. Indian Pediatr Case Rep 2022;2:47-51.

About 95% of the pathogenic variants encountered in CAH are present in this pseudogene. Thus, approximately 70% of *CYP21A2*, disease-causing variants are pseudogene derived, i.e., they are transferred from the pseudogene (*CYP21P*) to the functional gene (*CYP21A2*) by nonreciprocal transfer of deleterious mutations, a phenomenon referred to as gene conversion.

CYP21A2 is a part of the larger genetic unit comprising RP2-C4B-*CYP21A2*-TNXB genes and known as the RCCX module. Most individuals have bimodular haplotype, i.e., two modules present on each chromosome. However, on occasion monomodular and trimodular chromosomes resulting from the deletion or duplication of RCCX module, respectively, exist. In the trimodular haplotype, either two *CYP21A1P* and one *CYP21A2,* or one *CYP21A1P* and two *CYP21A2* genes are present on each chromosome.[4] In the second scenario, the presence of two copies of the functional gene on a chromosome result in duplication of the *CYP21A2* gene. In this case report, we discuss the clinical implications of duplication of the functional *CYP21A2* gene by describing the clinical outcome of an expectant couple, in which the wife was affected with SV CAH, and her asymptomatic husband was found to harbor a variant of the *CYP21A2* gene.

This report highlights a very important message regarding the role of pediatricians in providing continuity of care to children and their families with rare inheritable genetic disorders throughout their life course. The index case had been diagnosed with CAH during adolescence, and her family had been offered genetic counseling. We describe the sequence of events that occurred when the couple was planning to conceive and end with the quandary that emerged when the protocol for postnatal diagnosis of CAH was undertaken.

Clinical Description

A 33-year-old primigravida was referred to us for preconceptional counseling. She had been diagnosed with SV CAH at the age of 14 years when she had sought medical attention for hirsutism and irregular menstrual cycles. Genetic testing had not been included in the work-up. At that time, the family had undergone genetic counseling in which the cause of the disorder, clinical manifestations, course of illness, treatment, complications, etc., had been explained.

Now that she had come for a different purpose, the primary goal of counseling was to calculate the risk of recurrence of disease in the family, which is essential for any autosomal recessive genetic disorder. In this case, the first step would be to evaluate the proband and her spouse for pathogenic variants in the causative gene. The next step would be to investigate the fetal deoxyribonucleic acid (DNA) for any mutations that were found in the parents. A detailed algorithmic approach of genetic testing of an affected individual and prenatal testing in a family at high risk of CAH is depicted in Figure 1.

We proceeded to evaluate both partners for pathogenic variants in the *CYP21A2* gene. Multiplex ligation-dependent probe amplification (MLPA) and Sanger sequencing of the *CYP21A2* gene in the mother revealed c. 373C>T (p.Arg125Cys) variant on one allele [Figure 2a], and a deletion of exon 1–6 on the other allele. This variant c. 373C>T (dbSNP rs371412889) has been previously reported, is documented to exhibit 16% enzymatic activity, and is associated with the SV clinical phenotype.[5] Her asymptomatic husband was evaluated for carrier status for CAH, and found to harbor a c. 939+5G>A variant in intron 7 of the *CYP21A2* gene [Figure 2b]. This variant has not been included in the genomic databases that are available in the public domain, i.e., http://www.cypalleles.ki.se/cyp21.htm, https://www.ncbi.nlm.nih.gov/SNP/; and http://evs.gs.washington.edu/EVS/. It was also absent in GenomeAsia 100K (https://genomeasia100k.org), but present in gnomAD (https://gnomad.broadinstitute.org), with a reported frequency of 0.00003654. As per various *in silico* tools (Mutation Taster, TRAP, DANN, NetGene2, MaxENTScan, BDGP splice site prediction tool, and Splice Site Score Calculation, dbscSNV Database), the variation c. 939+5G>A found was deemed likely pathogenic, as it alters the donor site and affects the normal splicing of proteins. Thus, in this specific clinical scenario, with the affected mother harboring two variants, and the father identified as a carrier of a variant, the possible risk to the fetus for mild CAH was up to 50% for every pregnancy. This was discussed with the parents, and the option of prenatal testing was explained and offered.

The parents consented to chorionic villus sampling that was performed at 11 weeks of gestation. The extracted fetal DNA was subjected to Sanger sequencing, which detected the presence of both the paternal c.939+5G>A and maternal c. 373C>T variants [Figure 2c and d]. On the basis of this, the fetus was predicted to have a SV phenotype like the mother, since this particular combination correlates with the milder variant of classical CAH.[4] The couple was counseled and explained about the expected phenotype spectrum in affected males and affected females. The couple opted to continue with the pregnancy. A baby boy was born at 38 weeks of gestation through a cesarean section, the indication being a primigravida with breech presentation.

Management and Outcome

The neonate had an Apgar score of 8/10 and 9/10 at 1 min and 5 min, respectively. The vital parameters were normal and oxygen saturation (SpO2) was 98% on room air. Anthropometry performed after stabilization was normal. Hyperpigmentation was not seen. The external genitalia appeared to be that of a boy, without evidence of any ambiguity. The remaining general physical and systemic examinations were normal. We proceeded to investigate the baby as per the protocol for determining the diagnosis of CAH.

Serum 17-hydroxylaseprogesterone on day 1 of life was 9.05 ng/mL (0.49–4.10 ng/ml). However, this can be elevated in a small proportion of unaffected newborns who are preterm or sick. Although our patient was neither, we repeated

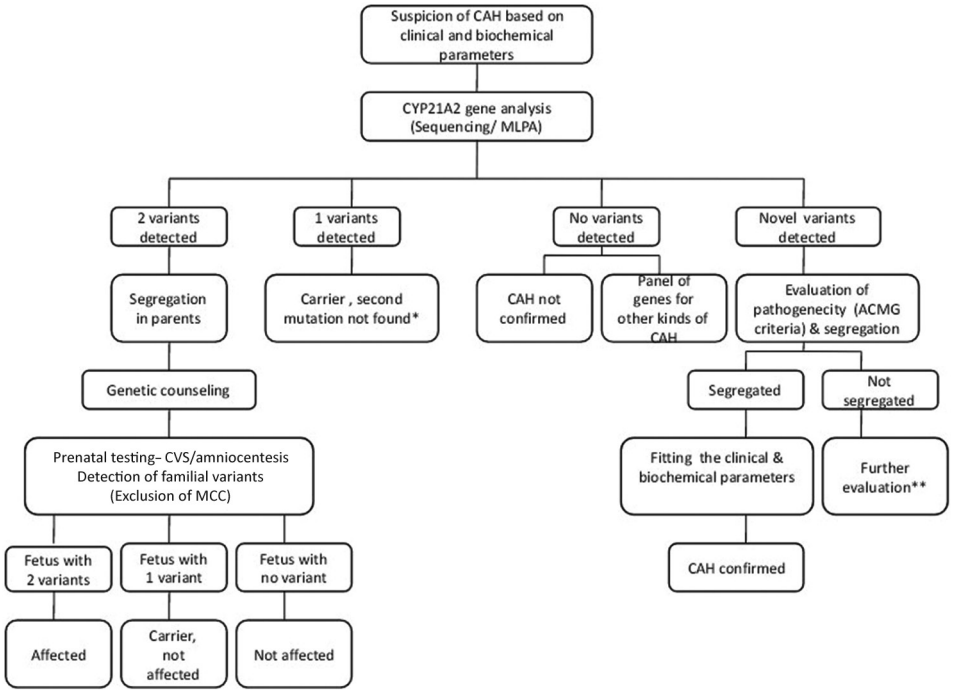

Figure 1: Flowchart showing approach to genetic analysis of congenital adrenal hyperplasia. *Heterozygous cases where the second mutation is not found but they have manifestation of disease.[11] **Further evaluation includes i.e., re-phenotyping or alternative diagnosis, 17-OHP levels, possibility of *de novo* variant

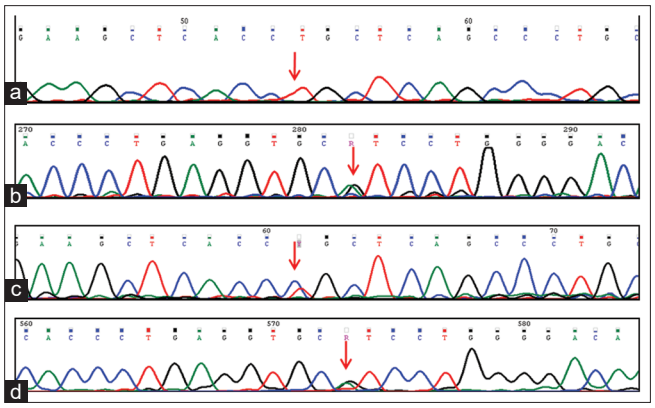

Figure 2: Partial electropherogram showing variants identified in couple and fetus. (a) c.373C>T (p.Arg125Cys) variant in exon 3 of *CYP21A2* gene in mother. (b) Father showing heterozygous c. 939+5G>A variant in intron 7 of *CYP21A2* gene. (c) Fetal sample showing heterozygous maternal c. 373C>T (p.Arg125Cys) variant. (d) Fetal sample showing heterozygous paternal c. 939 + 5G>A variant. All variants are indicated by red arrows

the test after one week, the morning level of which was normal, 2 ng/mL. Electrolytes remained in the normal range; sodium (139 mEq/L) and potassium (5.7 mEq/L). Cortisol was low (8.55 ug/dL, normal 10–20 ug/dL), and testosterone was normal 115.3 ng/dL (75–400 ng/dL), as expected in a male baby with SV CAH. The adrenocorticotropic hormone (ACTH) test that detects levels of 17-hydroxyprogesterone before and after stimulation with ACTH was normal. The neonate remained hemodynamically stable without any of the aforementioned symptoms or metabolic derangements. At discharge, the parents were counseled regarding the clinical red flags including vomiting and lethargy and instructed to report immediately if they occurred.

The baby was kept under close follow-up. Karyotype confirmed the physical male phenotype of a boy with a 46, XY genotype. The variants that had been identified in the prenatal sample were rechecked in the postnatal sample, and the biallelic variants were confirmed. As the investigative workup was not consistent with CAH, we decided to revisit the molecular analysis. MLPA identified duplication of *CYP21A2* in the neonate [Figure 3], as well as in the father. Thus, the final diagnosis was that the infant was a carrier, like his father, and not affected with CAH like his mother.

Discussion

The *CYP21A2* gene is susceptible to deletions and duplications resulting from misalignment during meiosis. This is due to its location in the highly variable RCCX region that contains pseudogenes and tandem repeat sequences. Duplications of *CYP21A2* were previously considered rare,[6] until they were reported in 1.6% of the Swedish population that equals the carrier frequency of CAH.[7] Duplications were also reported in 14% of normal Caucasian subjects, wherein 12.3% of subjects carried duplication of *CYP21A1P* and 1.7% carried duplication of *CYP21A2*.[8] Usually, only one of the duplicated *CYP21A2* gene carries the pathogenic variant, but a few cases in which

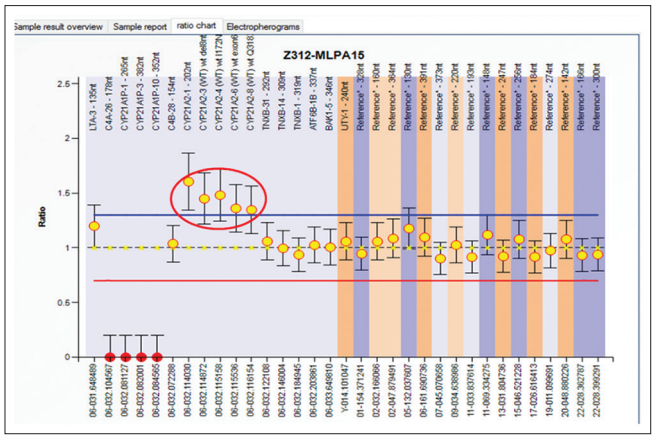

Figure 3: MLPA ratio chart showing three copies of exons 3-7 or duplication of *CYP21A2* gene in fetal DNA. Three copies of exons 3-7 of *CYP21A2* are encircled by a red circle, indicating duplication of the entire gene. Normalized peak height ratio between 0.7 and 1.3 was considered as normal in the proband's DNA with respect to control DNA. The X-axis labels denote the length in the base pair of each probe generated during multiplex ligation-dependent probe amplification polymerase chain reaction

both copies of *CYP21A2* harboring the pathogenic variant have been reported.[6,9]

Although there are no functional studies available on duplicated alleles, duplications are usually considered to exhibit normal function as they are observed to be more prevalent in the healthy general population than in the CAH patients.[10] They are only considered pathogenic if both the duplicated genes have variants. Therefore, it is important to check whether the pathogenic variant is located on the allele with one *CYP21A2,* or on the allele with duplicated *CYP21A2,* to correctly determine the carrier status of an individual. That is why family segregation studies are very important, as they determine whether the occurrence of a given trait shared by members of a family, cannot be readily accounted for by chance.

In this case, the infant had no clinical, metabolic, or biochemical parameters suggestive of CAH. This can be explained by the fact that he was carrying the c.373C>T variant on the chromosome with the single *CYP21A2,* and the c.939+5G>A variant on other chromosome with the duplicated *CYP21A2* gene. That is why the pathological effect of the c.939+5G>A variant was getting masked by the second normal copy of *CYP21A2,* and normal enzyme was being produced. Hence, the infant was a carrier and not affected with CAH. This reiterates the fact that it is very important to investigate whether the pathogenic variant is present on the allele with the single *CYP21A2* gene, or the allele with the duplicated *CYP21A2* gene to avoid misdiagnosis. Since the *CYP21A2* locus is variable and complex, there is an increased likelihood of error. The recent guidelines of *CYP21A2* genotyping have extensively addressed the issues relating to the complexities of the *CYP21A2* locus. It is recommended to use multiple and appropriate methodologies for accurate and comprehensive analysis of the *CYP21A2* gene,[11] as was done in this case.

To conclude, the presence of the closely placed highly homologous pseudogene, and two copies of the *CYP21A2* gene on one chromosome complicates the molecular analysis and the interpretations of results. As duplications are largely restricted to c.955C>T (p.Gln319Ter) pathogenic variant, it is of paramount importance to look for duplications whenever this variant is encountered. However, this case highlights the fact that duplications should also be suspected with variants other than c.955C>T (p.Gln319Ter). Notably, it is imperative to rule out duplications in preconception work up in couples at risk of CAH, as their identification has important implications on confirmation of carrier or affected status, prenatal diagnosis, and genetic counseling.

Pediatricians play various important roles in context to CAH; ensuring that babies undergo newborn screening in which the early diagnosis of CAH can lead to timely initiation of specific treatment, keeping a high index of suspicion for features of SW in newborns, and of late-onset virilization in older children, diagnosing CAH as per the recommended protocols, offering or referring families at risk for genetic counseling, and ensuring liaison between multiple professionals so that there is continuity of care of the affected individuals and families, throughout the life course.

Lessons learnt

- CAH is an autosomal recessive disorder in which two pathogenic variants in the *CYP21A2* gene must be identified in the proband
- In preconceptional counseling, if one partner is affected with CAH, it is important to evaluate the spouse for carrier status. If the spouse is a carrier, then the risk of CAH in the fetus needs to be ascertained, by prenatal testing
- In specific scenario when clinical presentation in the child after birth is not consistent with the genotype (mutations identified), repeat genetic analysis should be considered to rule out duplication of CYP21A2 gene
- The presence of duplications has an important bearing on whether the individual is a carrier or affected with CAH.

Acknowledgement

We are thankful to Dr Deepti Gupta, Scientist at Institute of Medical Genetics and Genomics for her valuable support in helping with the in-silico prediction tools.

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

An Unusual Cause of Acute Encephalopathy: D-Lactic Acidosis Secondary to Short Bowel Syndrome

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Abstract

Background: Blood D-lactate levels increase in short bowel syndrome (SBS) and may lead to neurological manifestations. **Clinical Description:** A 5-year-old boy, postoperative case of SBS, presented with loose stools, generalized weakness, and lethargy for 2 days. The child had undergone significant intestinal resection in the past. On examination, he had some dehydration, and was drowsy, but arousable. Remaining examination was normal. Metabolic abnormalities detected included metabolic acidosis (pH of 7.1, HCO_3 7 mmol/L), high anion gap (20 mmol/l), and normal lactate levels (2 mmol/L). Other baseline investigations were normal. He was treated as a case of acute gastroenteritis with some dehydration and metabolic acidosis and improved. He was discharged after 5 days. After 2 months, he was readmitted with drowsiness and unsteady gait. This time there was no diarrhea or dehydration. Investigations again revealed severe metabolic acidosis, high anion gap, and normal lactate levels. **Management:** We considered SBS induced D-lactate encephalopathy but were unable to prove it by assay due to unavailability of tests. The child was kept nil per orally and given bicarbonate infusion, on which he showed dramatic improvement. He was also given a low carbohydrate diet and oral metronidazole. The family was counseled at discharge 5 days later regarding dietary modifications and microsupplementation. The patient had 6 admissions for D-lactic encephalopathy over 4 years that coincided with dietary lapse. **Conclusion:** D-lactate acidosis is an underrecognized condition and its diagnosis and management is challenging. A high index of suspicion should be kept in patients with history of intestinal resection presenting with acute encephalopathy and unexplained metabolic acidosis.

Keywords: Carbohydrate restricted diet, D-lactic acidosis, encephalopathy, enteral nutrition, short bowel syndrome

Short bowel syndrome (SBS) is essentially the loss of length of the small intestine (either due to a congenital malformation or following surgical resection), which leads to inadequate absorption of enteral nutrients.[1] It is not defined only in terms of length of residual bowel length, as the function of the remnants is also dependent on the site of the resected bowel and quality of function of the remnant bowel.[1] The diagnostic criterion of SBS is the need for parenteral nutrition for >60 days after intestinal resection, or a bowel length of <25% of the expected length.[2] The cause of SBS depends on the age of the patient. In infants and older children, the common causes include malrotation with volvulus, intestinal gangrene secondary to mesenteric vein thrombosis, hernia, or intussusception. Other causes include Crohn's disease, abdominal tumors, and radiation enteritis.[2] SBS is characterized by an inability to maintain protein–energy, fluid, electrolyte, and micronutrient balance, resulting in diarrhea, dyselectrolytemia, and deficiencies.[1-3] The short length of the remnant small bowel decreases the transit time, causing unabsorbed carbohydrates (CHO) to reach the colon and undergo fermentation by the colonic bacteria.[1-3] This causes bacterial overgrowth which results in more malabsorption, metabolic acidosis, and the likelihood of sepsis, and mortality.[1-3]

Metabolic acidosis occurs due to multiple causes such as sepsis, hypoxemia, cardiogenic shock, and liver failure. It is mainly due to overproduction of L-lactic acid, the predominant form of lactate found in the blood whenever there is increased anaerobic metabolism, which can be detected in specific laboratory tests, namely lactic acid assay.[4] In contrast, its enantiomer, D-lactic acid, is produced in very small quantities, due to fermentation of unabsorbed CHO in the colon by commensal bacteria.[4,5] This usually remains undetected, as D-lactic acid cannot be detected by the aforementioned assay

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Submitted: 22-Nov-2021 **Revised:** 31-Jan-2022
Accepted: 03-Feb-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_347_21

How to cite this article: Jain P, Prasad A, Sharma R, Vasudevan V. An unusual cause of acute encephalopathy: D-lactic acidosis secondary to short bowel syndrome. Indian Pediatr Case Rep 2022;2:52-5.

used to estimate L-lactic acid. As explained earlier, there is increased CHO fermentation in SBS, which means the levels of D-Lactate will increase. This results in a variety of neurological symptoms (slurred speech, ataxia, gait disturbances, weakness, lethargy, tachypnea, and rarely acute encephalopathy),[5] and a typical metabolic profile (metabolic acidosis, high anion gap, but with normal lactate levels).[5]

We describe a postoperative case of SBS who got repeatedly hospitalized for neurological presentations, and was subsequently diagnosed as D-lactic acidosis. We also present a brief systemic review of literature. The goal of sharing this case is to sensitize pediatricians to ask about previous surgery and explore the possibility of SBS in the setting of acute encephalopathy with unexplained metabolic acidosis.

Clinical Description

A 5-year-old boy, postoperative case of SBS presented to our emergency department with progressively increasing lethargy for 2 days. The mother said that though responding to all the commands, the child was displaying excessive sleepiness throughout the day. There were no associated seizures, abnormal movements, sudden onset of abnormalities in vision and hearing, deviation of eyes, difficulty in swallowing or chewing, drooling, facial asymmetry, and neck stiffness. There was no history suggestive of decreased movement or use of limbs, cranial or focal neurological deficits, or sensory impairments. There was no history of fever, trauma, dog bite, accidental drug ingestion, vomiting, emanation of any unusual odor, abdominal pain, abdominal distention, jaundice, pallor, or difficulty in breathing. The clinical phenotype appeared to be of acute, noninfectious, and nontraumatic encephalopathy. Further probing revealed that the child had diarrhea for the last 2 days. He had multiple watery stools, small amount, without any blood. The child was passing urine with the same frequency as before the onset of illness. The child was born to a nonconsanguineous couple with immunization appropriate for age. The family history was unremarkable. There was no significant or similar complaints in other family members or neighbors. The child was not on any chronic medication. The child had a significant past history of undergoing extensive small bowel resection 8 months earlier at our center, for intestinal gangrene secondary to superior mesenteric vein thrombosis (for which low molecular weight heparin [LMWH] was started), diagnosed when the child presented with abdominal pain and bleeding per rectum. Initially approximately 110 cm of jejunum and 10 cm of ileum had been preserved along with ileocecal junction. The postoperative period had been stormy: the child had required mechanical ventilation for 72 h and developed peritonitis that warranted exploratory laparotomy and requiring further resection of small bowel due to areas of fresh gangrene identified in the terminal ileum. After the second operation, around 95 cm of jejunum and 5 cm of terminal ileum including the ileocecal junction were left. The child required prolonged nutritional rehabilitation comprising total parenteral nutrition and hydrolyzed feeds. Enteral autonomy was achieved after 2 months of hospitalization, and he was discharged on a normal diet, vitamin and mineral supplementation, and continuation of LMWH. Thrombophilia workup had been done as per standard protocol, and found to be normal.

Management and Outcome

At present admission, it was noted that the airway, breathing, and circulation were not compromised. The preliminary impression was that of a drowsy child who was transiently arousable on painful stimulation. The heart rate was 120 beats/minute, respiratory rate 22/min, capillary filling time <2 s, blood pressure of 100/70 mmHg (90th centile), temperature 98.5°F, and saturation 98% at room air. The weight and height of the child were 14.5 kg and 91 cm, respectively, while the body mass index (BMI) was 16.9, all of which were within the normal range. There were signs of some dehydration. General physical examination did not reveal presence of pallor, rashes, cyanosis, jaundice, or signs of external trauma. There was no pedal edema and other signs of nutritional deficiencies. Salient central nervous system findings were a Glasgow Coma Scale (GCS) score of 11/15 (E3, M4, V4), bilateral pupils of normal size and reaction, normal fundus, and absence of focal cranial or peripheral neurological deficit. The tone, power, and deep tendon reflexes appeared normal as far as could be tested. There were no meningeal signs. Cerebellar signs could not be tested due to the lethargy. The remaining systemic examination was normal.

Based on the above, we managed to exclude acute infectious or traumatic encephalopathy. The differential diagnoses that was actively considered to explain the acute encephalopathy was mainly metabolic, like hypoglycemia and dyselectrolytemia or uremia, given the setting of diarrhea. We planned hematological, biochemical, and microbiological workup of the child, accordingly. The child was resuscitated with isotonic intravenous (IV) fluids, calculated as per standard protocol.

The first tier biochemical tests were within normal limits. {blood sugar (110 mg/dl), serum electrolytes (serum sodium, potassium, and chloride were 137 meq/L, 3.7 meq/L, and 109 meq/L, respectively), renal and liver function tests (urea 28 mg/dl, creatinine 0.5 mg/dl, total/direct bilirubin 0.2/0.19 mg/dl, respectively, albumin 3.8 g/dl, serum aspartate transaminase and serum alanine transaminase 35 IU/L and 28 IU/L, respectively)}. Thus, we excluded hypoglycemia, dyselectrolytemia, uremia, and hepatic derangement. A blood gas analysis showed severe metabolic acidosis with respiratory compensation (pH 7.24, pCO_2 22 mmHg, HCO_3 7 mmol/L, with high anion gap [21 mmol/l; normal level 12–16 mmol/L] and lactate 1.5 mmol/L [normal range <2 mmol/L]). Serum ammonia was within normal limits (76 ug/dl;

normal <100 ug/dl). Routine urine examination showed normal pH and was negative for ketones.

The sepsis workup was negative: Hb 12 g/dl, total leukocyte count 12,000/cmm with 64% neutrophils and 44% lymphocytes, total platelet count 2.5 lakh/cmm, C-reactive protein 3.5 mg/dL, and sterile blood and urine cultures. Stool routine microscopy was normal. A lumbar puncture was not done as there was no history of fever, the workup for sepsis was negative, and the sensorium improved markedly within a few hours. The child's dehydration and metabolic acidosis resolved within the next 48 h, respectively. Based on the clinical phenotype, a final diagnosis of acute gastroenteritis with some dehydration and metabolic acidosis was kept. The child was discharged after 5 days of admission.

After 2 months, he was readmitted with excessive drowsiness for 1 day. This time parents noticed that he had slurring of speech, was unable to walk steadily since morning, and was frequently falling down. Apart from this, and the fact that he did not have diarrhea, the presentation was the same as the first one. At admission vitals were stable, there was no dehydration, and GCS score was 10/15 (E2M4V4). No other abnormalities were identified on examination. The investigations again revealed severe metabolic acidosis with respiratory compensation (pH 7.15, pCO_2 25 mmHg, HCO_3 10 mmol/L with high anion gap of 24 mmol/L, and normal lactate of 1 mmol/L). The routine first tier hematological, biochemical, and microbiological investigations were normal.

The findings of unexplained severe metabolic acidosis with a high anion gap and normal lactate levels, in a setting of a child with previous extensive intestinal resection, prompted us to suspect a diagnosis of D-lactic acidosis secondary to SBS. We revisited the history to look for specific clues like excessive intake of sweetened beverages and sweets. It emerged that he had attended a family function at the time of the first episode, and currently, he had just celebrated his birthday. Further investigations were planned accordingly. The stool was positive for reducing substances and fat globules. Vitamin B12 (296 pg/ml) and Vitamin D (45 ng/ml) were normal, probably since he was receiving supplements.

Once SBS was established clinically, we tried to objectively prove that the metabolic acidosis was due to D-lactic acid, by estimating the levels. However, this test was not available in standard laboratories. Since no other diagnostic alternatives were available, we decided to keep the child nil per orally (stop enteral CHO) and start IV bicarbonate to correct the metabolic acidosis, as per standard protocol. A dramatic improvement in sensorium was seen over the next 12 h. The metabolic acidosis resolved within 48 h (pH 7.3, HCO_3 16.5 mmol/L, pCO2 32 mmHg, and lactate 1.0 mg/dl). The child was started on a low CHO diet and oral metronidazole (to counter bacterial overgrowth). There was no recurrence of lethargy or concurrent metabolic acidosis, and the child was discharged after 5 days. A low CHO diet was planned in consultation with a dietician, the goals being prevention of future recurrences, and maintenance of adequate calories, proteins, and micronutrients.

The child was kept under regular follow-up. He subsequently had 6 admissions for D-lactic encephalopathy over a period of 4 years. Each time it occurred when there was a dietary lapse for some reason. The child is otherwise doing well. He is now 9 years old, is active, studying in class 4, and has a good academic performance. His height (100 cm), weight (16 kg), and BMI (16) are all normal. Although a formal assessment of his intelligence quotient or psychometric testing has not been undertaken, till date he does not exhibit any clinical symptom or sign of any permanent neurological sequelae.

Discussion

D-lactic acidosis causing D-lactate encephalopathy is an uncommon metabolic complication of SBS.[4-6] The short length of the postoperative small bowel remnants leads to CHO being incompletely digested. These undigested macronutrients reach the colon and undergo fermentation by the colonic bacteria.[6-8] This results in excessive production of organic acids that exceeds the amount that can be normally metabolized by the body. Thus, there is an accumulation of organic acids, short chain fatty acids, and D-lactate, all of which result in metabolic acidosis and an increased anion gap.[7,8]

The increased acidity of the gut environment favors the growth of acid-resistant bacteria like lactobacillus species, which in turn produce D-lactate.[6] Another reason for an increase in D-lactate levels is the inhibition of D-2-hydroxydehydrogenase (the primary enzyme that metabolizes D-lactate) by the acidic environment.[7] Other factors which can contribute to increased levels are poor colonic motility, dehydration, and renal and hepatic failure.[7,8] However, although the D-lactate levels are increased, paradoxically the lactate levels will remain normal, due to failure of routine tests to detect this form.

The body can deal with excess L-lactate as it is metabolized quickly, but has limited capacity to deal with accumulation of its "D" isomer, due to the inhibition of D-2-hydroxydehydrogenase (the primary enzyme that metabolizes D-lactate) by the acidic environment.[6,8] The pathogenesis of encephalopathy is complex and poorly understood. The two main mechanisms that have been proposed are: (1) a direct toxic effect of D-lactate on the brain since it crosses the blood–brain barrier; and (2) low levels of D-2-hydroxydehydrogenase in the brain.[7,8] A poor correlation between the D-lactate levels and clinical presentation has been reported in some cases.[8] In our case, there was no other identifiable cause for the acute encephalopathy or the characteristic acid-base abnormalities (metabolic acidosis with increased anion gap, in the presence of normal lactate and ketone levels). Although we were unable to demonstrate increased levels of D-lactate by laboratory tests, it can be argued that the child responded well to the trial of decreased

CHO in the diet by exhibiting resolution of metabolic acidosis. The recurrence of symptoms and metabolic acidosis whenever there was noncompliance can in a way also be considered failure of a therapeutic trial.

The clinical manifestation of D-lactic acidosis includes recurrent episodes of encephalopathy. Clinical manifestations include altered mental status, slurred speech, ataxia, gait disturbances, and confusion. Cerebellar signs are prominent in D-lactic acidosis as the cerebellum metabolizes D-lactate poorly.[4] A systemic review of 45 pediatric cases with SBS and D-lactic acidosis,[7] observed that the mean age group was 5.1 years (2.8–9 years), and the most common presentation was altered mental status (78%) and Kussmaul breathing (24%).

The diagnosis of D-lactate encephalopathy is challenging because of the various other causes of noninfectious and nontraumatic encephalopathy that need to be excluded (especially at initial presentation). In the high-income countries, the diagnosis is confirmed by a serum level of D-lactate levels >3 mmol/L (normal undetectable or <0.2 mmol/L) that is estimated by D-lactate assay. However, as was seen in our case despite the best of our efforts and availability of finances, we were unable to get these levels estimated in India.[4] In these circumstances, when no other option is available and there is a setting of SBS, indirect evidence like improvement of clinical and laboratory parameters with treatment should be used to clinch the diagnosis.

The goals of therapy are correction of acidosis, dietary modification (restriction of CHO intake to approximately 1/3rd the recommended dietary allowance), frequent and low volume meals, and measures to prevent further episodes. The acute phase is managed by correction of dehydration with lactate free IV fluids and IV bicarbonate along with restricting oral intake of CHO.[8] The role of antibiotics and probiotics is still controversial.[6,8] Nonabsorbable oral antibiotics (clindamycin, vancomycin, metronidazole, neomycin, etc.) may reduce D-lactic acidosis by altering some of the gut microbial flora, but may paradoxically also lead to overgrowth of the D-lactate producing bacteria.[6] A similar observation has been made with the use of probiotics.[6,7] Prevention of recurrence can be attempted by restricting simple CHO (since these get metabolized to D-lactate very rapidly). Ensuring strict compliance in children will always remain a major challenge, as was evident in this case.

Lessons learnt

- Children who have undergone any surgical intervention involving resection of the small intestines should be monitored for short bowel syndrome
- D-lactate encephalopathy should be considered in such children presenting with acute encephalopathy in the presence of metabolic acidosis, high anion gap, and normal levels of blood lactate and urinary ketones
- The diagnosis D-lactate encephalopathy is challenging because of non-availability of D-lactate estimation
- Clinical and biochemical response to therapeutic trials may be considered helpful in establishing diagnosis when laboratory tests are not available.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Salmonella, an Uncommon Cause of Multiple Brain Abscesses in an Infant

A 4-month-old boy was brought to the hospital actively seizing. He was euglycemic. Postseizure control, he was intubated for altered sensorium and poor respiratory efforts. Circulation was maintained. The infant was febrile, and history revealed high-grade, fever for a week, followed by multiple seizures for 3 days (brief up rolling of eyeballs) without loss of consciousness in between. There was no preceding trauma, ear discharge, and respiratory, gastrointestinal, or urinary symptoms. The infant was the first issue of non-related parents, born at term with normal birth weight. There was no significant past, antenatal, perinatal, or family history. The child was breast fed for the initial 3 months. Currently, he was being bottle-fed with diluted cow's milk. He was immunized and development was age appropriate.

His anthropometric measurements were normal. Cranium, sutures, fontanelle, and spine were unremarkable. Neurocutaneous markers and dysmorphic features were absent. The only salient examination findings was firm hepatosplenomegaly (liver span 6.5 cm and spleen 2 cm below costal margin). No cranial/focal neurological deficits or tone abnormalities were identified. The clinical diagnosis was acute febrile encephalopathy. Blood counts revealed hemoglobin 10.3 g/dL, white blood count 24 × 10^3/μL (80% neutrophils and 20% lymphocytes), and platelet count 330 × 10^3/μL. Serum electrolytes were normal. Cerebrospinal fluid (CSF) was grossly turbid with 200 leukocytes/mm^3 (all neutrophils), hypoglycorrhachia (CSF glucose 35 mg/dL, blood glucose 118 mg/dL), and elevated protein (200 mg/dL). Blood and CSF cultures grew *Salmonella enterica* subspecies *enteritidis*, sensitive to ciprofloxacin and ceftriaxone. Despite antibiotics and multiple antiepileptics, seizures persisted, and he developed signs of increased intracranial pressure. Plain and contrast-enhanced computed tomography showed multiple brain abscess [Figure 1]. Intravenous antibiotics continued for 6 weeks. There was no indication for surgical intervention: fever abated; seizures ceased; sensorium improved; he was extubated, discharged, and kept under follow-up. Primary and secondary immunodeficiencies were excluded. After 6 months, serial head circumference monitoring demonstrates normal growth trajectory, whereas hearing assessment and neurodevelopmental status are normal.

Salmonella neuroinfection is uncommon in infants. This includes meningitis, subdural/epidural empyema, ventriculitis, venous infarcts, cerebritis,[1-3] and intracranial abscesses (100 case reports found). The clinical presentation of abscesses comprises of fever (~100%), seizures (75%), altered sensorium (60%), and focal deficits (40%).[2] High-risk factors include immunodeficiency states, asymptomatic carrier caregivers, and contaminated feeds. Diagnosis is established by the clinical phenotype, neuroimaging, and cultures. The primary management is prolonged antibiotic therapy. The surgical intervention including drainage of abscess and/or subdural effusion, or placement of ventriculoperitoneal shunt, is individualized. *Salmonella meningitis* has high likelihood of morbidity, acute complications, and neurological sequelae (epilepsy, visual/hearing impairment, locomotor disability, etc.).[3] Early recognition is associated with better prognosis.

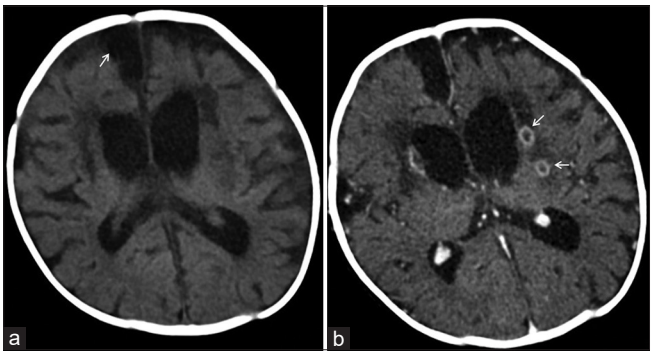

Figure 1: (a) Non-contrast computed tomography (CT) brain demonstrating dilated ventricular system, and extra-axial subdural effusion bilateral (arrow); (b) Contrast-enhanced CT brain showing multiple peripherally enhancing lesions with surrounding edema (arrows) in periventricular brain parenchyma and basal ganglia

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given their consent for patient's images and other clinical information to be reported in the journal. The patient's parents 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.

Acknowledgment

We thank Dr. S. Krishnamurthy, A.C. Chidambaram, and Dr. N. Shanmugasundaram for assistance in patient management.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 22-Jan-2022 **Revised:** 24-Jan-2022
Accepted: 26-Jan-2022 **Published:** 25-Feb-2022

How to cite this article: Sugumar K, Deepthi B. Salmonella, an uncommon cause of multiple brain abscesses in an infant. Indian Pediatr Case Rep 2022;2:56-7.

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DOI: 10.4103/ipcares.ipcares_22_22

Case Video

Inspiratory Whistling in a Child – An Unusual Occurrence

A 4-year-old boy presented with a history of accidental inhalation of a small toy whistle while blowing it, 6 h earlier. This was followed by coughing, choking, and gagging. There was no history of bluish discoloration, loss of consciousness, or seizures. Subsequently, the child was producing a whistling sound while breathing. An otorhinolaryngology consultation was sought. The child was hemodynamically stable, without respiratory distress. Saturation was maintained in room air. Paroxysmal bouts of coughing were observed and a whistling sound was audible that increased in intensity on deep inspiration [Video 1 (video available from: *https://www.ipcares.org/articles/2022/2/1/images/IndianPediatrCaseRep_2022_2_1_57_338494_sm2.mp4*)]. Throat inspection was unremarkable. Air entry was bilaterally normal and equal. An expiratory chest X-ray was normal. Keeping a diagnosis of foreign body aspiration (FBA), we performed rigid bronchoscopy. A whistle was retrieved from the right lower lobe bronchus [Figure 1].

FBA is common in children, mostly preschoolers, due to their tendency to mouth objects, and incomplete chewing while eating (due to noneruption of the third molars). Sudden posterior propulsion of an object in the oral cavity may result in reflex inhalation. There are a few reports of accidental aspiration of small whistles in older children that have lodged in the tracheobronchial tree. FBA is a potentially life-threatening condition requiring prompt recognition and early management.[1] The usual triad is coughing/wheezing, respiratory distress, and decreased air entry.[2] The diagnosis may get delayed in young children when the acute event has not been witnessed, and the child is later asymptomatic. When the child is old enough to give definite history, diagnosis is easier. The standard modality of treatment is rigid bronchoscopy, which has a high success rate.[2]

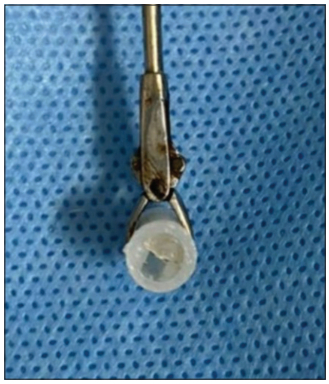

Figure 1: Toy whistle caught in an alligator forcep

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images/video and other clinical information to be reported in the journal. The guardian 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.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 30-Dec-2021 **Revised:** 23-Jan-2022
Accepted: 24-Jan-2022 **Published:** 25-Feb-2022

Video Available on: www.ipcares.org

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_380_21

How to cite this article: Patigaroo SA, Showkat SA. Inspiratory whistling in a child – An unusual occurrence. Indian Pediatr Case Rep 2022;2:57.

Managing a Child with Post-streptococcal Glomerulonephritis in a Remote, Rural Clinic

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Abstract

AMRIT Clinic in Bedawal village, located about 25 km from the nearest town and 100 km from Udaipur city, serves about 3000 tribal families. In this article, we discuss the management of a child with poststreptococcal glomerulonephritis (PSGN), who presented to us in unusual circumstances. Although PSGN is not an uncommon clinical condition, the goals of sharing this experience are threefold: sensitizing our urban counterparts to the challenges of managing such cases in the rural settings; describing the criticality of maintaining a balance between traditional beliefs and evidence-based medicine; and highlighting the value of "upstream" prevention rather than "downstream" treatment.

Keywords: Glomerulonephritis, prevention, rural

Case Study

Ram (*name changed*), an 8-year-old boy was brought to our clinic by his mother. She had noticed swelling of his face a week earlier that gradually progressed to his abdomen and legs. The child had stopped passing urine for 3 days, was not eating anything for 2 days, and had started vomiting since that morning. On probing further, we learned that he had numerous skin pustules a few weeks back, for which he received some topical and oral medication. Currently, the child was receiving some traditional medicine (a concoction made from tree bark and water).

Ram's father was a migrant manual laborer who worked in Udaipur. He had met with an accident recently and was admitted in a hospital there. He was being looked after by his 15-year-old son and an elderly relative. Ram's mother was a homemaker who could not read and write.

The child was lethargic and afebrile. His blood pressure (BP) was 115/80 mm of Hg (>95th centile), pulse rate was 79 beats per minute, respiratory rate was 28 per minute, and oxygen saturation in room air was 98%. He weighed 22.2 kg. Salient general physical examination findings included signs of some dehydration, facial and bilateral pedal edema, and generalized healed skin lesions. There was no evidence of congestive heart failure or jaundice**.** Apart from ascites, the remaining systemic examination was normal.

A presumptive diagnosis of poststreptococcal glomerulonephritis (PSGN) was made. A blood sample was sent to the nearest laboratory (25 km away) for complete blood counts (CBC), serum potassium, serum creatinine, and blood urea. From the past experience, we expected the reports to be available after 12 h. An antiemetic was administered, followed by oral rehydration solution over 4 h. A single dose of intramuscular benzathine penicillin (600,000 IU) was injected, after test dose. Intravenous furosemide and oral amlodipine were started for hypertension and anuria. We decided to add broad-spectrum antibiotics (ceftriaxone) for a possible urinary tract infection. The child passed cola-colored urine after 2 h, and on subjecting it to multi-strip testing, we noted blood (3+) and albumin (4+). His BP and urine output were monitored closely. His mother was explained the nature of illness, the medications being provided, and the details of further management (including possible referral to the city hospital for dialysis). This was done in simple vernacular language, at the level of her understanding. We, in turn, were informed that she wanted to continue the traditional medication. After negotiating, we agreed to allow that, provided it did not exceed the permissible fluid restriction.

Ram's lethargy decreased after a few hours and he ate some food. By the next morning, he had passed urine several

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_20_22

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Submitted: 20-Jan-2022 **Revised:** 30-Jan-2022
Accepted: 01-Feb-2022 **Published:** 25-Feb-2022

How to cite this article: Nithin PI, Goel G, Mohan SB, Mohan P. Managing a child with post-streptococcal glomerulonephritis in a remote, rural clinic. Indian Pediatr Case Rep 2022;2:58-60.

Figure 1: Courtesy: Dr Gargi Goel. Ram with his elder brother after recovery, outside AMRIT Clinic

times, the facial and pedal edema had decreased, and BP was 115/74 mmHg. Blood reports revealed normal CBC parameters and serum potassium (4.79 mEq/dL), but elevated serum creatinine (5.26 mg/dL) and blood urea (188 mg/dL). We again emphasized the need for referral; however, because of the family circumstances and expense involved, the mother was unable to manage alone. She also wanted to consult another traditional healer. After mutual discussion, we agreed to let her take the child to him, provided Ram returned by the evening, which he did.

Over the next 2 days, both modalities of treatment continued. He remained normotensive, the edema and ascites continued to decrease, and urine output was satisfactory. As the child lived nearby, and the mother was facing difficulties in managing everything by herself, we discharged him on oral medication (furosemide, amlodipine, and cefixime). Home visits by our team members were planned to monitor his BP and status and ensure compliance. On the 3rd day, it was noted that his BP had increased (118/80 mmHg, >95th centile), edema had increased, and urine output was less. By this time, Ram's brother had returned home to accompany him to the city, the family had greater trust in us, and they were willing to discontinue traditional therapy.

We arranged for transport and our team accompanied Ram to a hospital in Udaipur, where we helped him get admitted. He was continued on furosemide and amlodipine, and peritoneal dialysis was started. Within a few days, there was gradual symptomatic relief, the creatinine levels normalized, and he was discharged. On returning, he continued to visit our clinic for biweekly monitoring [Figure 1]. We gradually titrated the antihypertensive medication, and by 3 weeks, he was deemed recovered.

Discussion

PSGN is a common cause of acute renal failure in children. Although the prognosis is good if diagnosed early and timely management are started, many children develop complications such as acute kidney injury, hypertensive emergency, encephalopathy, and congestive heart failure.[1]

Annually, 470,000 cases of PSGN are reported worldwide, 97% from developing countries. It has been observed that within countries, a huge inequality exists between the under and more privileged populations. In Northern Australia, a study reported that though the Aborigines constituted 30% of the total population, they contributed to 96% cases of PSGN.[2] Closer home, it was observed that most patients in a report of PSGN from a referral hospital in South India belonged to the lower socio-economic strata.[3] The main reason cited for this disparity is the higher prevalence of streptococcal skin infections in poorer populations. This occurs due to multiple factors; poor hygiene, overcrowding, neglect, delay or inadequate treatment of skin diseases, and scabies.

While managing Ram, our team members displayed multiple competencies that promoted family participation and shared decision-making. These included communicating in a culturally informed manner; acknowledging and understanding the family's beliefs and circumstances; and displaying respectful and nonjudgmental attitudes. These skills helped us deliver modern healthcare with simultaneous traditional therapy, without triggering conflict. By helping them and winning their trust, we managed to convince the family to take Ram for appropriate treatment. We also took the responsibility of coordinating his care beyond what was feasible in the Clinic setting, i.e., enabling transport and facilitating hospital admission.

All these efforts saved the child from developing complications of PSGN and his family from the associated financial burden. Although it is critical to ensure access to such care for children living in remote and rural areas everywhere, even a well-functioning health system will get inundated with delivering such care. Prevention of illness, therefore, assumes paramount importance.

Let us revisit the framework of disease prevention based upon the natural course of the disease and its consequences. There are several levels: primordial (modifying the environmental risk factors before the illness enters the community); primary (individual actions taken before the onset of illness); secondary (actions taken to halt the progress of disease in early stages, such as early diagnosis and adequate treatment); and tertiary (rehabilitation to minimize the long-term consequences of the illness). In public health, upstream efforts (primordial and primary prevention) are often considered more cost-effective than downstream efforts (secondary and tertiary prevention). By reduction in illness, there is a corresponding decrease in the burden on health systems, enabling more quality care,[4] as well as an improvement in the overall health and well-being of the population being cared for.

With respect to PSGN and similar illnesses, the following measures would be effective:

- Primordial prevention: At the systemic level, improving living conditions to prevent overcrowding and infections, and increasing the availability of water, thus promoting hygiene
- Primary prevention: In the intense heat and humid conditions of rural India, water scarcity and lack of clean clothes are major constraints faced by underserved communities to maintain hygiene. Educating families on hygienic behaviors (hand hygiene, daily bathing, and cough etiquette) can, however, offset some of these constraints. Appropriate and early treatment of impetigo and scabies at the primary care level will reduce PSGN. Mass ivermectin prophylaxis is an effective control measure in areas with widespread scabies, which will indirectly decrease skin infections, and subsequent PSGN
- Secondary prevention: As demonstrated in this case, early detection and timely management required competent primary healthcare providers, a pediatrician available for consultation, and access to diagnostics. Primary healthcare services should be expanded at scale to replicate this
- Tertiary prevention: As PSGN is primarily an acute disease in children, this is not applicable.

Understanding and contributing to the underlying causes will help improve health and well-being of all children, especially the most underserved. Pediatricians tend to focus on providing "downstream" care, when the child is ill. However, we are equipped with the understanding and mandate to work "upstream," which tends to get neglected. Increasing the focus on the latter can effectively reduce illness load. This would provide us with opportunities to offer better quality care to sick children, and at a lesser cost.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given consent for images and other clinical information to be reported in the journal. The patient's parents understand that the 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.

Conflicts of interest

There are no conflicts of interest.

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Recurrent Pneumonia in a Child: Knitting Clinical and Radiological Features to Clinch the Diagnosis

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Abstract

Childhood pneumonia is a very common cause of morbidity and mortality in children, especially in developing countries. A small proportion of these are due to recurrent pneumonias. This is defined as the occurrence of more than one episode of pneumonia within a single year, or greater than 3 episodes within any duration; with radiographically documented clearing between episodes. A diligent, step-wise clinical approach and judicious laboratory investigations are required to establish clinical diagnosis. In this article, we describe the approach used to establish etiology in a case of recurrent pneumonia.

Keywords: Chest X-ray, chronic granulomatous disease, computed tomographic scan, recurrent pneumonia

Childhood pneumonia is a very common cause of morbidity and mortality in children, especially in developing countries. A small proportion of these is due to recurrent pneumonia. This is defined as the occurrence of more than one episode of pneumonia within a single year or more than three episodes within any duration, with radiographically documented clearing between episodes. Diligent, step-wise clinical approaches and judicious laboratory investigations are required to establish clinical diagnosis. In this article, we describe the approach used to establish etiology in a case of recurrent pneumonia.

Clinical Description

A 10-year-old girl presented with a history of recurrent episodes of fever, cough, and respiratory distress, since 6 years of age. The first episode lasted for 4 weeks, during which there was no loss of weight or diminished appetite. A chest X-ray showed heterogeneous opacities and areas of breakdown in the left upper zone [Figure 1a]. The treating physician presumed it to be tuberculosis (TB) and prescribed anti-TB therapy (ATT), without microbiological confirmation. She received standard regimen ATT for a total duration of 7.5 months. The parents reported strict compliance and there was resolution of cough and fever, and weight gain within 8 weeks.

Eight months after completion of ATT, she again developed low-grade fever, dry cough, weight loss, and rapid breathing. Consultation was sought at a national-level institute designated for TB. The chest X-ray showed diffuse reticulonodular opacities [Figure 1b]. Gastric lavage samples were negative for *Mycobacterium tuberculosis* by GeneXpert. Nevertheless, she was diagnosed with pulmonary TB and prescribed ATT for 6 months again. Within 6 weeks, she became afebrile, the cough and respiratory distress ceased, and she started gaining weight.

However, within 3 months of completing ATT, the child developed multiple episodes of fever, cough, and respiratory distress every 3–4 months. Each episode was managed with oral antibiotics. During one of these episodes, the chest X-ray showed diffuse bilateral reticulonodular opacities [Figure 1c]. Although there was intermittent, transient relief with each course of antibiotics, she gradually developed worsening breathlessness. She was referred to our institution with a history of moderate-grade fever, cough with mucopurulent expectoration, and breathlessness at rest for 1 month.

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Submitted: 22-Jan-2022 **Revised:** 23-Jan-2022
Accepted: 23-Jan-2022 **Published:** 25-Feb-2022

How to cite this article: Reddy A, Singh S, Mathew JL, Bhatia A, Rawat A, Jayashree M, *et al*. Recurrent pneumonia in a child: Knitting clinical and radiological features to clinch the diagnosis. Indian Pediatr Case Rep 2022;2:61-4.

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_23_22

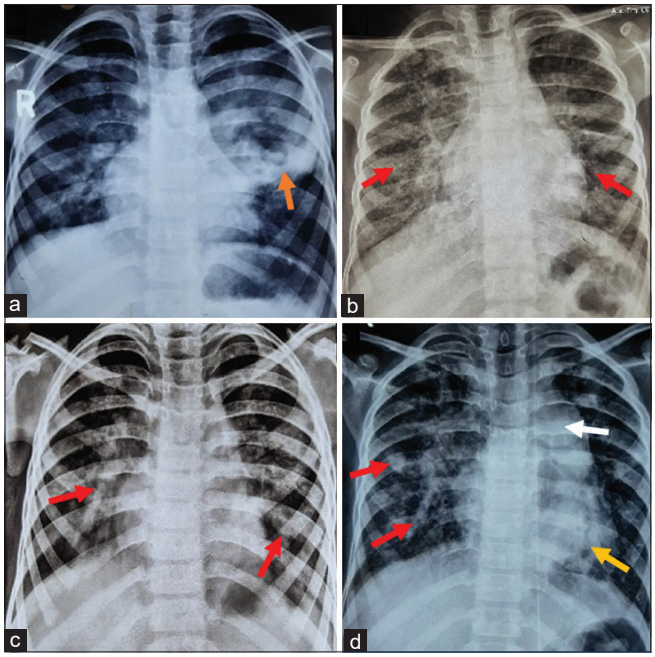

Figure 1: Chest X-rays during the course of the illness. (a) X-ray during the first episode showed left upper lobe consolidation with breakdown areas (orange arrow). (b) X-ray during the second episode showed reticulonodular opacities (red arrows) in both lungs. (c) X-ray during a subsequent episode showed multiple reticulonodular opacities (red arrows) in both lungs. (d) X-ray during the current admission showed retrocardiac cosnolidation (gold arrow) with bilateral reticulonodular opacities (red arrows) with prominent pulmonary conus (white arrow)

What specific history should be asked in such a clinical setting and why?

Table 1 depicts a broad (i.e., nonexhaustive) list of details to be elicited and the common causes of recurrent pneumonia that can be excluded.

The child was second in birth order, born of a third-degree consanguineous union (parents were second cousins). Both her siblings, aged 13 and 9 years, were healthy. However, her mother had three spontaneous, first-trimester abortions after the third child's birth. There was no history of TB or any similar illness in any family member. Development had been normal, and she was currently in class IV. Vaccination was age-appropriate.

The heart rate was 132/minute, respiratory rate was 44/minute, blood pressure was 90/56 mmHg, and temperature was 99°F. She displayed intercostal and subcostal retractions, and oxygen saturation was 80% in room air. With administration of oxygen through nasal prongs, the saturation improved but did not normalize, and she was placed on continuous positive airway pressure (CPAP) support. The work of breathing remained high, necessitating noninvasive ventilation with synchronized intermittent mandatory ventilation-pressure control via nasal cannulae. Ceftazidime and cloxacillin were administered empirically to provide broad-spectrum antibiotic cover.

The weight was 18 kg (−3.57 Z score), height 115 cm (−3.12 Z score), and body mass index 13.61 (−1.54 Z score). There were pallor and grade 3 pandigital clubbing, but no icterus, lymphadenopathy, elevated jugular venous pressure, or signs of micronutrient or vitamin deficiencies were noted. The tonsils were not inflamed, and the aural examination was unremarkable. There were no signs of healed scars on the torso or limbs. The BCG scar was visible.

Chest examination revealed a centrally positioned trachea, appropriately located apex beat, diminished breath sounds over the left mammary area, coarse crackles, and occasional expiratory wheeze all over the chest. Cardiovascular examination revealed a nonpalpable, loud second heart sound with normal splitting. There was no evidence of right-sided heart failure. Abdominal and neurological system examinations were normal.

What are the salient features in serial chest X-rays?

All chest X-rays were reviewed. The X-ray done during the first episode [Figure 1a] showed a large area of consolidation with breakdown in the left upper lobe. This favored necrotizing pneumonia rather than pulmonary TB. The X-ray from the second episode [Figure 1b] showed bilateral reticulonodular opacities. This could be considered compatible with pulmonary TB radiologically. The third X-ray after two courses of ATT [Figure 1c] also displayed bilateral reticulonodular opacities, but with relative improvement. Radiologically, the persistence of opacities suggested progression to chronic lung disease. X-ray done in our institution, at admission, showed inhomogeneous air space opacities in both lungs with retrocardiac areas of consolidation and prominent pulmonary conus. The bony structures, thoracic soft tissues, cardiac shadow, and costophrenic angles appeared normal [Figure 1d]. There was no evidence of bronchiectasis in any of the X-rays.

What clinical diagnosis can be considered based on history, examination, and chest radiographs?

A syndromic diagnosis of recurrent pneumonia resulting in chronic suppurative lung disease (CSLD) with secondary pulmonary hypertension was considered. The underlying cause was thought to be the past pulmonary TB infection. The possibility of a concurrent secondary immunodeficiency (i.e., HIV infection) or hitherto unrecognized primary immunodeficiency was considered. Among the latter, chronic granulomatous disease (CGD) was considered most likely, based on the age at presentation, pattern of infections, and clinical findings. Disseminated BCG infection and Mendelian susceptibility to mycobacterial disease were considered remote possibilities. Other causes mentioned in Table 1 were ruled out clinically as well as based on the chest X-rays.

What investigations should be planned?

Investigations were planned to identify: (1) the underlying cause of recurrent pneumonia; (2) the microbial etiology of the current episode; and (3) any complications of CSLD. The blood culture at admission was sterile. Sputum Gram stain did not

Table 1: History that should be elicited in a child with recurrent pneumonia for determining etiology

History to be elicited	Diagnosis
Delayed passage of meconium at birth, salty taste when kissed, passage of greasy, or bulky stools	Cystic fibrosis
Persistent purulent nasal discharge, recurrent episodes of ear discharge, recurrent sinusitis	Primary ciliary dyskinesia
Lymph node swellings, salivary gland enlargement, recurrent diarrhea, oral thrush, skin infections (pustules, boils, etc.), previous unsafe blood transfusion or injections	HIV infection
Infections at multiple and/or unusual sites, prolonged infections, failure to thrive	Primary immune deficiency*
Episodes of choking, or swallowing difficulty, or aspiration during eating or drinking	Aspiration syndromes
Chest pain, palpitations, fatigue on exertion, swelling of the feet	Heart disease with shunting

*Some diseases have specific clinical pointers HIV: Human immunodeficiency virus

identify any organisms, while its bacterial culture yielded only commensal organisms. Sputum fungal studies were also sent; though yeast species were identified on smear microscopy, it was considered insignificant, as the culture did not yield anything. Blood galactomannan assay (to identify invasive *Aspergillus* infection) was not elevated. Multiple gastric lavage specimens (as per our institutional protocol) were examined for acid-fast bacilli and GeneXpert, both of which were negative. Thus, an active infection was unlikely, but a past infection could not be ruled out. HIV serology was nonreactive. Screening nitro blue reduction test was positive, suggesting CGD. Dihydro rhodamine (DHR) assay showed reduced stimulation index of the patient's neutrophils compared to the control confirming CGD. A 2-D echocardiography showed mildly dilated main pulmonary artery (diameter 20 mm compared to the ascending aorta diameter of 17 mm), normal biventricular function, but no regurgitation across the tricuspid or pulmonary valves. Therefore, pulmonary arterial hypertension could not be confirmed on echocardiography.

Investigations for allergic bronchopulmonary aspergillosis were done, considering the presence of wheezing. The serum total IgE was elevated (2507 IU/ml, normal <100 IU/ml), as was *Aspergillus*-specific IgE (4.18 kUA/l, normal <0.35 kUA/l). This was consistent with fungal sensitization. A contrast-enhanced computed tomography (CT) of the chest was done [Figure 2] as per the guidelines of the European Respiratory Society to identify bronchiectatic changes.[1]

What does the computed tomographic scan show?

Figure 2 shows multiple, variable-sized acinar nodules in both lungs (orange arrows) with bilateral diffuse confluent areas of ground-glass opacities with interstitial thickening (blue arrows) and fibrotic changes. There was a patch of consolidation in the left lower lobe showing breakdown and air bronchograms (green arrow). The mediastinal window sections showed dilatation of the main pulmonary artery (red arrow). There were multiple calcified and noncalcified conglomerate mediastinal and hilar lymph nodes without central necrosis (yellow arrows), the largest measuring 13 mm. Bronchiectasis was not noted. The radiological impression was active pulmonary infection, possibly fungal.

What would be the next modalities of investigation?

Since sputum examination was negative, but suspicion of fungal infection was apparent from the CT scan, flexible

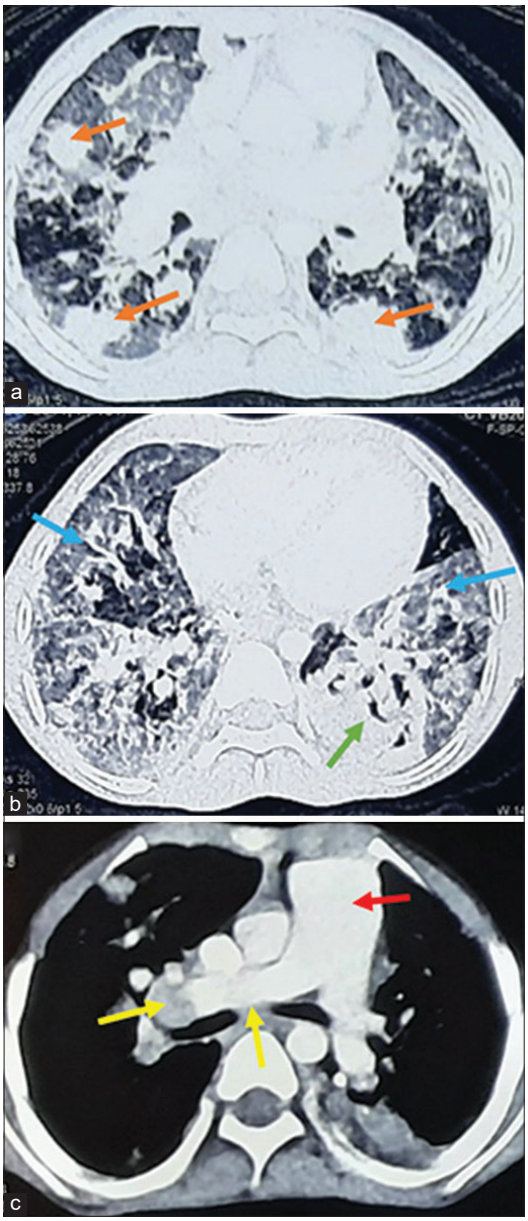

Figure 2: Selected axial contrast-enhanced computed tomography sections highlighting the important findings. (a) Lung window) showing bilateral variable sized acinar nodules (orange arrows). (b) Lung window showing extensive ground glass opacities with interstitial thickening (blue arrows) and an area of consolidation with breakdown in the left lower lobe (green arrow). (c) Mediastinal window showing dilated main pulmonary artery (red arrow) and enlarged bilateral hilar lymph nodes (yellow arrows)

fiberoptic bronchoscopy was performed. It showed the presence of mucopurulent secretions in the airways. Analysis of bronchoalveolar lavage (BAL) fluid showed 1625 cells/mm^3 (60% polymorphs, 25% monocytes, and 15% lymphocytes). BAL fluid Gram stain and bacterial culture were negative, AFB was not identified, and GeneXpert did not detect *M. tuberculosis*. Fungal elements were absent on BAL fluid smear, but galactomannan was elevated to 1.92 (laboratory cutoff 1.0), suggesting *Aspergillus* in the lung.

There was a dilemma regarding the decision to start antifungal therapy. The likelihood of fungal infection was strong: No bacteria had been identified; there was minimal improvement with the broad-spectrum antibiotics; CT scan findings were suggestive, and BAL galactomannan was elevated. On the other hand, blood galactomannan index was not elevated, sputum smear examination showed only yeast, and fungal hyphae were not detected on BAL examination. Taking everything into consideration, the treating team decided to start amphotericin on clinical grounds, to which she responded. The severity of cough reduced, sputum production ceased, and the respiratory status improved so that NIV support could be gradually omitted over the next 2 weeks.

Discussion

CGD is a rare primary immunodeficiency disorder caused by an inherited defect of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NADPH oxidase transfers electrons to molecular oxygen to generate superoxide anion (O_2^-), which further dismutates to reactive oxygen species (ROS) including hydrogen peroxide, that is highly microbicidal. CGD is characterized by inadequate production of ROS due to mutations in genes encoding the NADPH oxidase complex. This results in decreased phagocytic capability to kill pathogens, particularly catalase-positive organisms, and recurrent pyogenic infections, such as pneumonia, abscesses, suppurative lymphadenitis, osteomyelitis, bacteremia, fungemia, and subcutaneous infections.[2] *Staphylococcus aureus, Burkholderia cepacia, Serratia marcescens, Nocardia,* and *Aspergillus* spp. are the usual responsible microorganisms.[3]

Fungal pneumonia in CGD is most commonly due to *Aspergillus* species affecting one or both lungs.[4] Radiographic manifestations include segmental or lobar consolidation (as seen in bacterial pneumonia), multiple subsegmental vaguely-defined opacities, and miliary nodules (akin to miliary TB).[5] Common CT scan findings include pulmonary nodules (often the initial radiologic manifestation of fungal infection), consolidation, pulmonary scarring, and bronchiectasis.[6,7] Invasive pulmonary aspergillosis may present with a chronic nodular radiological picture (as in this case) or chronic progressive "microgranulomatous aspergillosis," which is characterized by diffusely scattered, discrete, and confluent granulomas of the same age, in which the organisms are confined within the granulomas. Patients with CGD generally do not develop hyphal angioinvasion, the characteristic halo sign on CT scan, or cavities, unlike neutropenic patients in which *Aspergillus* causes angioinvasion and infarction.[8]

To conclude, a child with recurrent pneumonia and evidence of chronic nodular pneumonitis on chest X-ray should be investigated for CGD, even if the characteristic radiological patterns associated with *Aspergillus* infection are absent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Margarita with a Straw

Editor's comment: Last year, we published several book reviews to showcase narratives of children and adolescents with various medical conditions. This year, we decided to change the format and present brief "trailers" of films in prose instead. The aim remains the same, to bring out the "human" aspect of illnesses, a dimension that even the most observant of clinicians usually fails to see. We hope it will induce you to watch the films.

We present "Margarita with a Straw" a film in Hindi that was released in 2014. It was written by Shonali Bose and Nilesh Maniyar and directed by the former.

I have watched "Margarita with a straw," in the theater, on the 1st day of its release in 2014. Well, not many will find it a theater worthy film, because after all it is not a "mainstream" movie, is it? The word "mainstream" is the catch here. It depends on how you interpret it. Moreover, that is exactly what the movie tries to draw our attention to.

"Margarita with a straw" is a movie about a college student with a keen interest in music and creative writing who starts an undergraduate course in Delhi University but decides to pursue her education in New York after the first semester, partly due to her tryst with the "mainstream." Kalki Koechlin, quite convincingly, plays the lead role of Laila who happens to be a girl with cerebral palsy. The movie begins with an apparently normal family in a Matador driven by her mother. Everyone seems to be "typical" till Laila begins to speak, and you realize that she has locomotor dysfunction. The movie subtly presents to you a family that has worked through the accommodations and adjustments necessary for their elder child who happens to have a disability. The Matador is modified to accommodate the wheelchair which Laila maneuvers around a campus that does not have a ramp, but she manages in the film. Which brings to mind that in stark reality, not every student with a similar problem may be fortunate enough to have an automated wheelchair, or friends and cooperative helpers who are willing to manually lift them with their adaptive transport equipment to their classrooms when the lift is not working.

Theatrical release poster. Available from: https://en.wikipedia.org/wiki/Margarita_with_a_Straw. Last accessed 2022 Jan 27

It is just like any other movie…a teenager experiences as she comes of age – learning how to adjust to college life in a new city while living on her own; handling the tumultuous emotions of loving someone, the exploration of her own sexuality, and trying to balance the equations in family and life! The difference lies in the depiction of her experiences with a society that sees her differently. She showcases a song that she has composed in a competition, and wins, but only because the judges see her wheelchair as a more suitable reason to be given the first prize, than the beauty of her composition! She can love like any other teenage girl but will still be judged for her physical state instead. A friend in a wheelchair reminds her, "being friends with 'normal' people does not make you 'normal' Laila!" What/who is "normal" really? Why don't you watch the movie and decide for yourself?

The movie attempts to highlight the fact that individuals with disability are but like the rest of us, as mainstream as can be! Moreover, it deserves to be enjoyed like a Margarita…sip by sip, with a straw!

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 28-Jan-2021 **Revised:** 31-Jan-2022
Accepted: 01-Feb-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_33_22

How to cite this article: Sharma M. Margarita with a straw. Indian Pediatr Case Rep 2022;2:65.

Finding Meaning in Medicine – The Rural Urban Divide

"What is the problem with your little boy?" I ask. The man in the white turban, skin deeply tanned from toiling many summers in the fields, looks flabbergasted. It is an unfair question. "You tell me – you are the doctor!" he finally retorts. After two decades as a pediatrician in Madhya Pradesh, I now know that often when a villager plans a hospital visit to the city, everyone gets bundled into the jeep. Sometimes, the mother gets left behind; a little wonderstruck child reaches the doctor with no one to explain why and the doctor simply has to do his best. "Village" eyes ensnare you. They are clear and true. They know that you *will* do the right thing. "City" eyes are muddy, as the river after the monsoon. When the city child comes in; in walks a cloud of anxiety, mistrust and fear. But my village patients are full of peace. Even in the Pediatric ICU. "You go ahead Ma'am." They tell me as I unhappily explain that I have to ventilate their child. "Do your best. God is always there."

A couple of years ago, ten of us (several doctors) decided to cycle out into the countryside without food, money, or a phone. Food would be earned in exchange for work. When we started, we were a feisty group, but by noon, spirits were running low. We looked ridiculously out of place as we approached a line of mud huts. "Doctor Saheb! Welcome! What an honor! Do come in. You must have a meal with us! The excitement was dizzying. We hesitantly told them that we would work for food. "Nonsense. Do you want to shame us?" Their generosity was humbling. We were eventually led us to a feast that had been specially prepared. We slept under the stars that night. The village sky was black velvet, resplendent with stars. The next day, we received a tearful farewell. A stray thought kept nagging me on the journey home. "What would I do if ten scruffy villagers landed unannounced on my doorstep?" It was a hypothetical question. However, I feared I would find the city had shrunk my heart.

Among my patients, the most striking are the gypsies. In their brilliant flared clothes, flashing with mirrors, they stand out in the mundane hospital environment. They settle down on the floor spreading their skirts. Their confidence is unshakable. Their eyes sparkle like the chunky silver bangles on their arms. A beautiful baby dressed in all its finery is presented to me. I remembered resuscitating him at birth. "Oh! the little darling," I coo. "What have you named him?" The grandfather smirks. "Ambu Prasad. We call him that because when he was born, you kept on yelling, "Ambu, Ambu."

Sometimes, I have nothing concrete to offer. A patient with cerebral palsy comes from a remote village with no rehabilitative services. What do you do when you are up against a wall, I wonder? Make a hole? I remember the story of an educationist from Delhi who made a hole in the wall between his office and a slum so that the children had free access to his computer. Nobody taught them, but nevertheless, they learned. The hole-in-the-wall was a resounding success. All it needed was somebody standing by and encouraging them. I struggle for simple solutions to offer the family. I try my best. Today, I am still in awe of how much the mother achieved on her own after 5 years of grit and sweat. The child can walk, goes to school, and holds a pencil. All I did was shower the mother with praise whenever she came. She found her own solutions and made her way.

I have a friend who runs a hospital for tribal people with four other friends. They all left the easy comfort of being ivory tower academicians in Delhi to muddy their hands in an incredibly poor district of Chhattisgarh. It has been more than 20 years. The poorest of the poor receive treatment there that you may not even dream of. They have developed innovations that amaze and uplift me- solar powered refrigerators for storing snake venom antidote, blood culture bottles that are incubated on the health workers thighs, school children who help carry malaria slides. People stream in from everywhere. They come with mosquito nets, goats, and cooking pots, marking their places unchallenged with a stone in the queue outside buildings overgrown with orange bougainvillea. They sit in such peace. It is a lost art in the city. To be still and wait with composure and grace.

Some time ago, I was in Hyderabad. A friend took me to show me the swanky interiors of an office on the Microsoft campus. Techies in their twenties were swarming everywhere. There were unbelievable luxury cafeterias with eye-popping menus, sleeping pods, open-air amphitheaters, even an indoor golf course. "They are paid very well, work for just 4 h a day, but it is still a challenge to retain them," my host says. I could not believe him. "Why? Which young doctor in his twenties earns that much and lives in such comfort? I think of the 36-h duties that my resident doctors do! "They quit because they find no purpose in their work." I am dumbstruck by my sudden epiphany. "True, in medicine, the hours may be long. But, every moment has meaning."

Acknowledgment

To all my patients whom I have interacted with.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 28-Oct-2021 **Revised:** 23-Jan-2022
Accepted: 27-Jan-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_328_21

How to cite this article: Passi GR. Finding meaning in medicine – The rural urban divide. Indian Pediatr Case Rep 2022;2:66.

1. Identify the inheritance pattern in the pedigree tree [Figure 1]
2. In which inborn errors of metabolism will you get a positive ferric chloride test?

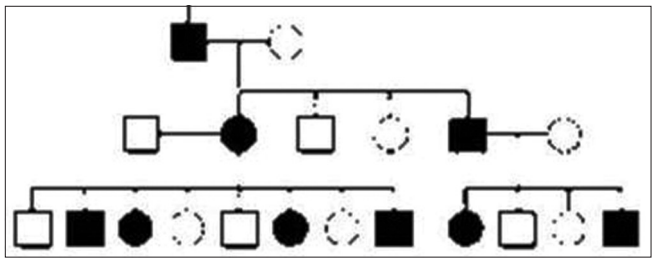

Figure 1: Pedigree tree

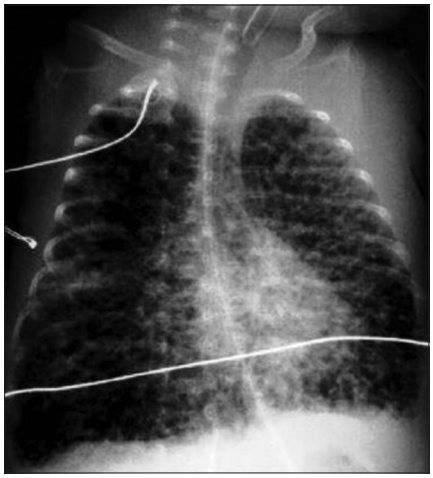

Figure 2: X-ray of the chest of term baby taken just after birth

3. How long after birth can colonic gas shadow be appreciated in an abdominal X-ray of a newborn?
4. A newborn-term baby develops marked respiratory distress immediately after birth. The chest X-ray [Figure 2] reveals the following radiological features. Identify the condition
5. A large for gestational age baby girl was born at term with an omphalocele. She was shifted to an intensive care setting and provided with supportive care, including a radiant warmer and intravenous fluids. Despite this, 2 h later, she developed hypoglycemia and hypothermia. What is the most likely diagnosis?
6. What is the most common sequela of a periventricular hemorrhagic infarction in a preterm baby?
7. The metabolic profile of a 96-h-old newborn with a suspected inborn error of metabolism comprises of a normal pH, normal carbon dioxide concentration, in the presence of increased levels of ammonia (180 μmol/L) and plasma citrulline (1250 μmol/L). What is the most likely diagnosis?

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Editor Prof. Sharmila B. Mukherjee. Printed and published by Wolters Kluwer India Private Limited on behalf of Indian Academy of Pediatrics, Mumbai and printed at Nikeda Art Printers Pvt. Ltd., Bhandup, Mumbai, India and published at A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol, Andheri, Mumbai, India