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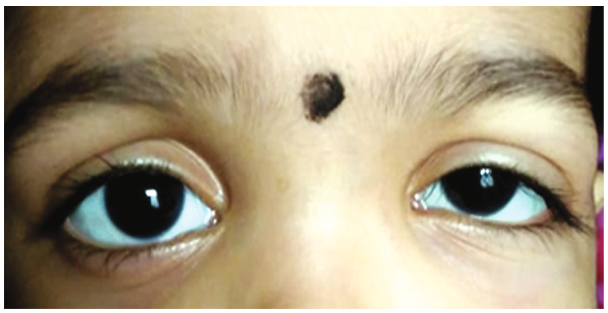

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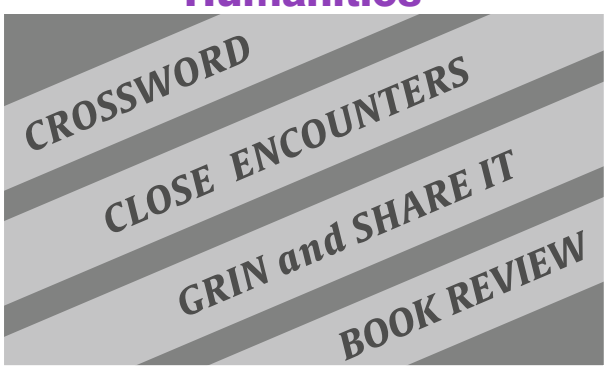

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Contents

Contents (contd.)

Preparing a Case Series and Integrating the Clinical Approach in Scientific Writing

It is hard to believe that a year has passed since the first issue was published. The *Indian Pediatrics Case Reports* Editorial team is now ready with the fourth issue of 2021. There are three dimensions that emerge from this one, and I would like to share them with you.

A discerning reader may appreciate the fact that we have a new addition to our table of contents; the case series. We have recently received quite a few submissions in this category. This may be because authors have become cognizant with the fact that the Medical Council of Indian guidelines (dated February 12, 2020) accept publication of case series as one of the criteria for faculty promotion (there has not been any update since its conversion to the National Medical Council). I would also like to hope that another reason is because our journal is becoming more popular, being read by more pediatricians, and attracting the interest of more budding or established authors. Following inquiries from our readers, we have added separate guidelines in the "Instructions to authors" (accessible on the webpage) to make it easier for them to write them more scientifically. The Editorial Board has also decided to give more weightage in publication to case series, provided there is something novel and interesting that emerges from the article.

It is that time of the year when there is an increase in allergies throughout India due to the seasonal change, and in Delhi, due to the annual escalation in pollution. I think it befitting that this issue carries two articles related to pediatric hypersensitivity; a case series on "Skin Prick Tests and Subcutaneous Immunotherapy" (from which I personally learnt a lot) and the news excerpts on "Uncommon allergic manifestations in children" (this has a common factor with one of the other case series. Let us see if you can figure it out!).

Last but not the least, I would like our readers to appreciate that our authors are painstakingly highlighting the clinical approach they used to establish diagnosis. Our reviewers, editorial board, and CARE guidelines insist on this. Simply giving a sketchy clinical history and examination, listing investigations, and enumerating differential diagnoses, is not enough. There are many questions that have to be resolved to make a case report meaningful and a learning experience to whoever reads it; *What were the salient clinical clues on history and examination that indicated the course of investigation to take? What was the rationale underlying the work up that was planned? Why were some investigations done and others left out? What were the clinical points for or against that made the clinician include or exclude a diagnosis?* There is a lot of to-and-fro communication between all concerned and the authors, until the line of clinical reasoning becomes clear to the reader.

In this issue, we have case reports that have outlined the approach to the following clinical scenarios: unexplained aggression and decline in school performance; refractory allergic rhinitis; neonatal onset of nephrotic syndrome; sudden unexplained neonatal collapse; dysmorphic neonates; unexplained neonatal encephalopathy; persistent neonatal hyperglycemia, recurrent epistaxis; unusual presentations of common conditions (adverse drug reactions, anemia in Dengue, and Mongolian spots) and inability to provide a specific diet in a metabolic disorder due to financial constraints. Case reports are ideal teaching–learning tools for clinicians. I hope you enjoy and learn from each one of them, as much as I have while organizing the contents.

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Conflicts of interest

There are no conflicts of interest.

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Case Series

Using Drama Therapy as an Effective Intervention for Bullying among Siblings

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Abstract

Background: Sibling bullying is repetitive aggressive behavior that is motivated by the desire to dominate and incite distress on the victims. It is a hidden epidemic, with nearly 50% of children being victimized sometime in their lives. Since this is associated with adverse consequences for victims and abusers, it requires prompt recognition, evaluation, and management. **Clinical Description:** We present three families of sibling bullying. Comprehensive individual in-depth interviews (individual and group) were conducted by a team of professionals. The goal was to understand the psychological impact on the children, the family dynamics, and underlying psychosocial issues. Common factors identified were inadvertent positive reinforcement of bullying by parental inability to set limits to the abuser's aggression, failure to model respectful communication, and lack of using appropriate conflict resolution strategies. **Management and Outcome:** Drama therapy was used as the primary modality of intervention. This involved putting families in hypothetical situations in which they reenacted a bullying incident. Family members played various roles interchangeably in multiple sessions. The role-plays and ensuing discussions created awareness of the adverse effects of sibling bullying on the entire family. This coupled with instruction on positive disciplining and use of conflict resolution and anger management strategies resulted in a gradual decline in bullying. **Conclusions:** Sibling bullying can be effectively managed by strategies that promote positive interpersonal relationships. Pediatricians need to recognize cases of sibling bullying and consider referral to mental health professionals for evaluation and appropriate management.

Keywords: Creative therapies, drama therapy, intrafamilial aggression, sibling bullying

Sibling bullying is a common, repetitive, and extremely harmful form of intrafamilial aggression. Given its covert nature, it can be considered a hidden epidemic, especially since 40%–50% of all children are victimized at some time in their lives.[1] Despite the high prevalence, both the general public and professionals fail to recognize it as deviant behavior, or confuse it with sibling rivalry. These terms are often used interchangeably, but it is important to realize that both have different constructs and outcomes. Sibling relationships naturally involve conflict. Instances of minor hostility, competition or aggression, unwillingness to share and cooperate can be classified as sibling rivalry. In contrast, aggressive behaviors that are severe, repetitive, and predominantly motivated by the desire to dominate and incite fear or distress in the victims are referred to as bullying. Ineffective parental disciplining such as lack of consequences for the abuser may worsen the problem.[2]

Sibling abuse is often observed in dysfunctional families with multiple stressors, such as marital conflict, maternal depression, economic stress, substance abuse, and family disorganization.[2] Other risk factors for victimization include belonging to a large family, being younger, and having male siblings. Research has ascertained that sibling bullying victims experience higher rates of mental health problems such as depression, anxiety, trauma-related symptoms, and self-harm behaviors.[2] Evidence indicates that perpetrators of sibling bullying use aggression to attract attention, gain material resources, and establish social dominance within the family.[2] Involvement in bullying at home significantly increases the likelihood of participation in school bullying.[1] Sibling bullying has not been widely researched in the Indian setting,

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despite its prevalence and serious negative consequences for both victim and perpetrator.

Strategies to help parents manage sibling aggression include improving their children's social skills and teaching them mediation techniques for resolving conflicts. Recent research has highlighted the use of creative therapy like drama therapy in managing peer aggression, but its usefulness in sibling conflict is yet to be established. Drama therapy involves using various theatrical techniques (i.e. puppetry, masks, improvisation, and role-play) to facilitate the exploration of interpersonal problems within the context of social learning to achieve psychotherapeutic goals in an imaginative, controlled, and safe way. This is recognized as a powerful intervention tool to achieve psychological growth by exploring underlying emotions and increasing the awareness of the perspectives of affected individuals.[3] No script is provided to the players/performers, and children are neither named nor blamed. Role-play provides a unique opportunity to share experiences and revisit them within the boundaries of fantasy and safety of the therapeutic setting.[3]

In this paper, we share the creative use of dramatic role-play to effectively manage three families with children exhibiting sibling bullying, and how we used it to promote empathy and cooperation among them.

Clinical Descriptions

Family 1

A middle-class nuclear family sought help for their daughters, RK and MK, aged 9 and 13 years, respectively, due to concerns regarding their behavior. Both repeatedly engaged in aggressive and hostile acts such as physical violence, name-calling, and belittling each other for the last 2 years. The girls were evaluated by the child psychology team, first individually, and then together along with their parents, over three sessions each lasting about an hour. Each of them and the parents were invited to put themselves in a hypothetical hostile situation, and play the role of the other person to appreciate the "other" person's perspective. They were told that it was a collaborative pretend exercise, wherein they had the freedom to make up their own storyline, provided it revolved around sibling conflict and did not exceed 15 min.

This role reversal and the ensuing discussion helped in gaining insight into each other's perspectives and feelings, regarding the effects of the bullying on each other. The reasons for the elder girl's desire to dominate and control were explored, and she was counseled to develop her interests in sports and channelize her energy in outdoor activities, i.e., cycling. The parents reported a substantial decline in sibling aggression and improvement in their interpersonal relationships (increased sharing and cooperation) over the next 6 months.

Family 2

AB, an 11-year-old boy, studying in class five in a government school was referred to us by his class teacher who was worried about the significant deterioration in his school performance over the previous 3 months. History revealed that AB was a timid boy with an elder 15-year-old brother, SC, who teased him mercilessly, called him names like "stinky" and "filthy," and would often physically abuse him. AB's parents were indifferent to these aggressive acts, considered them normal, and thus, failed to intervene despite AB's evident distress. Further probing also revealed that the father had a "drinking problem" which the family was struggling to cope with.

During the interview with our team, AB talked about his desire to be loved and accepted by his family, particularly his older brother, whom he admired for his physical prowess, muscular body, and academic excellence. The siblings were asked to enact a recent incident of bullying with role reversal, and the family members were given time to elaborate upon on how they felt during the scene. Constructive strategies for handling anger (e.g., deep breathing, etc.,) and alternatives for conflict resolution (i.e., amicably negotiating a solution) were discussed. Follow-up after 3 months revealed a marked decline in the bullying episodes and improvement in the academic grades of AB.

Family 3

M, a 13-year-old boy presently studying in class 7 of a private school, was diagnosed with a specific learning disability in class 5. He has been struggling with his academic work despite classroom accommodations and special education. this led to him being ridiculed by his schoolmates. His 16-year-older brother, V, was ashamed of his brother's scholastic backwardness and actively avoided him at school. At home, he used disparaging language to humiliate M that often escalated to physical abuse. The parents were unable to manage V's misbehavior and usually resorted to harsh discipline in their attempts to control the conflicts.

Drama therapy was initiated to help parents to appreciate the thoughts and feelings of their sons and understand what they were each going through. They were counseled regarding the need for creating an emotionally supportive home environment, fostering bonding, and preempting V's attempts to intimidate M. Follow-up after 6 months revealed that, except for occasional episodes of conflict, there was an overall decline in the sibling bullying.

Discussion

In recent years, sibling bullying has been recognized as a serious problem that can negatively impact functioning in children. Failure to recognize and support the victim's emotional distress can exacerbate the expression of negative emotions and/or externalizing problems (i.e., aggression) to other settings beyond the home.[2] Behavioral problems are entrenched in dysfunctional parenting marked by a lack of insight into their children's need for a supportive home environment. Inappropriate parenting styles of intervening inadvertently result in the development of toxic sibling relationships. Parental indifference has been known to exacerbate dysfunctional interactions and sibling conflicts well into adulthood.[4] Techniques that improve parental insight

Table 1: Summary table of specific issues and management techniques used for sibling bullying

Family	Victim	Perpetrator	Specific issues identified	Specific interventions	Common interventions
1	9-year-old girl RK	13-year-old girl MK	Desire to dominate and control in the older sibling	Elder sister counseled to channelize her energy in outdoor physical activities	Individual and group interviews Opportunity for venting Using drama therapy to facilitate the exploration of interpersonal problems and increasing the awareness of the perspectives of affected individuals
2	11-year-old boy AB	15-year-old boy SC	Dysfunctional family, lack of parental involvement, and indifference toward sibling aggression	Constructive strategies taught for handling anger and using constructive alternatives for conflict resolution	
3	13-year-old boy V	16-year-old boy M	Specific learning disability in victim, feeling of shame in perpetrator, use of negative parental disciplining strategies	Teaching skills that focussed on positive parenting, and creating an emotionally supportive home environment to nurture harmonious familial relationships	

and strengthen their skills in nurturing harmonious sibling relationships can greatly reduce the family's psychosocial burden and increase sibling well-being.[4,5]

These cases [Table 1] were presented to illustrate the urgent need to address sibling bullying, and also demonstrate the feasibility and effectiveness of drama therapy to reduce sibling bullying. There is emerging evidence to indicate that theatrical techniques help in achieving psychological growth for all participants and trigger parental reflection and introspection that lead to positive interpersonal relationships within the family.[3,6] The utility of school-based drama therapy in alleviating peer victimization in the classroom has been scientifically demonstrated.[5] An intervention program started in a primary school in Finland reported a decrease of 21% in bullying.[7] However, not all studies have found role-playing to be successful in reducing victimization, particularly if the intervention is brief.[8,9] Reductions in peer aggression tend to be more marked when the interventions are intensive and sustained over time.

There is scientific evidence that links sibling and peer bullying. A recent study suggested that adolescents victimized by both their siblings and peers were most likely to develop clinical depression and suicidal ideation in adulthood.[10] It is important to recognize that perpetrators of bullying also suffer adverse consequences, are likely to remain aggressive beyond childhood, and engage in high-risk and anti-social behaviors as adults.[2,9] Timely addressal of intrafamilial aggression attenuates the effect of early-life toxic stress and has long-term implications, i.e. promoting subjective well-being in adulthood. When encountering cases of sibling bullying in their practice, pediatricians should never disregard them lightly or give false reassurances, but consider referring the family to mental health professionals for comprehensive evaluation and holistic management.

Lessons learnt

- Both victims and abusers involved in sibling bullying are at high risk of developing behavioral and emotional problems.
- The use of drama therapy in managing sibling bullying facilitates the exploration of interpersonal problems within the family. This results in positive familial relationships and a decrease in sibling bullying.
- Since sibling conflict may not always be benign, pediatricians should not disregard voiced concerns of children or parents, but consider referral to mental health professionals for further evaluation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, 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 patient identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Series

Skin Prick Tests and Subcutaneous Immunotherapy with Standardized Allergens in Children with Moderate-to-Severe Allergic Rhinitis

Nihar Ranjan Mishra, Karthik Nagaraju[1], Kasyapi Voorakaranam[2]

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Abstract

Background: Allergic rhinitis is common in Indian children, one of the common triggers being house dust mites. Skin prick tests (SPTs) and subcutaneous immunotherapy (SCIT) using standardized extracts of these aeroallergens are increasingly being used in the diagnosis and the management of allergic rhinitis in India. **Clinical Description:** We describe three children with moderate-to-severe allergic rhinitis who were considered ideal candidates for SCIT based on persistent typical clinical symptoms causing significant functional impairment, despite multiple medications for years, and positive family history. Each displayed characteristic local signs (crease over nasal bridge, pale nasal mucosa, and hypertrophy of the inferior nasal turbinates) and normal systemic examination. **Management:** Each of the children displayed significant sensitization with allergens containing standardized preparations of *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df) on the basis of which it was decided to start them on SCIT using the standard protocol. Large local reactions developed and were managed conservatively. All three responded well to bi-weekly shots of progressively increasing concentrations used in the induction phase of SCIT, and are currently asymptomatic on monthly maintenance doses that will continue for 2–3 years. **Conclusion:** Pediatricians should consider referring children with moderate-to-severe allergic rhinitis to Pediatric Allergists for SCIT if significant wheals are observed on SPT. SCIT not only stops the progression of disease, and improve the quality of life, but is also known to prevent the development of bronchial asthma.

Keywords: Aeroallergen, house dust mite, immunotherapy, skin prick tests, standardized allergen

Allergic rhinitis is one of the most common allergic diseases worldwide, affecting 10%–25% of the population.[1] In India, allergic rhinitis is responsible for 55% of all allergies. Its incidence is 20%–30%, with prevalence apparently increasing over a few years.[2] The skin prick test (SPT) is the first line of investigation for evaluating immediate immunoglobulin E (IgE)-mediated allergies such as allergic rhinitis, rhinosinusitis, conjunctivitis, bronchial asthma, atopic dermatitis, and food allergies that manifest with acute hypersensitivity.[3] In STP, the allergen is administered intracutaneously and the size of the wheal measured; ≥3 mm considered significant.[3] The reliability of SPTs depends on the technique and materials of allergens,[4] the nature of which vary according to the allergy. For example, for allergic rhinitis, the extracts are made from common inhalant allergens such as house dust mite (*Dermatophagoides* species) and grass pollen. A stringent protocol of standardization, monitoring, and approval is followed for international extracts, which ensure inter- and intra-manufacturer consistency of mean allergen content.[5] Many indigenous extracts are now available in India. However, there is lack of a universal standardization in their preparation, though attempts are being made to use uniform immune-biochemical methods.[6] There is limited data comparing their potency and side effects with the international extracts.

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Subcutaneous immunotherapy (SCIT) is being used widely for allergic rhinitis.[7] This is the practice of serial desensitization by supervised administration of progressively increasing doses of aeroallergens to which an individual exhibits specific IgE-mediated hypersensitivity. The schedule of the induction phase comprises administrating 5 sequential monthly vials of increasing concentration. The 1st vial is the most diluted (strength based on SPT wheal size); we generally start with 1:100,000 and end with 1:10. Multiple doses are administered from the same vial bi-weekly (at least 72 h apart) each month, with the volume increasing with each shot. When a high level of sensitization to a particular allergen is noted (wheal >10 mm in SPT), a less concentrated dose is used. Common adverse effects include large local reactions (LLR) at the injection site (swelling, pruritus, erythema, or pain).[3] These can be treated with supportive measures such as ice packs, topical or systemic corticosteroids, and second-generation antihistamines. Anaphylaxis occurs in <1%, mostly delayed-onset reactions, rather than life-threatening events.[8] In the maintenance phase, usually, the last dilution that was used in the induction phase is continued as a single-monthly-dose for 2–3 years. There are no published clinical trials from India, or local recommendations regarding allergen use in our population, i.e., content, dilution, etc. Most allergists use protocols based on the international guidelines and personal experience.

Besides having to deal with frequent health visits, multiple medications, and their adverse effects, children with moderate-to-severe allergic rhinitis suffer considerable impairment in their daily lives; irritability, fatigue, disturbed sleep, school absenteeism, poor scholastic performance, impairment in routine and recreational activities, and behavioral issues. SCIT not only alters the progression of disease but also reduces the likelihood of asthma, and financial implications. This case series aims at creating awareness among pediatricians about the use of SPT and SCIT in allergic rhinitis, and also highlight the importance of using standardized protocols.ng levels.td.

Clinical Description

Case 1

A 12-year-old boy presented with frequent episodes of watery nasal discharge, sneezing, nasal irritation and blockade, headache, and mouth breathing for 7 years. Initially during the rainy seasons, the complaints now persisted throughout the year. His parents had consulted several physicians and he had received multiple medications (antihistamines, oral and intranasal steroids, and antibiotics and nasal decongestants), without improvement. There was a history of disturbed sleep (snoring, sleeping with mouth open, and daytime sleepiness), poor scholastic performance, and frequent school absenteeism. There was significant history of immediate nasal irritation, itching and redness of the eyes after eating prawns, and recurrent itchy, skin lesions on his thighs, since a few years. Additional details are given in Table 1.

The patient was thin built with normal vitals. Body mass index (BMI) was 16 kg/m^2 (50th percentile). Local examination revealed thin and profuse nasal secretions, a crease over the nasal bridge, and pale nasal mucosa with hypertrophy of the inferior nasal turbinates. Dry cracked lips and bilateral hypertrophied tonsils were noted. The skin was dry and eczematous over his back and extensor surfaces of thighs. Remaining systemic examination was normal. The child was diagnosed as moderate-to-severe allergic rhinitis with atopic eczema.[9]

Management and outcome

Investigation results are detailed in Table 1. Since the child had refractory symptoms and SPT revealed sensitization to *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df), it was decided to administer SCIT with both allergens as per the international guidelines.[10] The child was asked to maintain a symptom diary. There was no significant wheal formation with the first 3 vials of standardized allergens (Dp and Df mix) used in the induction phase. However, he developed a swelling (10 cm × 8 cm) at the injection site after the first dose (0.05 ml) of the 4th vial (in the 4th month) as per the standard protocol.[10] There was no itching or redness. These events resolved within 6 h after treatment with only ice packs and oral levocetirizine. Pretreatment was given with levocetirizine, 30 min before each subsequent shot, and no further reactions were observed. The child became asymptomatic within 3 months [Figure 1] and is currently on monthly maintenance for a year[10] [Table 2].

Case 2

An 11-year-old boy was brought with history of thick profuse nasal discharge, recurrent sneezing, and nasal blockade for 6 years. The symptoms were initially observed during winters, but later were present throughout the year. School attendance was intermittent. Details of history are given in Table 1. The

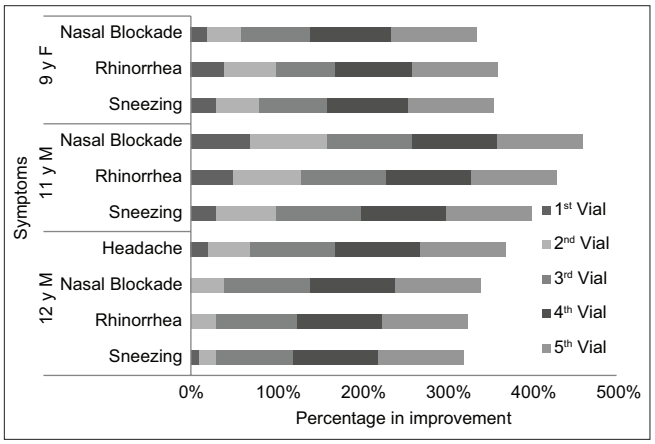

Figure 1: Timeline showing improvement in symptoms of the three children during the induction phase of subcutaneous immunotherapy

Table 1: Comparison of allergic rhinitis specific history and examination in all three cases

History	12 years male	11 years male	9 years female
Clinical manifestations			
Allergic rhinitis	+	+	+
Allergic conjunctivitis	−	−	+
Atopic dermatitis	+	−	+
Bronchial asthma (wheezing/asthmatic cough)	−	−	−
Immediate allergic reaction to food items	Prawns +	Prawns +	−
Functional impairment			
Irritability and fatigue	+	+	+
Disturbed sleep (snoring, frequent awakening, etc.)	+	+	+
School absenteeism	+	+	+
Poor school performance	+	+	+
Impairment in activities of daily living	+	+	+
Impairment in recreational activities	−	+	+
Impairment in sports	+	+	−
Behavior issues[#]	+	+	−
Risk factors			
Positive family history	+	+	+
Exposure to passive smoking at home	−	−	−
Household pets	−	−	−
Examination			
Infraorbital edema and darkening (allergic shiners)	+	+	+
Folds below lower lids (Dennie Morgan lines)	+	+	+
Transverse nasal crease	−	−	−
Allergic facies*	+	−	+
Typical ear, nose, and oral examination	+	−	−
Systemic examination	−	−	−

*High arched palate, open mouth and dental malocclusion, [#]Hyperactivity, depression, or poor self-esteem

child was obese (BMI >99th percentile) with stable vitals. Nasal examinations revealed thick and profuse nasal secretion, dark lines over the nasal bridge, and pale nasal mucosa with hypertrophy of the inferior nasal turbinates. The oral cavity examination and systemic examinations were normal. The child was diagnosed as moderate-to-severe allergic rhinitis.[9]

Management and outcome

Based on the clinical profile [Tables 1 and 2], SCIT with standardized Dp was planned. He became asymptomatic within 2 months [Figure 1] and is on monthly maintenance for 3 months.

Case 3

A 9-year-old girl presented with unresolved nasal discharge, sneezing, and nasal blockade for 4 years. An initial seasonal trend had become perennial since the previous year. There was history of recurrent episodes of dry and itchy skin lesions on her extremities and itching and redness of both eyes. Due to these complaints, the child unable to attend school regularly. Other details are given in Table 1. The girl was overweight (BMI >95th percentile) and stable. Salient examination findings were thick and profuse nasal secretions, dark lines underneath both eyes, and pale nasal mucosa with hypertrophy of the inferior nasal turbinates. The skin was dry and scaly over the extensor surfaces of the upper extremities, abdomen, and back. Both eyes were red and congested. The oral cavity was normal, as was the systemic examination. She was diagnosed with moderate-to-severe allergic rhinitis, allergic conjunctivitis, and atopic eczema.[9]

Management and outcome

Details of investigations and management are given in Tables 1 and 2. Refractory symptoms and sensitization to Df prompted us to start SCIT. Figure 1 depicts the response; resolution of symptoms within 4 months of induction, and is presently on monthly maintenance for 6 months.

Discussion

All three cases were diagnosed as moderate-to-severe allergic rhinitis,[10] displayed a high degree of sensitization to house dust mites on SPT, and showed significant improvement on SCIT, without requiring additional medication. We shall briefly discuss each of these aspects.

Allergic rhinitis is considered persistent if symptoms are present for more than 4 days a week for >4 consecutive weeks. Moderate-to-severe manifestations encompass symptoms that are severe enough to cause sleep disturbances, impairment of daily, scholastic, or recreational activities and persist despite pharmacologic therapy and avoidance of triggers. House dust mites (Dp and Df) are major allergens

Table 2: Comparison of allergic rhinitis specific investigations and management in all three cases

Investigations and management	12 years male	11 years male	9 years female
Absolute eosinophilic count (/mm^3)	568	322	283
Nasal eosinophil count*	Grade 5	Grade 4	Grade 3
SPT with standardized allergens			
D. pteronyssinus in mm (Dp)	16	15	3
D. farinae in mm (Df)	18	4	18
B. tropicalis in mm	7	6	5
Prawn in mm	3	3.5	3.5
CT scan: nose and paranasal sinus	Normal	Normal	Normal
Serum-specific immunoglobulin E**			
D. pteronyssinus (kUA/L)	28.6	17.3	3.6
D. farinae (kUA/L)	31.2	1.3	27.8
Prawn (kUA/L)	0.6	0.35	-
Component resolved diagnosis (immunoCAP method)	Der P 1: 58.3	Der P 1: >100	Not done
Significant value >0.35 kUA/L	Der P 10: 0.02	Der P 10: 12.3	
	Der P 23: 7.6	Der P 23: 27.2	
Adverse events post SCIT			
Size of LLR (cm^2)	10 × 8	12 × 10	11 × 11
Resolution: Ice packs and levocetirizine	+	+	
Duration before resolution (h)	6	8	12
Oral prednisolone and mometasone furoate	–	–	–
Development of LLR: Vial number	4th vial	4th vial	5th vial
Dose	First dose	Second dose	First dose
Volume (ml)	0.05	0.1	0.05
Dilution	1:100	1:100	1:10

*Secretions from the inferior nasal turbinates are collected by swab sticks, smears made, stained with Hansel's stain and examined under microscopic oil immersion. In Grade 5, Approximately 50% of the cells seen are eosinophils, In Grade 4, Approximately 25% of the cells seen are eosinophils, In Grade 3, Eosinophils present but scanty throughout the smear, **ImmunoCAP method; Phadia 100, Thermo Fisher Scientific Inc., Phadia AB, Upsala, Sweden. SCIT: Subcutaneous immunotherapy, SPT: Skin prick test, LLR: Large local reaction, *D. farinae: Dermatophagoides farinae, D. pteronyssinus: Dermatophagoides pteronyssinus, B. tropicalis: Blomia tropicalis*

that are responsible for 80% of sensitization, globally.[5] That is why it is commonly used for SPT and SCIT in allergic rhinitis. The common first line of treatment includes antihistamines, intranasal steroids, saline irrigation, surgeries, avoidance of allergens, parenteral education, etc.[7] Indications for SCIT are: (i) moderate-to-severe allergic rhinitis (as in this case series); (ii) presence of definite allergy triggers; (iii) concurrent asthma or nasal polyposis; (iv) significant complications of allergic rhinitis such as recurrent otitis media or sinusitis; (v) intolerable adverse effects from medications or interference with scholastic performance or work productivity; and (vi) no improvement despite medications.

In SCIT, predefined doses of standardized allergens are given subcutaneously in the arm. The allergen preparation is individualized based on the allergen profile established from SPT response,[3,10] the dose and dilution depending on the wheal size. For example, if child A develops a wheal of 12 mm to Dp, while child B develops a size of 6 mm to the same allergen, the 1st vial of Induction dose should be more diluted in A because of higher likelihood of a LLR. The biggest challenge in using indigenous Indian products is the lack of standardization, which makes following these principles of immunotherapy difficult. We hope this case series will trigger researchers to address the current unresolved areas particular to SPTs and SCIT in the Indian scenario.

Lessons learnt

- Children with moderate-to-severe allergic rhinitis should be considered for SPTs and SCIT
- These should be performed using standardized allergens and standard protocols
- SCIT halts the progression of disease and improves the quality of life.

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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Finnish Variety of Congenital Nephrotic Syndrome in Association with Cytomegalovirus Infection: Double Jeopardy

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Abstract

Background: The term "congenital" is used for cases of nephrotic syndrome (NS) that manifests in the first 3 months of life. They are rare diseases mainly due to genetic causes but sometimes attributed to congenital infections. The prognosis depends on the type of mutation in the former and whether remission occurs with specific therapy in the latter. **Clinical Description:** We describe an 11-week-old baby who presented with generalized edema and features of septic shock that responded to antibiotics. The presence of hypoalbuminemia, proteinuria, and hypercholesterolemia completed the clinical phenotype of NS. Mesangioproliferative glomerulonephritis was confirmed on histopathology. The presence of persistent hepatosplenomegaly, neurological findings, decreased head circumference, and poor nutritional status prompted us to investigate for congenital infections. Positive antibody levels for *Cytomegalovirus* (CMV) and positive polymerase chain reaction confirmed CMV infection, though we were unable to establish whether it was congenital or acquired postnatally. A novel genetic mutation (c. 712+1G>C) was identified in the NPHS 1 gene. **Management:** The baby was initiated on specific antiviral therapy and attained partial remission of renal symptoms after 4 weeks. The patient was lost to follow-up after 6 months. **Conclusion:** The coexistence of the Finnish variety and CMV infection might have caused the severity of phenotype. The authors emphasize the importance of performing a genetic test in cases of congenital NS and also working up for acquired causes on an individualized basis.

Keywords: Congenital nephrotic syndrome, *Cytomegalovirus* infection, Finnish type, ganciclovir, NPHS 1

Congenital nephrotic syndrome (NS) is defined as NS presenting within the first 3 months after birth. Cases who present later but within the 1st year are referred to as infantile NS. Congenital NS is mainly due to mutations in certain genes that code for the structural proteins forming the glomerular filtration barrier, i.e., NPHS 1, NPHS 2, NPHS 3, WT1, and LAMB2. A minority is secondary to acquired causes which disrupt the podocytes and/or the basement membrane, such as toxins (mercury) or infections with congenital syphilis, congenital toxoplasmosis, or cytomegalovirus (CMV) infection. The exact pathophysiology of CMV-associated glomerulopathies is still unclear.[1] We could only find 12 cases of CMV IgM-positive congenital NS from India on an exhaustive literature search. This may be due to low detection and reduced incidence or simply because of decreased reporting and publication of such cases.[2]

The Finnish type of congenital ns is due to biallelic pathogenic variants in the NPHS 1 gene that encodes for "nephrin," a protein present in the slit diaphragm of the podocytes.[3] In this report, we describe a young infant with the Finnish variety of congenital NS due to a novel mutation that was complicated by co-existing CMV infection. We share the challenges that we faced in establishing diagnosis and management.

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Clinical Description

An 11-week-old girl presented with loose stools for 4 days, generalized swelling of the body for 2 days, and seizures for a day. Though the episodes of loose stools were just 3–4 per day and not associated with blood or mucus, they were semisolid

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to watery in consistency. The parents noticed swelling of the body, which started as periorbital puffiness and progressed to the abdomen and lower limbs over 2 days. Increased frothiness of the urine and decreased frequency of urination were also noted. On the day of presentation, the baby was brought to the emergency in a depressed state following a single episode of multifocal seizures that lasted for 3 min, involved the upper and lower limbs, and was associated with up rolling of eyes.

The baby was the second issue of a nonconsanguineous union. The antenatal period had been uneventful till the 36th week of gestation, when the mother perceived decreased fetal movements. An ultrasonogram identified moderate oligohydramnios. There were no renal or other organ anomalies. An emergency cesarean section was performed. The Apgar score was 7 and 8 at 1 and 5 min, respectively, and the birth weight was 2200 g (10th percentile). Though the placenta was not weighed, retrospectively, the mother recollected that it had been almost as big as the baby. There was no history of similar complaints or infantile deaths in the family, and the firstborn son was healthy.

At presentation, the baby was afebrile and had impaired perfusion with tachycardia (180/minute) and tachypnea (62/minute). The weight was 3.7 kg (weight for age −2.48 Z), length was 50 cm (length for age −3.48 Z, weight for length 1.07 Z), and head circumference was 35.5 cm (−2.28 Z), indicative of malnutrition and possibly poor head growth. The only salient general physical examination findings were pallor and generalized edema (periorbital, bilateral pedal, and genital). There was no dysmorphism (sutural diastasis, abnormal facies, ambiguous genitalia, absent patella, microcoria, or joint contractures), jaundice, lymphadenopathy, rashes, petechiae or ecchymoses. The abdomen was distended with a palpably enlarged liver (3 cm below the right costal margin) and spleen (2 cm below left costal margin). The cardiovascular system was unremarkable, and air entry was bilaterally equal, with no adventitious sounds. The baby was conscious, but irritable, was moving all four limbs spontaneously, and had normal tone and reflexes.

Management and outcome

This baby was admitted to the pediatric intensive care unit in view of septic shock. Fluid resuscitation was done as per the standard protocol and intravenous antibiotics were started. Blood sugar and serum calcium and electrolyte levels were normal. The hemogram showed hemoglobin levels of 9.4 g/dL, neutrophilic leukocytosis, and a peripheral smear with microcytic hypochromic anemia and anisocytosis. The reticulocyte count, serum iron, and ferritin levels were normal. Blood urea and serum creatinine were normal. Serum bilirubin and liver enzymes were within normal limits, but severe hypoalbuminemia (0.89 g/dL) was noted. The urinary protein dipstick level was 4+, indicative of high proteinuria. The cholesterol level was 211 mg/dL. In view of the hallmark indicators of NS being present, and factoring in the age of presentation, we kept a provisional diagnosis of congenital NS, with septic shock. A lumbar puncture could not be done due to unstable condition.

The baby was given supportive treatment with 20% albumin infusions with furosemide. She also received packed red blood cell transfusions, intravenous third-generation cephalosporin, phenobarbitone, enalapril, and spironolactone. Thyroid-stimulating hormone levels were high (11.48 mIU/L), while free T3 and T4 levels were low, consistent with hypothyroidism due to severe hypoalbuminemia. TSH levels normalized within 2 weeks of treatment with levothyroxine supplements to 5.7 mIU/L.

Ultrasonography of the abdomen showed normal-sized, hyperechoic kidneys with loss of corticomedullary differentiation, moderate ascites, and confirmed hepatosplenomegaly. There were no additional lesions or anomalies. A congenital infection was suspected in view of the hepatosplenomegaly. Thus, we performed serological tests for *Toxoplasmosis*, *Rubella*, CMV, and herpes virus infections, which showed CMV IgM positivity. The CMV polymerase chain reaction (PCR) was also positive (9542 copies/mL). Maternal levels of CMV IgG antibodies could not be estimated, hence making differentiation between congenital and perinatal CMV infection not possible. Tests for hepatitis B and C were negative.

Magnetic resonance imaging of the brain showed white matter hyperintensities in the right frontal region without any ventriculomegaly or periventricular calcification in the T2 weighted images (as seen in CMV infection).[4] Electroencephalogram showed generalized epileptiform discharges. Echocardiogram and otoacoustic emission tests were normal. Brainstem-evoked response audiometry was planned on follow-up. Ophthalmological examination revealed no evidence of CMV retinitis. An ultrasound-guided renal biopsy was performed. Analysis of the 32 glomeruli retrieved [Figure 1] showed mesangioproliferative glomerulopathy without diffuse mesangial sclerosis. Electron microscopy revealed occasional endothelial tubuloreticular inclusions with diffuse effacement of podocytes [Figure 2].

The clinical diagnosis was congenital NS, probably due to CMV infection; however, since a genetic cause could not be ruled out conclusively, we ordered Sanger sequencing as well. Intravenous ganciclovir (30 mg/kg/day) was initiated and given for 2 weeks, after which she was switched over to oral valganciclovir (30 mg/kg/day) for 2 weeks. Neutropenia was monitored on a weekly basis. CMV DNA became undetectable in plasma after 3 weeks of antiviral therapy [Table 1] and the proteinuria improved. At the end of the antiviral therapy, the baby attained a state of partial remission (>50% reduction in proteinuria from the baseline).

The Sanger sequencing result revealed a novel pathogenic homozygous 5' splice site (c. 712+1G>C) variant mutation in the NPHS 1 gene. This was classified as a likely pathogenic

Table 1: Clinical, histopathological, and genetic profile of young infants with cytomegalovirus infection

Age, sex and reference	Clinical findings	Renal histopathology	Genetic variants	Outcome
15 days, male[5]	No symptoms	Vacuolar and granular degeneration of tubular epithelial cells, small focal atrophy. Focal lymphoid, interstitial mononuclear cells and eosinophil infiltrates. Fibrosed and thickened small arterial walls. No CMV inclusions	NPHS 1 variant reported as c. 2396G >T (p.Gly799Val) and c. 1339G >A (p. Glu477Lys), COL4A5 variant not specified	Chronic kidney disease at 13 months
57 days, female[6]	Generalized edema, hypertension, respiratory symptoms, and anemia	Focal tubular atrophy, fibrosis, and tubular dilatation. Inflammatory infiltrates in some tubules. Cytomegalic inclusion bodies seen	Not done	Hypertension and anemia resolved. Remission at 14 months
45 days, female[7]	Generalized edema, ascites, pleural effusion, vitritis HI	Normal tubulointerstitial compartment. Single inclusion body in distal tubule	NPHS2 mutation-Homozygous for nonsense mutation c. 412C <T (p.Arg138X), both parents' carriers	Resolution of HI and vitritis at 6 months. End stage renal disease at 21 months
51 days, male[8]	Failure to thrive, ascites, anemia	Interstitial fibrosis and tubular atrophy. Patchy, moderate tubular-interstitial infiltrates present	NPHS 1 heterozygous c. 2713G >A p.(Ala905Thr), missense variant in ITSN2	PCR CMV negative at 4 weeks. Death due to sepsis at 8 months
77 days, male This report	Seizure, generalized edema, fever, and hepatosplenomegaly	Mesangioproliferative glomerulopathy. Occasional endothelial tubuloreticular inclusions and diffuse podocyte effacement	Novel pathogenic homozygous 5' splice site (c. 712+1G >C) variant mutation in NPHS 1 gene	Partial remission with therapy. Death due to sepsis at 2 years

HI: Hearing impairment, CMV: Cytomegalovirus, PCR: Polymerase chain reaction

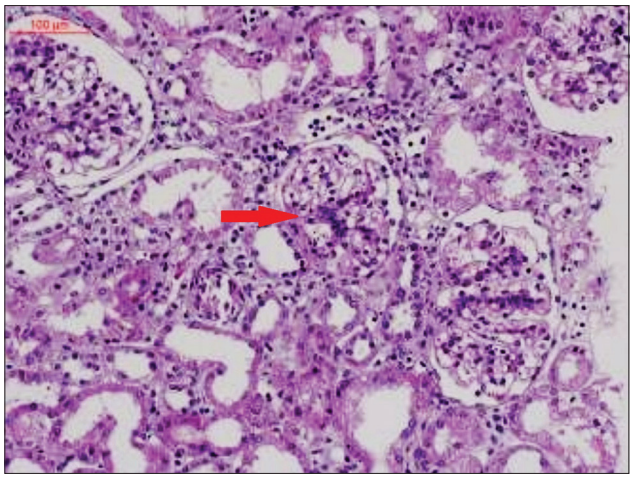

Figure 1: Light microscopy of the kidney biopsy specimen with periodic acid silver methenamine staining revealing glomeruli containing focal and segmental mild-to-moderate mesangial hyperplasia

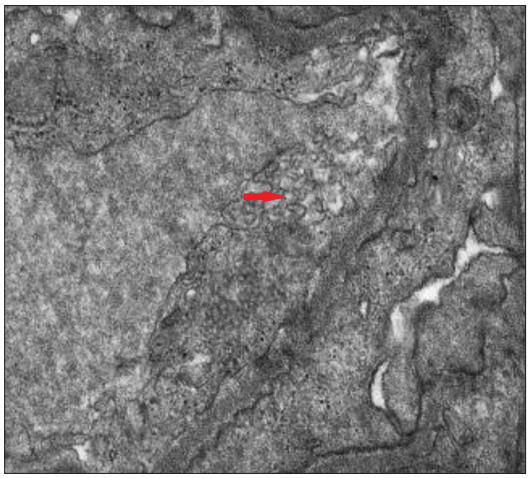

Figure 2: Electron microscopy of the kidney biopsy specimen showing diffuse effacement of the visceral epithelial foot processes were seen with no electron dense deposits. Tubuloreticular inclusions identified in glomerular endothelial cell cytoplasm

variant. The parents were provided prenatal diagnosis and counseled regarding the risk of recurrence in future pregnancies. Angiotensin-converting enzyme inhibitor was started after the completion of antiviral therapy. Follow-up became erratic after the parents relocated to another city. We learned that the baby received 6 weeks of oral prednisolone, which were discontinued when there was no symptomatic improvement. At the age of 2 years, she became terminally ill and died.

Discussion

This patient exhibited features of classical (Finnish type) congenital NS due to a homozygous NPHS 1 pathogenic variant, complicated by a CMV infection. The baby had microcephaly, hepatosplenomegaly, and white matter hyperintensities in the right frontal lobe. The renal histological findings were consistent with what has been described in CMV-related congenital NS reported by Chen *et al*., including mesangioproliferative lesions, diffuse podocyte effacement, and endothelial tubuloreticular inclusions.[5] This phenotype is more severe, is associated with marked inflammation, and presents earlier.[6] CMV infection is the most common congenital infection reported from low- and middle-income countries, with prevalence rates of 1%–6%.[9] If CMV infection is detected 3 weeks after birth, it may be either perinatal or congenital in original,

and it is often difficult to distinguish between the two.[10] There have been reports of congenital NS due to other congenital infections (congenital syphilis and congenital toxoplasmosis) who demonstrated remission with therapy. Our case received anti-CMV therapy for 4 weeks and attained partial remission. The role of anti-CMV therapy in curing CMV-related renal injury is not fully clear, as is the mechanism of CMV-induced glomerular injury. Some studies suggest direct virus-mediated tissue injury, insult mediated by T-cell response, as well as immune complex formation.[11] An extensive literature search of the cases of CMV-associated congenital NS that we identified in PubMed and Google Scholar is depicted in Table 1.[5-7,12,13] Although there are no guidelines for management of renal involvement in CMV infection, we decided to administer specific therapy after suitable scientific discussion.

The novel homozygous mutation identified in this baby has not been reported in the 1000G and ExAC databases. Genotype–phenotypic correlation will be difficult in this case as the co-existence of CMV infection could have contributed to the severity of presentation. Sinha *et al*. described genetic mutations in a large proportion of patients (23%) with congenital NS.[2] It is important to perform genetic testing to establish diagnosis, provide genetic counseling, and be able to offer prenatal diagnosis in subsequent pregnancies.

Lessons learnt

- Concurrent Finnish type NS and CMV infection contributed to the severity of symptoms and cannot be solely attributed to the novel mutation identified. conditions might contribute to the severe clinical symptoms.
- A genetic work up should be done in congenital NS to exclude mutations in the 5 associated genes.
- Though genetic causes are the most common etiology of congenital NS, if there is the slightest suspicion of an acquired cause, it should be thoroughly investigated as the remission of symptoms has been reported in some cases with specific therapy.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Compound Heterozygous Mutation of SLC25A1 Gene in Glutaric Aciduria Type 2

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Abstract

Background: Sudden unexplained postnatal collapse (SUPC) is a condition in which a newborn born at term or near term, and an Apgar score >8 at 5 min and deemed healthy, presents with sudden unexpected cardiorespiratory collapse within the 1st week of life. This can be due to multiple, heterogeneous causes. **Clinical Description:** A term male neonate developed lethargy and refusal to feed at 56 h of life. The baby was cyanosed, apneic, in peripheral circulatory failure and normothermic. Supportive management was started. Sepsis and congenital heart disease were ruled out. The presence of hypoglycemia, metabolic acidosis and hyperammonemia prompted us to think of a metabolic disorder. Metabolic profile was suggestive of glutaric acuduria (GA). Exome sequencing showed heterozygous missense variants in in exon 7 and 8 of SLC25A1 gene indicative of GA II but reported as of uncertain significance. Both parents were carriers. **Management:** The final diagnosis was neonatal onset GA II without congenital anomalies. He was started on riboflavin and carnitine. Mechanical ventilation and inotropes were gradually withdrawn and breastfeeding started. Genetic counseling was done. The baby was doing well at the 4-month follow-up visit. **Conclusions:** Identifying and managing a newborn with SUPC is critical for the outcome. An individualized and rational approach should be used to identify the cause. The management of GA II is primarily supportive with tiding over of metabolic crises and dietary modifications.

Keywords: Compound heterozygote, hyperammonemia, hypoglycemia, metabolic acidosis, sudden unexpected postnatal collapse

Sudden unexplained postnatal collapse (SUPC) is a condition in which a newborn born at term or near term, and an Apgar score >8 at 5 min and deemed healthy, presents with sudden unexpected cardiorespiratory collapse within the 1st week of life, which requires resuscitation, and may result in death, or encephalopathy.[1] Most occur within the first 3 days (36% within 2 h, 29% between 2 and 24 h, and 24% between 25 and 72 h), while 9% occur between 4 and 7 days of life.[2] The common causes of SUPC include congenital infections, congenital anomalies (especially cardiac), respiratory disorders, anemia, hypoglycemia, congenital adrenal hyperplasia, neurological/neuromuscular disorders, and inborn errors of metabolism (IEM).[3,4] Electron transfer flavoprotein (ETF) serves as the electron acceptor for flavoprotein dehydrogenases which are important in fatty acid beta-oxidation and amino acid catabolism.[5] Impaired beta-oxidation result from defects in ETF and manifest as hypoglycemia, hyperammonemia, and metabolic acidosis.

We report a case of SUPC who was diagnosed with an IEM, by keeping a high index of suspicion, and following an individualized, rational, diagnostic approach that included simultaneous clinical, biochemical and genetic evaluation, while stabilizing a sick neonate.

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Clinical Description

A 2-day-old boy was shifted from the postnatal ward to the intensive care unit at 56 h of life with a history of acute-onset lethargy, poor responsiveness, and not being able to suckle. Breast feeding had been established successfully within an hour of birth and the baby had been feeding well, crying, and moving all limbs spontaneously, prior to these events. There was no history of any trauma, vomiting, loose motions, or being

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fed anything, besides breast milk. The baby was born at term gestation by a normal vaginal, institutional delivery. There was no history of any maternal or environmental risk factors for sepsis. The birth weight was 2660 g. The Apgar scores were 8 and 9, at 1 and 5 min, respectively. The antenatal period had been uneventful, with no history of substance abuse, and whatever health records were available, were normal. He was the second issue of a nonconsanguineous union. There was no significant family history.

On examination, the baby had peripheral cyanosis, poor respiratory efforts, bradycardia, low volume peripheral pulses, delayed capillary refill time, nonrecordable blood pressure, and normothermia. No abnormalities were detected on the general physical examination. The baby was limp with minimal spontaneous movement and absent neonatal reflexes. The pupils were normal. The cardiovascular, respiratory, and abdominal examinations were normal. Hypoglycemia and severe metabolic acidosis (arterial bool gas analysis-pH 7.1, base deficit-16, normal lactate and anion gap) were present. Serum electrolytes, liver, and renal function tests were within the normal range. The clinical and metabolic profile led us to consider differential diagnoses of a critical congenital heart disease, early onset neonatal sepsis, or an IEM.

Management and outcome

The baby was resuscitated as per the standard protocol and started on mechanical ventilation. Intravenous fluids were administered by multiple lines including glucose infusion (@10 mg/kg/min), sodium bicarbonate, and inotropes. The hemogram was normal and sepsis screen negative. The baby passed the oxygen saturation test, while a 2-dimensional echocardiogram did not detect any structural or obstructive defects. The abdominal ultrasonogram was normal, ruling out any renal or adrenal abnormalities. First tier metabolic workup showed elevated ammonia levels (515 μm/l). The baby was kept nil per orally and empiric management of hyperammonemia was started with sodium benzoate (250 mg/kg), Carnitine (100 mg/kg/day), and megavitamins; thiamine (10 mg twice a day), biotin (10 mg/day), and riboflavin (20 mg/day). The urinary gas chromatography mass spectrometry analysis revealed an increase in the excretion of 2-hydroxyglutaric acid, glutaric acid, and related organic acids. The tandem mass spectrometry report showed increased levels of C4-C18 acylcarnitines. Both of these biochemical abnormalities were indicative of glutaric aciduria (GA).

A whole exome sequencing test was ordered. This revealed heterozygous missense variants (c.634G>A [p. Asp212Asn] and in exon 7 c.769C>T [p. Arg257Trp] in exon 7) of the SLC25A1 gene, associated with DL-2 hydroxyglutaric aciduria, but of unknown significance. After posttest genetic counseling, the parents underwent Sanger sequencing to segregate and understand the inheritance pattern of these

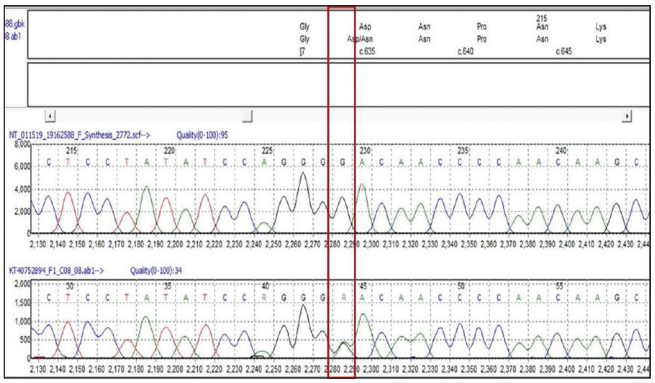

Figure 1: Sanger sequencing report of the mother showing nucleotide change at chromosome 22: c.634G>A, (p. Asp212Asn) in SLC25A1 gene

variants. The mother was a carrier for the c.634G>A variant [Figure 1] and the father carrier for the c.769C>T variant [Figure 2], making the baby compound heterozygous for GA II, i.e., the atypical allele inherited from either parent was located at different loci within the same gene. Considering the onset, clinical features, biochemical profile and genotype, the final diagnosis was neonatal onset, GA II without congenital anomalies due to a compound heterozygous mutation in the SLC25A1 gene.

Inotropes were stopped by the 5th day of admission and he was weaned off ventilation by the 6th day. Megavitamins were stopped once the diagnosis was established (day 7). The baby was allowed breastfeeding on day 8, and he was discharged by the 12th day on oral riboflavin and carnitine. The parents were counseled regarding the disorder, sick day management protocol, and the need for regular follow-up that included monitoring for hypoglycemia, rhabdomyolysis, and liver dysfunction. They were also informed about the option of prenatal diagnostic testing for the next pregnancy. At the 2-month follow-up visit, the baby was well, gaining weight adequately, and had attained a social smile. His neurodevelopmental assessment was normal for age.

Discussion

Sudden unexpected postnatal collapse in a well newborn is a rare event, with multiple causes [Table 1].[2,6] Irrespective of etiology, the consequences are serious; mortality or severe neurological disability among survivors.[5] Rapid identification and initiation of resuscitation are critical. After initial stabilization, evaluation for the underlying cardiac, endocrine, and metabolic causes must be carried out according to clinical clues. In our case, an apparently well baby with acute onset encephalopathy, absence of trauma, sepsis, dyselectrolytemia, and cardiac anomalies, in the presence of hypoglycemia and metabolic acidosis, indicated an IEM.

GA II is an autosomal recessive disorder caused by mutations in the α or β subunit of the mitochondrial ETF protein or

Table 1: Differential diagnosis of sudden unexplained postnatal collapse

Congenital heart disease
Obstructive left heart lesions: Hypoplastic left heart syndrome, coarctation of the aorta, interrupted aortic arch, critical aortic stenosis, obstructive right heart lesions (tetralogy of Fallot, critical pulmonary stenosis, and tricuspid/pulmonary atresia), transposition of the great vessels, single ventricle circulation, neonatal cardiomyopathy, fetal arrhythmia, cardiac tamponade, large atrial or ventricular septal defect
Sepsis/common causes of infection
Bacterial (maternal Group B *streptococcus, Listeria monocytogenes, Escherichia coli, Staphylococcus aureus*), viral (herpes simplex virus, enteroviruses, and parechoviruses) and fungal (*candida* spp.)
Endocrinal disorders
Congenital adrenal hyperplasia, maternal thyrotoxicosis, congenital hypothyroidism, and causes of hyperinsulinism
Metabolic disorders
Fatty acid oxidation defects, urea cycle defects, organic acidemias, and glycogen storage disorders, mitochondrial disorders
Nonaccidental injury
Abusive head injury, fractures, intraabdominal injury, intracranial hemorrhage, and hypothermia
Respiratory
Pulmonary hypertension, pneumonia, pneumothorax, large congenital pulmonary airway malformation
Gastrointestinal
Intussusception, malrotation/volvulus, necrotizing enterocolitis, and Hirschsprung enterocolitis
Neurological
Seizures, congenital malformations (e.g., anencephaly, lissencephaly, and hydrocephalus)
Toxins
Opioids, Diphenhydramine, accidental overdose (beta antagonist, calcium channel antagonist, digoxin, sulfonylureas)

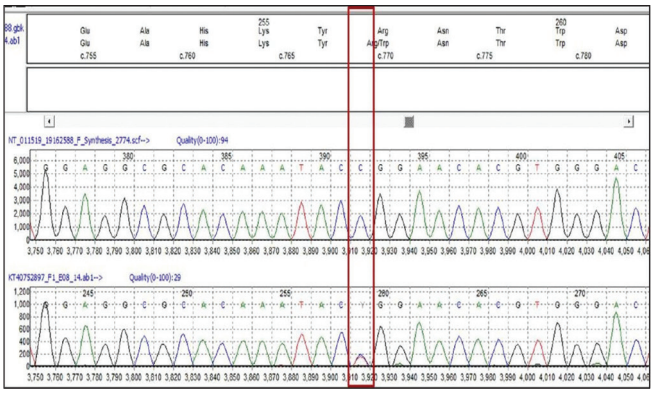

Figure 2: Sanger sequencing report of the father showing nucleotide change at chromosome 22: C.769C>T, (p. Arg257Trp) in SLC25A1 gene

ETF dehydrogenase (ETFDH) protein. Its prevalence is 1:250.000 and affects both genders.[7] GA II is sub-grouped as IIa, IIb, and IIc according to the defects in the ETFA, ETFB, and ETFDH genes, respectively.[8] The mutations result in deficient or complete absence of enzyme activity of multiple acyl-CoA dehydrogenase that catalyze the breakdown of fats and proteins in the body. Mutations in ETFA and ETFB result in neonatal onset presentation, whereas those in ETFDH result in the type that presents later and with milder severity. Dysfunction of either flavoproteins coded by these genes lead to impaired fatty acid oxidation and amino acid degradation that alters production energy and other molecules needed by the body.

Clinicians should suspect GA in a newborn with vomiting, hypotonia, encephalopathy, and/or hepatopathy, associated with unexplained hypoglycemia and metabolic acidosis. There are three types of presentations depending upon the age of onset. In the neonatal period, GA II may present with congenital anomalies (high-arched palate, craniotabes, dolichocephaly, rocker bottom feet, hypotonic abdominal wall, hypospadias, and renal cysts) which is lethal; or without. Thus, an IEM should still be considered in a neonate with multiple congenital anomalies, especially if there is unexplained clinical deterioration.[9] Late onset GA II manifests later, in infancy, childhood or even adulthood, with progressive myopathy, respiratory failure, acute renal failure and repeated episodes of hypoglycemia with hypoketosis. This form is due to partial defect of ETF/ETF-DH that may respond to riboflavin (100 mg/day).

GA II does not have any specific treatment. The goal of management is supportive medical management (riboflavin and carnitine), and treatment of metabolic crises, and dietary modifications: High carbohydrate, low protein and low fat, and frequent meals avoid the episodes of hypoglycemia.

Lessons learnt

- SUPC is a condition in which a healthy newborn born at term or near term, and an Apgar score>8 at 5 min, presents with sudden unexpected cardiorespiratory collapse within the first week of life
- It is caused by multiple, heterogeneous cause and an individualized, rational, approach should be used to determine the cause
- There is a high risk of mortality or severe neurological disability, unless the condition is rapidly identified, managed, and cause determined.

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

Neonatal Osteosclerotic Bone Dysplasia (Raine Syndrome)

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Abstract

Background: Raine syndrome is a rare autosomal recessive neonatal osteosclerotic bone dysplasia caused due to mutations in the FAM20C gene. It has an early and aggressive onset which often results in death in the first few weeks of life, although there have been cases of patients surviving into childhood. **Clinical Description:** We describe the case of a neonate girl born with microcephaly, proptosis, triangular mouth, depressed flat nasal bridge, mid-face hypoplasia, low set ears, high-arched palate, and a wide-open anterior fontanelle. Based on the clinical phenotype, the differentials considered were a congenital infection and Crouzon syndrome. **Management:** Infantogram revealed generalized osteosclerosis. Based on the radiological phenotype, the differentials considered include Thanatophoric dysplasia, osteopetrosis, and Achondroplasia. Search for concealed anomalies revealed dysmorphic features in the brain and kidneys. The clinical exome demonstrated a heterozygous missense and heterozygous nonsense variant in exon-7 of the FAM20C gene, which established the diagnosis of Raine syndrome. **Conclusion:** Genetic analysis based on phenotype can aid in the early diagnosis of dysmorphic children and help in instituting appropriate management.

Keywords: Dysmorphic features, FAM20C gene, intracranial calcifications, osteosclerosis

Raine syndrome is a rare autosomal recessive neonatal osteosclerotic bone dysplasia due to a mutation in the FAM20C gene. The prevalence is <1 per million. This condition was included in the Online Mendelian Inheritance in Man as "Osteomalacia, sclerosing, with cerebral calcification" in 1986. Three years later, Raine *et al*.[1] expanded the phenotype to include microcephaly, exophthalmos, hypoplastic nose, low-set ears, gum hypertrophy, cleft palate/uvula, severe midface hypoplasia with choanal atresia, generalized osteosclerosis, and calcification on brain imaging.

We present this neonate with the characteristic phenotype of Raine syndrome corroborated with a pathogenic genetic mutation. The case is presented due to its rarity (incidence 1 per million) and also to highlight the approach a clinician should use in neonatal with craniofacial dysmorphism and generalized osteosclerosis.

Clinical Description

A 3-day-old girl was brought to us with parental concerns regarding unusual features. She was born of a third-degree consanguineous marriage and was third in birth order. The delivery was conducted at 36 weeks of gestation by cesarean section for oligohydramnios. The birth weight was 2800 g, and there were no perinatal complications. There was no history of any antenatal maternal illnesses, or exposure to teratogens. The family history was not contributory.

At admission, the baby was euthermic with a pulse rate of 125/min (min), respiratory rate of 52/min, and normal capillary filling time. The growth parameters were: Weight 2.8 kg [−1.22 standard deviations (SD)]; length 46 cm (−2.3 SD); and head circumference 30 cm (−3.8 SD). The baby had overt craniofacial dysmorphism with proptosis, microcephaly, wide-open anterior fontanelle, flat and broad nasal bridge, low set ears, midfacial hypoplasia, high-arched palate, and a triangular-shaped mouth [Figure 1]. There was no choanal atresia. The spine was normal, and there were no arthrogryposis or limb and trunk anomalies. The respiratory, cardiovascular, abdominal (including genitalia), and neurological examination was normal. Fundus and

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hearing (otoacoustic emission) evaluations were normal. Based on the presence of microcephaly and craniofacial anomalies, the differential diagnoses considered were a craniosynostotic syndrome (possibly Crouzon) or a congenital infection.

Management and outcome

The TORCH profile for congenital infections was negative. Additional tests were done to rule out concealed congenital anomalies. Ultrasonography of the brain detected bilateral periventricular hyperintensities, and that of the abdomen bilateral hydronephrosis. Computerized tomography scan of the brain delineated additional anatomical abnormalities; bilateral symmetrical calcifications (in the periventricular and capsule-ganglionic regions, dentate nuclei, and tentorium), proptosis, frontal bossing, and absent nasal bones [Figure 2]. The two-dimensional echocardiograph was normal. An infantogram (ordered to detect additional skeletal anomalies) revealed generalized osteosclerosis. There were no fractures or periosteal bone formation. Based on the clinical and radiological phenotype, the differentials were narrowed down to osteopetrosis, thanatophoric dysplasia, and achondroplasia.

Normal blood counts ruled out cytopenias that are seen in osteopetrosis. Serum electrolytes and kidney function tests were normal. A literature search (Google Scholar and PubMed) for cases of neonatal osteosclerosis and the identified dysmorphic features led us to consider another differential, Raine syndrome. A genetic consultation was taken, and next-generation sequencing (NGS) was advised (as per the protocol of an infant with multiple congenital anomalies). This revealed a compound heterozygous mutations involving the FAM20C gene in Chromosome 7p22. The first was a heterozygous nonsense variant in exon 7 of the FAM20C gene (chr7:296641C>G). This has been reported to results in a stop codon and premature truncation of the protein at codon 425 (p. Tyr425Ter; ENST00000313766.5). It is a pathogenic variant. A heterozygous missense variant mutation was identified in exon 7 of the FAM20C gene (chr7:296717G>A). This results in amino acid substitution of Asparagine for Aspartic acid at codon 451 (p. Asp451Asn; ENST00000313766.5) and has been observed to lie in the Golgi casein kinase, C-terminal, Fam20 domain of the FAM20C protein. It has previously been reported in Raine syndrome or neonatal osteosclerotic bone dysplasia. Thus, our clinical suspicions were confirmed. The parents were given genetic counseling and the patient kept under follow up. Subsequently, she developed generalized epilepsy, developmental delay, a humerus fracture following a trivial and expired at 2 years of age after an acute illness with respiratory distress and seizures. Having a genetic diagnosis helped the family understand the nature and course of her illness.

Discussion

This case highlights the approach that we used once we narrowed down on salient clinical clues; neonatal onset, microcephaly, absent nasal bones, and generalized osteosclerosis. A literature search gave us a clinical differential and NGS confirmed the genotype. However, we were unable to get segregation analysis, as the parents were not planning any further pregnancies.

Raine syndrome is a rare disorder that arises due to biallelic loss-of-function mutations of the FAM20C gene located on chromosome 7p22.3. Tagliabracci *et al*.[2] determined that the FAM20C gene phosphorylates caseins and other proteins involved in the biomineralization of bone like small integrin-binding ligand N-linked glycoproteins (SIBLINGs). Mutations occurring at this locus affects FAM20C kinase activity and secretion and results in abnormal phosphorylation of SINBLINGs and the typical biomineralization phenotype. Hung *et al*.[3] reported that all lethal pathogenic variants were situated close to functional protein regions (catalytic, dimerization, and glycosylation sites), whereas the healthy homozygotes had polymorphic changes detected in sites furthest away from the catalytic pocket or functional regions. Prenatal diagnosis is possible and has been reported in three fetuses with typical features; intracranial calcifications,

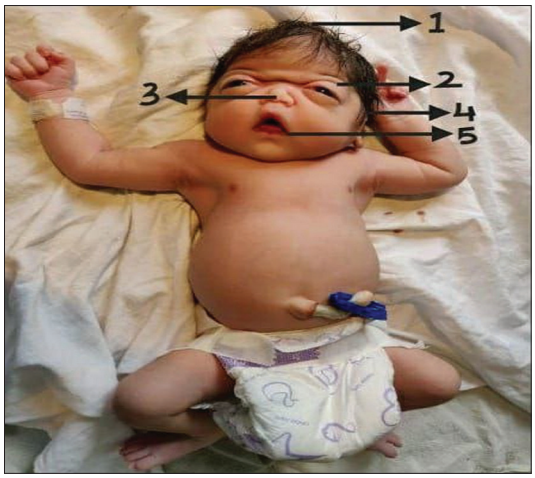

Figure 1: Newborn with microcephaly, exophthalmos, depressed nasal bridge, low set ears, and inverted U-shaped mouth

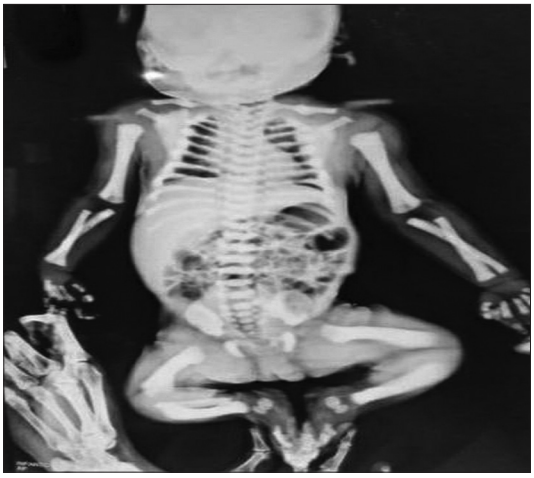

Figure 2: Infantogram with generalized osteosclerosis

hypoplastic nose, midfacial hypoplasia, ectopic renal and hepatic calcifications, and osteosclerosis.[4]

The life span of affected individuals is variable, ranging from early infantile deaths to survival into adolescence. Most patients die of severe respiratory distress during the neonatal period, due to pulmonary hypoplasia and choanal atresia/stenosis. Nonlethal variants have craniofacial, thoracic and limb abnormalities along with osteosclerosis, hypophosphatemic rickets, and neurological disorders such as seizures and development delay.

Lessons learnt

- An individualized step-by-step approach should be used for dysmorphic infants
- NGS should be ordered for children with multiple congenital anomalies
- Genetic counseling helps in the family making educated decisions and understands the nature of illness.

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

Neonatal Onset Aicardi-Goutières Syndrome with Congenital Corneal Edema, Expanding the Phenotype

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Abstract

Background: Type I interferonopathy is a group of autoinflammatory disorders associated with enhanced type I interferon levels, due to upregulation of activation mechanisms or downregulation of negative feedback. Aicardi-Goutières syndrome (AGS) is one of these conditions, characterized by encephalopathy that usually manifests in late infancy. A rarer presentation that mimics congenital trans-placentally acquired infection or a 'pseudo-TORCH' subtype has been described. **Clinical Description:** A boy of 36-week gestational age with intrauterine growth restriction, nuchal transparency and a normal antenatal microarray assay, was delivered by cesarean section for oligohydramnios and fetal distress. The baby cried at birth, but developed mild respiratory distress and was neurologically depressed. A congenital infection was considered in view of being hypoplastic small for date with microcephaly, encephalopathy, intracerebral calcifications, multiple congenital heart lesions, and hepatosplenomegaly. Bilateral corneal edema was noted. **Management:** Supportive treatment was initiated. Mother-baby serology for congenital infections was negative. Various differential diagnoses for pseudo ToRCH presentations were considered and genetic testing planned. Exome sequencing identified a homozygous, single base pair insertion (c. 56_57insG variant) in exon 2 of TREX1 gene on chromosome 3, previously reported in AGS. The baby did not survive, **Conclusion:** This paper describes the clinical approach that was used to establish diagnosis in a neonate with "pseudo ToRCH" phenotype. It also expands the clinical phenotype of AGS by reporting a hitherto undescribed ocular finding of congenital corneal edema.

Keywords: Corneal edema, pseudo-ToRCH, TREX1, type 1 interferonopathy

Type I interferonopathy is a group of autoinflammatory disorders associated with enhanced type I interferon (INF-α) signaling, either due to upregulation of its activation mechanisms or downregulation of negative regulatory systems. This results in increased IFN levels in the serum and cerebrospinal fluid. Currently almost 40 conditions are recognized. Though the clinical phenotypes are heterogeneous, they all share a few common characteristics, referred to by some as the "clinical IFN signature"; early onset of skin vasculopathy with chilblains, livedo reticularis and panniculitis, central nervous system manifestations, and/or interstitial lung disease.

Aicardi-Goutières syndrome (AGS) is a rare genetic encephalopathy that was one of the first type-1 interferonopathy to be described in 2003, when an overlap of clinical manifestations was observed among it, congenital viral infections, and autoimmune disorders like systemic lupus erythematosus. AGS is characterized by intracranial calcifications, white matter disease, and cerebrospinal fluid (CSF) lymphocytosis. Onset is usually in late infancy and early childhood.[1]

We present a genetically diagnosed newborn with AGS born to a primigravida who remained unidentified in the antenatal period, but manifested at birth with a multi-systemic pseudo-ToRCH presentation, and describe the clinical approach used to establish the diagnosis. We also expand the clinical phenotype of AGS by reporting congenital corneal edema, a feature that has not been described earlier.

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Clinical Description

A male neonate born at 36 weeks of gestation was admitted with respiratory distress since birth. He was delivered by an emergency caesarean section, indicated for oligohydramnios and fetal distress. The baby cried immediately after birth. The antenatal history was significant. Amniotic chromosomal microarray has been performed and reported normal, when ultrasonography had detected intrauterine growth restriction with increased nuchal translucency. There was no maternal history of placental insufficiency, febrile illnesses, or prior abortions. The baby was the first in birth order, born to a third-degree-consanguineous couple. The family history was not contributory.

On examination, vitals were stable apart from mild respiratory distress and low oxygen saturation that was corrected with low flow of oxygen. He was small for gestational age (birth weight 1.8 kg, <3rd centile), with length 40 cm (<3rd centile), head circumference 30 cm (<3rd centile), and Ponderal index 2.5 (indicating a hypoplastic, small for date baby). He had a widely open anterior fontanelle (3 cm × 3 cm), widely separated cranial sutures, bilateral corneal whitish haze [Figure 1], and generalized petechiae. There was no overt facial dysmorphism. The cardiovascular examination revealed a grade 3 pan-systolic murmur at the left upper sternal border. No abnormalities were detected in the respiratory system. The liver and spleen were enlarged. He was lethargic, had a poor cry, and decreased state-to-state variability, and poor spontaneous eye-opening. Neonate was hypotonic, with good anti-gravity movements and normal deep tendon reflexes, suggestive of central hypotonia. The neonatal reflexes (Moro's, palmar and plantar grasp, rooting, and sucking) were depressed. A provisional clinical diagnosis of a congenital infection was considered, and supportive management initiated.

Management and outcome

Investigations were planned accordingly. Chest radiograph was normal. Salient blood reports included thrombocytopenia (platelet count 18,000/mm^3), raised C-reactive protein (24 mg/dl), mild transaminitis (SGPT 143 IU/L, SGOT 288 IU/L). There was no anemia, and the blood glucose, serum electrolytes and renal function tests were normal. Calcium and phosphorus were normal and serum alkaline phosphatase was 157 IU/L. A small patent foramen ovale (PFO), 2.9 mm patent ductus arteriosus), and large peri-membranous ventricular septal defect (VSD) with bidirectional shunt were detected on echocardiography. Cranial ultrasonogram showed periventricular, basal ganglia, and thalamic hyperechogenic lesions [Figure 2]. Magnetic resonance imaging of the brain revealed simplified gyral pattern, periventricular, basal ganglia, and thalamic T2 hypointense lesions with blooming on the susceptibility-weighted image, suggestive of calcifications [Figure 3], and small hemorrhages in the occipital horns of lateral ventricles. An ophthalmological examination confirmed bilateral, symmetrical, diffuse corneal edema [Figure 1], which precluded a detailed retinal examination. Brainstem evoked response audiometry (BERA) was normal.

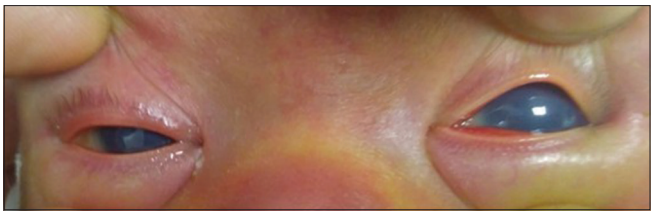

Figure 1: Bilateral corneal opacities

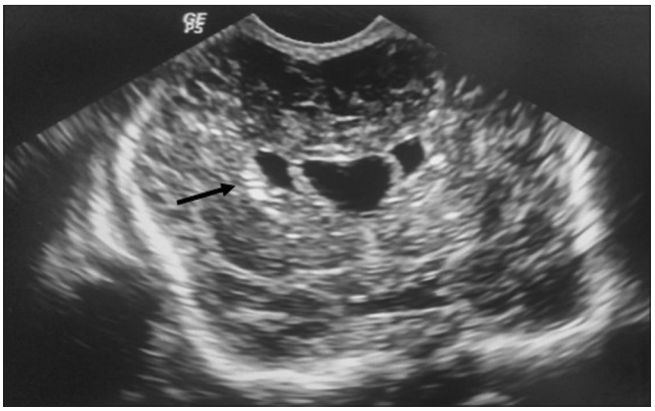

Figure 2: Cranial ultrasonogram (coronal section) showing intracranial calcifications

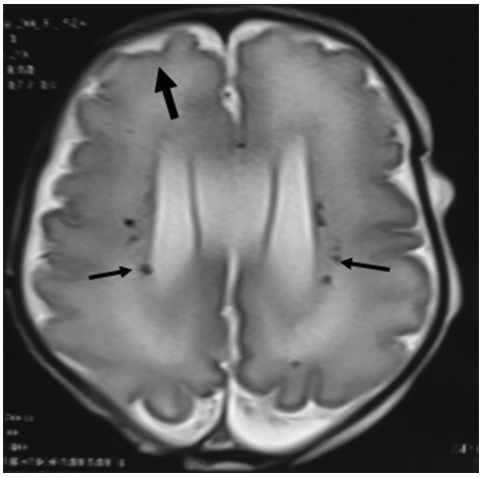

Figure 3: T2 weighted Magnetic Resonance Imaging (axial view) with hypodense peri-ventricular calcifications (thin arrows) and gyral simplification (thick arrows)

The paired ToRCH serology immunoglobulin (Ig) G and IgM for baby and mother was negative, as was the baby's urinary polymerase chain reaction for Cytomegalovirus. In view of the pseudo ToRCH presentation, the possibility of AGS was considered. Other differentials that were actively kept in view of the workup so far, included band-like calcification polymicrogyria syndrome (due to OCLN mutation), peroxisomal disorders, and mitochondrial cytopathies. A lumbar puncture was not done due to the thrombocytopenia. Genetic testing was planned. Clinical exome sequencing

revealed a homozygous single base pair insertion in exon 2 of the TREX1 gene (chr3:g. 48466711_48466712insG; depth: 213x). This results in a frame-shift and premature truncation of the protein 82 amino acids downstream to codon 20 (p. Glu20GlyfsTer82; ENST00000625293.3). The variant has been previously reported (c. 58_59insG) in a patient diagnosed as AGS.[2] It was planned to give the baby zidovudine (off-label use), but the baby expired.

Discussion

Initially a congenital infection was considered as the first differential, due to the combined presence of microcephaly, encephalopathy, intracerebral calcifications, and hepatosplenomegaly. Once the pseudo ToRCH clinical phenotype became apparent the differentials changed to AGS, Cockayne syndrome, hypoparathyroidism, pseudohypoparathyroidism, mitochondrial encephalopathies, biotinidase deficiency, and carbonic-anhydrase II deficiency.[3] Out of these a few were disregarded as they did not fit the clinical, biochemical and radiological profile. AGS was the top-most contender and was confirmed on genetic testing. Ocular manifestations like aniridia and congenital glaucoma have been described in AGS previously.[3] Diffuse, bilaterally symmetric corneal edema has never been reported before. We hypothesize that the corneal edema may result from immune-mediated inflammatory response, as has been reported in neonatal lupus presentation of AGS.[4]

The seven genes known to be associated with AGS include TREX1 (AGS1), RNASEH2A (AGS2), RNASEH2B (AGS3), RNASEH2C (AGS4), SAMHD1 (AGS5), ADAR1 (AGS6), and IFIH1 (AGS7).[5] Various genotype-phenotypes correlations have been described; prenatal-onset (TREX1, RNASEH2A, and RNASEH2C), classical/late infantile-onset (RNASEH2B, SAMHD1, and ADAR1), bilateral striatal necrosis (ADAR1), hereditary spastic paraparesis (ADAR1, IFIH1, and RNASEH2B), and SAMHD1-related cerebrovascular disease.[5,6] The "pseudo-ToRCH" phenotype forms a significant proportion (28%), with antenatal-onset in a smaller sub-group.[7] All these genes are involved in nucleic acid metabolism. Any mutation is associated with upregulation of INF which can be measured as INF level in the CSF or as expression of INF stimulated genes in the blood in response to retro-elements.[6] Most cases of AGS are autosomal-recessive. De-novo mutations occur in very few patients.

As AGS shows characteristics of both autoimmunity and auto-inflammation in response to retro-elements, targeted treatment options include immunomodulation by steroids, Azathioprine, Intra-venous Immune globulin, Anti-INF α antibody, and reverse transcriptase inhibitors (RTIs). Among anti-INF therapies, Janus Kinase (JAK1/2) inhibitor (Ruxolitinib) has shown promising results.[8]. A single-center pilot study demonstrated improvement in the INF scores in patients with AGS given a combination of three RTIs (Abacavir, Lamivudine, and Zidovudine) for 12 months.[9]

With rapid advances in understanding pathophysiology and potential therapeutic options, a high index of suspicion for AGS is needed in an infant manifesting with a "pseudo-ToRCH" presentation. Establishing the diagnosis by appropriate genetic testing helps to provide appropriate genetic counseling to the family, including recurrence risk and antenatal diagnosis in subsequent pregnancies.

Lessons learnt

- Aicardi-Goutières syndrome is a type 1 interferonopathy, that usually presents with late infantile onset encephalopathy and other multi-system manifestations
- A small proportion of affected babies exhibit "pseudo TORCH" presentation
- Bilateral congenital corneal oedema has not been described in Aicardi-Goutières syndrome before.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Atypical Mongolian Spots in an Infant: A Harbinger of Lysosomal Storage Disorders

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Abstract

Background: Atypical Mongolian spots are lesions that are aberrant in location (over the abdomen, back, legs, shoulders, or arms), extensive in distribution, persist beyond early infancy, and/or progressively increase in number. These are frequently associated with lysosomal storage disorders or neurocristopathies. **Clinical Description:** A 4-month-old girl presented with a common cold. Extensive aberrant Mongolian spots over the back, buttocks, lower limbs, and new onset grayish-blue macular spots over the abdomen prompted us to do a detailed evaluation to look for any underlying pathology. Other salient clinical findings included coarse facies, hepatomegaly, absence of significant developmental delay, bilateral macular cherry red spots, and ovoid-shaped vertebral bodies. The clinical phenotype was that of a lysosomal storage disorder possibly GM1 gangliosidosis. This was confirmed by deficient levels of ß-galactosidase. **Management:** The parents underwent genetic counseling. The infant was enrolled in an early intervention program. By the age of 6 months, the infant had not acquired any new developmental skills and new Mongolian spots did not develop. Subsequently, the family was lost to follow-up. **Conclusion:** Infants with aberrant Mongolian spots need to undergo an in-depth evaluation to identify underlying systemic disorders, even if they are asymptomatic. Diagnosis helps in providing supportive care to the child, specific therapy (if available) and the option of prenatal diagnosis in subsequent pregnancies.

Keywords: Atypical Mongolian spots, GM1 gangliosidosis, ß-galactosidase enzyme deficiency

Mongolian spots are congenital, hyperpigmented, nonblanching, and predominantly Grayish blue macules with irregular margins that may be observed in infants at birth or during the first few weeks of life.[1] Their typical distribution is over the lumbosacral and gluteal regions. Mongolian spots result from entrapment of melanocytes in the dermis due to arrested transdermal migration that normally occurs from the neural crest to the epidermis during embryogenesis. The lesions start disappearing naturally when these dermal melanocytes start getting enclosed by extracellular fibrous sheath. This starts *in utero* but is maximal during infancy.[2] Their prevalence varies according to ethnicity; being most common in Asians and Africans (90%–100%) 50% in Hispanics, and 10% in Caucasians.[3] Both sexes are equally affected.

Mongolian spots are considered atypical when they are aberrant in location (i.e., present on the upper back, face, legs, and chest); are extensive (i.e., display a generalized distribution);[4] are persistent (i.e., do not spontaneously disappear, but are present beyond infancy);[5] or are progressive (new lesions continue to appear beyond early infancy.[6] Atypical Mongolian spots have been reported in either lysosomal storage disorders, or neurocristopathies, a group of diseases caused by the abnormal generation, migration, or differentiation of neural crest cells [Table 1].

We report an infant with atypical Mongolian spots who was subsequently diagnosed with a lysosomal storage disorder. The infant was apparently asymptomatic, apart from the skin lesions, and was identified incidentally in a routine outpatient visit for some other innocuous complaint.

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Table 1: Conditions associated with atypical mongolian spots

Lysosomal storage disorders
Gm1 gangliosidosis
Mucopolysaccharidoses: Hunters disease and Hurler disease
Mucolipidosis type 1
Neimann pick disease
Mannosidosis
Neurocristopathies
A. Neurological disorders
Spinal dysraphism
Sjogren-larsson syndrome
Leptomeningeal melanocytoma
B. Phakomatosis pigmento vascularis
Struge weber syndrome
Non involuting congenital hemangioma
Klippel Trenaunay syndrome
Cutis marmorata telangiectatica congenita

Clinical Description

A 4-month-old girl presented with cough and coryza for 2 days. There was no respiratory distress, fever, rashes, loose motions, or vomiting. She was feeding well. She was born at term with a birth weight of 2.5 kg and had not required any resuscitation. There was no subsequent history of any hospitalization or outpatient visits besides for immunization. She was second in birth order to parents of third-degree consanguinity. There was no significant family history. The infant had still not achieved head holding, was unable to reach out for objects, could not vocalize, but had achieved social smile at 2 months and was able to recognize her mother. There was no history of loss of any acquired skills, seizures, stiffening or tightness of limbs, visual or hearing impairment.

The infant was active and displayed stable vitals. The weight was 6 kg (50th centile, −0.58 Z score), length 61 cm (between 15th and 50th centiles, −0.54 Z score), and head circumference was 42.5 cm (between 15th and 50th centiles, 1.48 Z score). General physical examination revealed coarse facial features with low set ears and a depressed nasal bridge [Figure 1]. Multiple, large irregularly shaped Mongolian spots were present on her back, buttocks [Figure 2], and ankle (that had apparently been present since birth). Multiple small bluish-green macules [Figure 3] were present on the abdomen and upper limbs (which, according to her mother were of recent onset). Her gums were soft with no lesions. The only salient abdominal finding was firm nontender hepatomegaly with a span of 8 cm. The respiratory and cardiovascular systems were normal. Cranial nerve examination was normal. There were no tone abnormalities, and reflexes were elicited normally. Developmental assessment confirmed partial neck holding, fixation and tracking, recognition of mother, and age-appropriate vision and hearing. The clinical phenotype was that of an infant with coarse facies, no developmental delay, hepatomegaly, atypical Mongolian spots, and a viral upper respiratory tract infection.

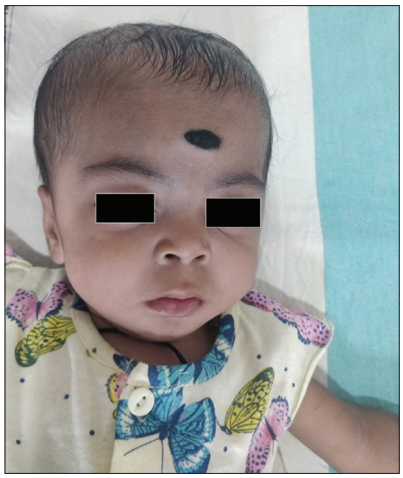

Figure 1: Depressed nasal bridge in the index child

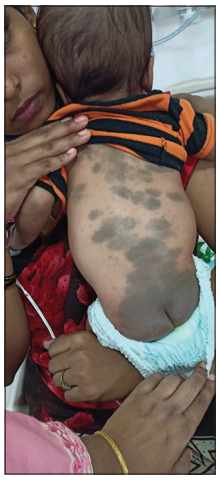

Figure 2: Multiple flat blue Gray ill-defined Mongolian spots involving back and gluteal region (size ranging from 2 cm to 20 cm)

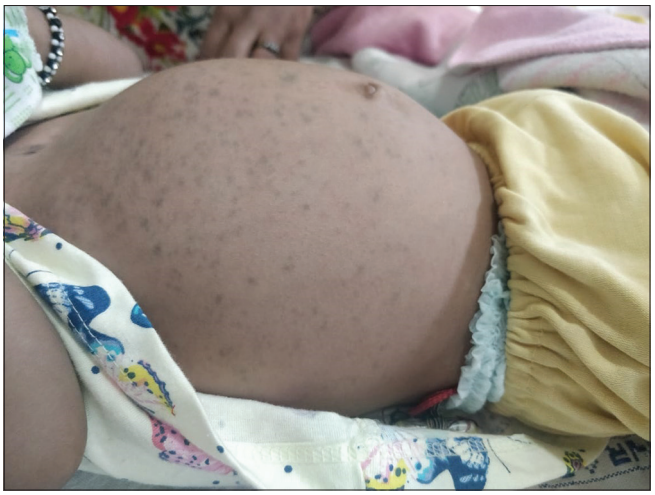

Figure 3: Multiple flat bluish macules measuring <0.5 cm on the abdomen which appeared 2 months after birth

Histopathology of the skin lesions showed mild pigmented melanophages scattered in the superficial and mid dermis, confirming Mongolian spots. Conditions presenting with atypical Mongolian spots were considered. The coarse facies prompted us to consider the possibility of lysosomal storage disorders. Ophthalmological examination identified bilateral cherry red spots, narrowing down the differentials to GM1 gangliosidosis, Neimann pick disease, and mucolipidosis. Brain stem-evoked auditory response was normal. Magnetic resonance imaging of the brain was also normal. Urinary glycosaminoglycan testing was negative, excluding mucopolysaccharidosis. The radiograph of the spine demonstrated atypical ovoid shaped thoracic vertebrae. The clinical phenotype of onset of symptoms within 6 months of age, plateauing of development (albeit currently no significant delay or hypotonia), coarse facies, hepatomegaly, cherry red spots, and vertebral anomalies was suggestive of GM1 gangliosidosis. An enzyme assay identified decreased ß-galactosidase levels, thus establishing the diagnosis of infantile onset GM1 gangliosidosis.

Management and outcome

The parents of the child underwent genetic counseling in which they parents were explained about the nature and course of the disease, associated prognosis, and role of prenatal testing in subsequent pregnancies. Although they were advised to get the mutational analysis, it could not be done due to financial constraints. The child was managed conservatively and enrolled in an early intervention program. By the age of 6 months, the infant had not acquired any new developmental skills and new Mongolian spots did not develop. Subsequently, the family was lost to follow-up.

Discussion

Atypical Mongolian spots may be the harbinger of many underlying storage disorders. Nerve growth factor (NGF) is an important factor for the transdermal migration of melanocytes. NGF acts on TrK protein, a tyrosine kinase receptor that is found on melanocytes. The metabolites that accumulate due to enzyme deficiencies in GM1 gangliosidosis and Hurler disease stimulate the activity of NGF by binding to TrK protein and result in the abnormal melanocyte migration.[1]

GM 1 gangliosidosis is a rare autosomal recessive neurodegenerative disorder with an incidence of 1 in 100000–1 in 200000 population.[7] It arises due to deficiency of the enzyme acid ß-galactosidase resulting from biallelic mutations of the GLB1 gene, located on chromosome 3p21.33i. The characteristic clinical features include developmental delay or neuroregression, macular cherry red spots, the hurler phenotype (coarse facial features, organomegaly, and dysostosis). Three forms are recognized; type 1 (infantile), type 2 (juvenile), and type 3 (adult type). The infantile form (as seen in our patient) is the most severe form with only 0.07%–1.3% of normal enzyme activity. It is associated with rapid progression, neuroregression, and death, commonly due to aspiration pneumonia and/or cardiomyopathy.[8] The juvenile form presents between 7 months and 3 years of age and has a relatively slower, although progressive course. Motor problems, muscle weakness, seizures, squint, lethargy, and easy susceptibility to infections are seen. The adult form manifests from 3 years of age to 30 years of age with progressive dementia, parkinsonism, and dystonia.[7] There is no specific management for this disorder, irrespective of subtype.

We have compiled the clinical manifestation of a few infants with GM 1 gangliosidosis who presented with extensive Mongolian spots and coarse facial features, as in our case [Table 2]. Other cutaneous manifestations that have been described in this disorder are angiokeratomas, eczematoid rashes, and ecchymoses, but are rare.[11] They were not seen in this case. This patient highlights the importance of keeping a high index of suspicion of other underlying disorders in patients with atypical Mongolian spots.

Lessons learnt

- Atypical Mongolian spots are lesions that are aberrant in location, extensive in distribution, persist beyond early infancy, and/or progressively increase in number
- These may indicate the presence of underlying lysosomal storage disorders or neurocristopathies
- Infants with atypical Mongolian spots should be carefully evaluated, even if they appear to be asymptomatic.

Table 2: Infants with GM1 gangliosidosis and atypical Mongolian spots

Source	Age/sex	Presenting feature	Coarse facies	Hepatomegaly	Cherry red spot	Dysostosis multiplex
Ashrafi *et al*., 2006[4]	12 months, male	Developmental delay	+	+	+	+
	15 months, male	Neuroregression	+	+	+	+
Draïss *et al*., 2009[7]	7 months, male	Lower respiratory tract infection (incidental)	+	+	_	_
Bersani *et al*., 2016[9]	8 months, male	Developmental delay	+	+	+	+
Kumar *et al*., 2016[8]	9 months, male	Developmental delay	+	NA	+	NA
Hackbart *et al*., 2013[10]	9 months, female	Developmental delay	+	+	+	NA

NA: Not available

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 identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Tubercular Sinonasal Mass: A Rare Cause of Recurrent Epistaxis

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Abstract

Background: Epistaxis is common in children. Almost 60% experience at least one episode by 10 years of age. Most are benign and self-resolving. Episodes that are severe, frequent, take longer to resolve, or unilateral should be investigated. Although extrapulmonary tuberculosis (TB) is common in children, presentation as a sinonasal mass is rare. **Clinical Description:** A 4-year-old girl presented with a history of recurrent, left-sided epistaxis for 2 months, with diffuse ipsilateral facial swelling for 2 weeks. There was a history of preceding oral swelling and weight loss. Nasal endoscopy revealed a friable left nasal mass. Imaging delineated an infiltrative, highly cellular lesion in the left maxillary sinus, infiltrating surrounding bone and extending into the left nasal cavity, jaw, and orbital floor. **Management:** Endoscopic biopsy was suggestive of noncaseating granulomatous lesion. Langerhans cell histiocytosis, granulomatosis with polyangiitis and microscopic polyangiitis, and malignancy were ruled out. Nucleic acid amplification tests and culture established microbiological diagnosis of primary sinonasal TB. Initiation of antitubercular therapy led to complete recovery. **Conclusion:** The diagnosis of sinonasal TB is challenging and requires multidisciplinary collaboration. Its rarity and nonspecific presentation requires a high index of suspicion by the treating team. Clinical, histopathological, and microbiological criteria should be used to establish a diagnosis. Primary sinonasal TB is a rare entity in young immunocompetent children.

Keywords: Epistaxis, extrapulmonary tuberculosis, sinonasal mass

Around 18 lakh cases of tuberculosis (TB) were notified in India in 2020, and out of these, around 5.7% were in children under 15 years of age.[1] Pulmonary TB is the most common presentation in children, while extrapulmonary TB occurs in 25%–35% of cases.[2] Among the latter, lymph nodes are the most common site. Epistaxis is common in children, with almost 60% of children experiencing at least one nasal bleed by 10 years of age.[3] The vast majority are benign, self-resolving, and do not require medical workup or intervention. Local causes such as trauma or mucosal irritation should be looked for. However, episodes that are more severe, frequent, take a longer time to resolve, or are unilateral should be investigated to exclude bleeding disorders, or pathological conditions such as tumors, granulomatous disorders, and vascular causes.

Nasal or sinonasal TB presenting as recurrent epistaxis has been described in children in scientific literature, but to the best of our knowledge, only 15 cases have been reported in the past two decades. Most are secondary, and primary sinonasal TB is rare.[4] We present a 4-year-old child with recurrent epistaxis due to primary sinonasal TB to increase sensitize about this rare entity among clinicians.

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Clinical Description

A 4-year-old immunized girl presented with recurrent, self-limiting episodes of nosebleeds from the left nostril for 2 months. The bleeding occurred spontaneously, was intermittent (every 7–10 days), of scant amount (around 10–15 drops per episode), increased on crying and bending forward, and got relieved by applying digital pressure on the nostrils. The child did not have a habit of picking her nose. There was no history of bleeding from other sites, easy bruising, bluish skin

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lesions, black stools, or progressive pallor. The episodes were not associated with fever or recurrent upper respiratory tract infections, symptoms suggestive of allergic rhinitis (excessive sneezing, nasal obstruction, or congestion), preceding nasal trauma, or use of nasal medications. Her parents had also observed a progressively increasing, diffuse, painless swelling over the left cheek for 2 weeks. It was insidious in onset, and associated with brown discoloration of the skin below her left eye. There was a history of significant weight loss; she had lost one kilogram (7%) over the past 3 months. There was a significant past history of having an oral swelling in the left upper jaw 6 months back, which was diagnosed as gingivitis by a dentist, and treated with oral antibiotics. There was no history of any contact with a case of TB. There was no history of any previous hospital admission. The family history was not contributory.

Management and outcome

On examination, the girl was hemodynamically stable and normotensive, with appropriate anthropometric parameters for age. Pallor was present. She had a diffuse, nontender, left maxillary swelling that resulted in a narrowed appearance of the left palpebral fissure [Figure 1, refer to cover page]. There was no significant lymphadenopathy, petechiae, or mucosal bleeds. Anterior rhinoscopy revealed reduced air blast and mucoid discharge on the left, with no active bleeding. The right-sided nasal cavity appeared normal. On direct nasal endoscopy, a diffuse, friable mass that bled on touch was seen emerging from the left maxillary ostium, completely blocking the left osteomeatal complex, and filling the middle meatus and left nasal cavity [Figure 2]. The medial wall of the maxilla bulged inside the nasal cavity causing medialization of the middle turbinate. No mass was seen in the nasopharynx and the nasal septum was in midline. Bulging of the gums was noted behind the left upper molars on examination of the oral cavity. The ophthalmological and systemic examination was unremarkable.

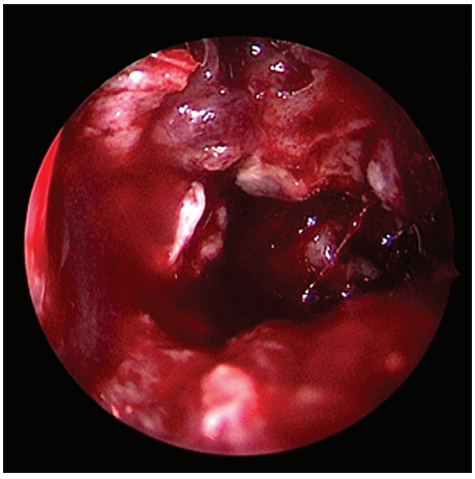

Figure 2: A diffuse, firm, friable mass coming from the left maxillary ostium, completely blocking left osteomeatal complex, filling middle meatus and left nasal cavity, on direct nasal endoscopy

On preliminary investigation, she was found to have hemoglobin of 6.6 g/dl, total leukocyte count of 11,400/mm^3, platelet count of 4.8 lakhs/mm^3, and microcytic hypochromic anemia. The coagulation profile was also normal. Computed tomography scan of the head and neck revealed a large soft tissue mass, completely opacifying the left maxillary sinus and destroying the surrounding bones. The mass was found to extend into the nasal cavity, with associated mucosal thickening and opacification of the ipsilateral ethmoid air cells. The radiological differentials given were a neoplasm or Langerhans cell histiocytosis (LCH). MRI of the paranasal sinuses was planned for a more detailed anatomical delineation. This showed an expansile, infiltrative, highly cellular lesion epicentered in the left maxillary sinus that extended into the left nasal cavity and infiltrated the maxillary bone (anteriorly), left ethmoid sinus (superomedially), and soft tissue in the left maxillary alveolar process (infero-anteriorly). The lesion encased the left upper premolars and canine causing bulging on the left orbital floor, and also encased the left infraorbital vessels, sparing the lamina papyracea, nasal septum, and orbital contents [Figure 3].

Endoscopic tissue biopsy from the left maxillary mass was performed under general anesthesia. This revealed noncaseating granulomas composed of histiocytes and multinucleated giant cells with entrapped bony fragments. Ziehl–Neelsen (ZN), Periodic acid–Schiff (PAS), and Grocott methenamine silver stains did not reveal any organisms. No lytic lesions were found in radiographs of the skull, ribs, vertebrae, or long bones. Immunohistochemistry performed to rule out LCH was positive for CD68 (histiocytes) and negative for S100 and CD1a. Serum angiotensin-converting enzyme levels were normal (45 U/L). Antineutrophil cytoplasmic antibodies (ANCA) – diffuse cytoplasmic (c-ANCA) and perinuclear (p-ANCA) – were negative by immunofluorescence assay, thus ruling out granulomatosis with polyangiitis and microscopic polyangiitis. The tuberculin skin test was strongly positive (27 mm induration at 48 h), but the chest radiograph and abdominal ultrasound were normal. An endoscopic excision

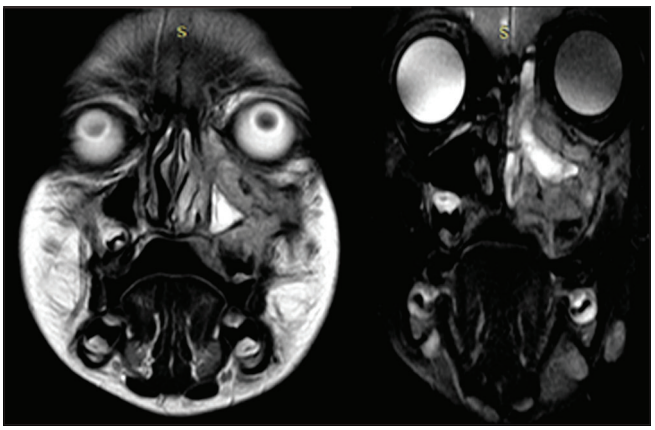

Figure 3: T1- and T2-weighted coronal magnetic resonance images showing ill-defined expansile lesion involving (L) maxillary sinus and adjacent structure, with no involvement of infraorbital region or intracranial extension

Table 1: Cases of nasal tuberculosis cases in children (circa 2000 onward)

First author, year	Age and gender	Clinical findings
Batra *et al*., 2002	11 years, boy	Nasal mass with epistaxis
Kim *et al*., 2006	17 years, girl	Ulcerative lesion on nasal septum
Dixit *et al*., 2008	10 years, girl	Ulcerative lesion on nasal septum
Tampi *et al*., 2009	17 years, boy	Polypoidal nasal mass
Singh *et al*., 2010	4 years. girl	Proliferative nasal mass
Thakur *et al*., 2011	12 years, girl	Ulcerative lesion on nasal septum
Etuwewe 2011	12 years, boy	Ulcerative lesion on nasal septum
Gupta *et al*., 2015	12 years, girl	Polypoidal nasal mass
Gupta *et al*., 2015	12 years, girl	Polypoidal nasal mass
Gupta *et al*., 2015	12 years, girl	Polypoidal nasal mass
Murat *et al*., 2016	10 years, girl	Ulcerative lesion in nose
Swain *et al*., 2017	16 years, girl	Ulcerative lesion on nasal septum
Raid *et al*., 2018	14 years, girl	Ulcerative lesion on nasal septum

biopsy of the lesion was undertaken but did not reveal anything different. However, the Xpert MTB/RIF Ultra for *Mycobacterium tuberculosis* was positive on the endoscopic tissue biopsy specimen (and incidentally also on the gastric aspirate), sensitive to rifampicin. Rapid mycobacterium culture (automated fluorescent MALDI-TOF-MS) grew *M. tuberculosis* complex, sensitive to first-line antitubercular treatment (ATT). HIV serology was nonreactive, and blood sugar profile was normal.

The final diagnosis was extrapulmonary primary sinonasal TB. ATT was initiated,[3] on which there was a gradual resolution of the facial and nasal swelling, with cessation of epistaxis within a month. After completing 6 months of ATT, the child was thriving with resolution of symptoms, and adequate weight gain.

Discussion

Sinonasal tumors are rare in children. They may be congenital (i.e., glioma and teratoma), benign (i.e., polyp, papilloma, hemangioma, or leiomyomas), or malignant (non-Hodgkin's lymphoma, rhabdomyosarcoma, or squamous cell carcinoma). Most malignancies present as rapidly growing nasal masses that manifest with recurrent epistaxis, deformities of the nose and cheek, weight loss, and constitutional symptoms.

Sinonasal TB presents with features of rhinosinusitis and has three subtypes: i) mucosal (the most common type) – presenting as a mucosal polyp with scanty purulent discharge; ii) bony – leading to fistula formation and development of a mid-facial defect; and iii) hyperplastic – causing granuloma formation and mimicking malignancy.[5,6] Our patient had overlapping features of both bony and hyperplastic subtypes. An exhaustive literature search identified 13 cases of nasal TB in children from 2000 onward, the details of which are given in Table 1. Only two cases of sinonasal TB were identified in addition to this one: a 15-year-old girl with a proliferative maxillary mass[7] and a 5-year-old boy presenting with sinusitis.[8]

The diagnosis of sinonasal TB is challenging. Its rarity and nonspecific presentation requires a high index of suspicion. Beltran *et al*.[9] proposed the following diagnostic criterion: (i) absence of clinical response to antibiotics; (ii) caseous granulomatosis on histopathology; and iii) identification of *M. tuberculosis* by polymerase chain reaction (PCR) assay, confirmation by culture, and response to ATT. Histologically, both caseating and noncaseating granulomas have been described. In our case, the granuloma was noncaseating and ZN staining was negative, but PCR assay was positive, the culture was confirmatory, and there was good response to medical management. Surgical excision and reconstruction are rarely required in cases with severe disfigurement.

Lessons learnt

- Epistaxis is common in children with almost 60% of children experiencing at least one nasal bleed by 10 years of age.
- Episodes of epistaxis that that are severe, frequent, take a longer time to resolve, or are unilateral should be investigated.
- Sinonasal tuberculosis, though rare, should be considered as a differential for recurrent epistaxis, especially in an endemic country like India.

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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Linezolid-Induced Ringed Sideroblastic Anemia and Thrombocytopenia in a Child with Extensively Drug-Resistant Tuberculosis

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Abstract

Background: With the ever-evolving guidelines and changing drug regimens for pediatric tuberculosis (TB), it is paramount for treating physicians to understand the efficacy and safety profiles of the drugs being used. Linezolid is included in the treatment of multidrug-resistant and extensively drug-resistant (XDR) TB in the intensive, as well as continuation phases. **Clinical Description:** A 12-year-old child with XDR central nervous system TB was treated with second- and third-line anti-tubercular drugs including linezolid. Three weeks after therapy started the boy presented with progressive pallor for a week, lethargy for few days, and rapid breathing since that morning. He was severely pale, acidotic, and in hypotensive shock. Investigations revealed severe anemia, thrombocytopenia, reticulocytopenia, normal liver and renal function, and no evidence of sepsis. He also had severe metabolic acidosis and hyperlactatemia. **Management:** The child was mechanically ventilated and administered red blood cell and platelet transfusions. The presence of ringed sideroblasts in the bone marrow confirmed acquired sideroblastic anemia. The clinical, hematological, and metabolic toxicities were considered most likely due to linezolid. It was discontinued and his drug regime was modified. There was a rapid symptomatic improvement with supportive therapy and gradual increase in hematological parameters with cessation of linezolid. **Conclusions:** Clinicians are used to treating Gram-positive infections with short courses of linezolid. Regular and planned monitoring is required when linezolid is used at higher doses and longer durations.

Keywords: Linezolid, ring sideroblasts, sideroblastic anemia, extensively drug resistant tuberculosis

The burden of pediatric multi-drug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) has been recognized as a major public health concern in India. While diagnosing drug-resistant TB is challenging and requires costly laboratory services, access to effective treatment of these conditions is also sometimes difficult. Establishing drug-resistant TB therapeutic regimens is arduous with several of the available drugs being expensive and toxic, and their efficacy uncertain.[1] Efforts have been made towards exploring the role of additional drugs and regimens.

Linezolid, the first oxazolidinone to be developed and approved for clinical use, has emerged as a viable option for the treatment of resistant TB.[2] It is active against a range of bacteria, especially aerobic Gram-positive drug-resistant organisms, such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*. and penicillin-resistant pneumococci.[2] After initially being included in "Group 5 drugs" of the World Health Organization treatment guidelines of MDR-TB (i.e., has unclear efficacy, or unclear role), it was upgraded to "Group A" (Fluoroquinolones) in the 2018 New classification of antitubercular therapy (ATT) reserved for MDR and XDR-TB,[3] with caution for close monitoring of adverse events. A variety of dosing strategies have been used for linezolid for drug-resistant TB,[3] and most treatment durations are long.

Though hematological and nonhematological adverse events are common following prolonged Linelozid use, the occurrence

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of sideroblastic anemia is rare.[4] We report a patient with XDR-TB on second- and third-line ATT who developed ringed sideroblastic anemia with thrombocytopenia following prolonged linezolid therapy.

Clinical Description

A 12-year-old boy, presented with multiple episodes of generalized tonic-clonic seizures for a day. There was no history of fever, vomiting, loose motions, preceding trauma, or ingestion of any drugs or other substances. There was no history of any altered or loss of consciousness, severe headache, projectile vomiting, abnormal posturing, or any recent unusual change in behavior, temperament, or sleep pattern. The child had a significant history of receiving chemotherapy and a stem cell transplant for Hodgkin's lymphoma 2 years earlier. There was no history of Koch's contact or epilepsy in the family. The child was completely immunized.

At admission, the child was afebrile with normal blood pressure and other vital parameters. He was underweight with a body mass index of 17.1 kg/m^2. There was no pallor, jaundice, rashes, petechiae, or significant lymphadenopathy. The sensorium was normal. No papilledema was detected in the fundus. There were no cranial or focal neurological deficits or meningeal signs. Plantar reflexes were flexor. The respiratory system was normal and there was no hepatosplenomegaly. Routine investigations were performed to rule of common causes of seizures. The blood sugar, serum electrolytes, liver, and kidney function tests were within normal limits. The hemogram was not suggestive of an acute bacterial infection. Normal platelet counts and coagulation profile ruled out risk factors for an intracranial bleed. At this point, given the background of the lymphoma and a possible immunosuppressed state postchemotherapy, two other differentials were considered; relapse of the malignancy or an indolent infection, involving the brain.

Management and outcome

Magnetic resonance imaging of the brain revealed communicating hydrocephalus with periventricular ooze, suggestive of tubercular meningitis. He was treated with anti-convulsant drugs (intravenous [IV] Leveracetam and Fosphenytoin), hyperosmolar therapy, and other neuroprotective measures. Pleocytosis and elevated proteins were reported in the cerebrospinal fluid. No acid-fast bacilli were detected in the sputum and the chest radiograph was normal. First-line ATT was started with pyridoxine considering central nervous system (CNS) TB. The human immunodeficiency virus status was nonreactive. Subsequently, the nucleic acid amplification test was positive for XDR-TB, and the diagnosis was modified to XDR CNS TB.

ATT was changed to second- and third-line drugs as per standard guidelines; pyrazinamide, cycloserine, clofazimine, ethionamide, and meropenem. After 3 weeks, the mycobacteria growth indicator tube culture report became available, demonstrating resistance to pyrazinamide. Hence, it was omitted and linezolid was added (600 mg twice a day) instead. The child underwent a ventriculoperitoneal shunt insertion in the 4th week, and was discharged within 7 days. The family was counseled regarding ATT and the need for close follow-up.

After 3 weeks he returned with progressive pallor for a week, lethargy for a few days, and fast breathing since that morning. There was no history of any fever, bleed from any site, seizures, headache, vomiting, diarrhea, or abdominal pain. At admission, he had tachypnea (acidotic breathing) and features of hypotensive shock (tachycardia, bounding pulses, and blood pressures <5th percentile for age). The child was severely pale, but there was no icterus, or signs of cutaneous bleeds. There was no evidence of congestive heart failure or any other salient findings on the systemic examination.

A clinical diagnosis of severe anemia in acute respiratory failure with hypotensive shock was kept. Severe metabolic acidosis and high levels of lactate were detected on arterial blood gas analysis. The child was started on IV fluids with adrenaline infusion and electively ventilated. Salient hemogram findings were hemoglobin (Hb) of 2.8 g/dl, mean corpuscular volume 81 fL normal total leukocyte counts, platelets 25,000/cmm, and reticulocyte count 0.5%. The peripheral blood smear showed predominantly normocytic normochromic erythrocytes, absence of hemolysis. Direct Coomb's test was negative. Blood sugar, serum electrolytes, liver, and renal function tests were normal. Biomarkers for infection and cultures were negative. The child was transfused with 2 units of packed cell volume (PCV). Once he became symptomatically better, ventilation was discontinued.

Bone marrow aspiration was done [Figure 1a-d], considering the possibility of drug-induced myelosuppression. The erythroid series showed relative hyperplasia with normoblastic erythropoiesis, and a few macronormoblasts displaying features

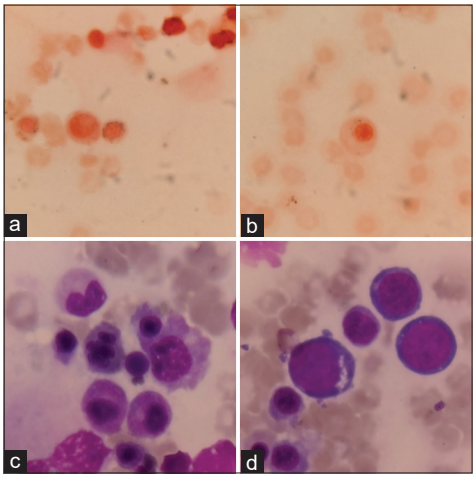

Figure 1: (a and b) Pearls Prussian blue stain showing many ringed sideroblasts (c and d) relative erythroid hyperplasia with normoblastic erythropoiesis. Few macronormoblasts are seen with features of dyserythropoiesis in the form of irregular nuclear contours, bilobed nuclei, karryorhexsis, and nuclear budding

of dyserythropoesis. Ring sideroblasts were present. The myeloid series showed normal maturation, whereas megakaryocytes were reduced. The most likely candidate was linezolid, given the combination of sideroblastic anemia, thrombocytopenia, metabolic acidosis, and elevated lactates, all known associations with its therapy. Linezolid was stopped and oral clofazimine, cycloserine, ethambutol and clarithromycin were continued. The child received another PCV transfusion and platelet transfusion. Over the next 2 weeks, serial hemograms demonstrated an increasing trend in the levels of Hb and platelet counts. Though isoniazid (INH) and cycloserine can also cause sideroblastic anemia,[5] we did not consider them seriously as the duration of INH had been brief, and hematological parameters improved despite continuing cycloserine. Thus, the final diagnosis was Linelozid induced sideroblastic anemia and thrombocytopenia. He was discharged on the revised ATT. A month afterward the Hb had increased to 9.6 g/dl and platelet count to 1.2 lakhs/cmm.

Discussion

Sideroblastic anemias are a heterogeneous group of disorders characterized by ring sideroblasts in the bone marrow and impaired heme biosynthesis.[5] The ring sideroblast is a pathological erythroid precursor that contains excessive deposits of nonheme iron in the mitochondria. These cells are identified on Prussian blue staining of the bone marrow aspirate, in which bluish-green inclusions (siderosomes) can be seen as a "ring" around the nucleus.[6] Sideroblastic anemia may be secondary to alcohol, drugs (i.e., chloramphenicol, pyrazinamide, D-penicillamine, and progesterone), toxins (arsenic and lead), nutritional deficiencies (copper and pyridoxine), myelodysplastic syndrome, or idiopathic in origin.[5]

With the increasing burden of XDR-TB in low- and middle-income countries, several new treatment options are being explored. Since the duration of treatment is longer than first-line ATT, the safety and tolerability of these require thorough investigation. The National TB Elimination Program prescribes Linezolid in MDR, as well as XDR-TB, in both intensive and continuation phases.[7] It has been recognized as a promising drug.[8] However, there are reports of variation in safety profiles related to dosage and duration of therapy.[9] The spectrum of adverse effects is hematological (anemia, leukopenia, and thrombocytopenia), neurological and gastrointestinal.

The anti-bacterial mechanism of action of Linezolid is the disruption of protein synthesis by the binding of the drug to the 70S initiation complexes in the bacterial ribosomes. However, the same mechanism also allows it to bind to human mitochondria and inhibit protein synthesis, resulting in its toxicity.[3] Ring sideroblasts develop due to abnormal intracellular iron metabolism with deposition within the mitochondria. Thrombocytopenia is attributed to the suppression of the final step of platelet release from mature megakaryocytes, as well as immune-mediated platelet destruction.[10] The mainstay of treatment is the withdrawal of the drug and supportive therapy.

Clinicians are used to treating Gram-positive infections with short courses of linezolid. Regular and planned monitoring is required when linezolid is used at higher doses and longer durations. When this drug is used in ATT, the treating physician should be aware of its side effects, tell parents about warning signs and regularly monitor clinical, hematological, and metabolic parameters for early detection to avoid life-threatening situations.

Lessons learnt

- Management of multidrug resistant and extensively drug resistant tuberculosis in children requires an in-depth understanding of drug related adverse effects as well as drug interactions
- Linezolid, though safe for use in hospitalized children requiring short-term therapy, its long-term use requires close monitoring of clinical, hematological and metabolic adverse effects
- Linezolid can cause a potentially life threatening acquired sideroblastic anemia and thrombocytopenia in children on long-term treatment with higher doses; both of which are reversible after cessation of the drug.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Permanent Neonatal Diabetes Mellitus in an Indian Infant Due to a Novel Mutation in the Glucokinase Gene

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Abstract

Background: Neonatal diabetes mellitus (NDM) is a rare condition, usually genetic in etiology, that presents with hyperglycemia requiring insulin within the first 6 months of life. Most cases of permanent NDM are caused by mutations in the KCNJ11 or ABCC8 gene, which are involved in the potassium adenosine triphosphate channels. **Clinical Description:** A 1.88 kg female infant product of a consanguineous marriage was delivered at term by cesarean section for oligohydramnios and intrauterine growth retardation. There was a strong family history of DM involving the mother, father, and grandparents. Clinical examination was normal. Routine blood sugar monitoring identified hyperglycemia at 1 and 3 h. There was no clinical or laboratory evidence of sepsis. **Management:** Persistent hyperglycemia continued that necessitated the administration of insulin from the 1st day onward. The abdominal ultrasonogram was normal. C-peptide was low, indicating poor endogenous insulin production. Genetic analysis revealed a novel mutation in the glucokinase (GCK) gene (p. Glu178Asp). A brief trial of sulfonylureas (glibenclamide) was ineffective. The infant attained control, although with considerable difficulty, on a mixture of NPH and long-acting insulin. After 5 months of follow-up, she is thriving well. **Conclusion:** GCK mutation is a rare but important cause of NDM. To the best of our knowledge, this is the first Indian infant to be reported with a GCK gene mutation.

Keywords: Glucokinase mutation, intrauterine growth retardation, neonatal diabetes

Neonatal diabetes mellitus (NDM) is defined as insulin-requiring hyperglycemia within the first 6 months of life, and is usually associated with intrauterine growth restriction and low birth weight.[1] NDM and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes, i.e., DM resulting from a mutation or mutations in a single gene.[2] NDM can either be transient (TNDM) or permanent (PNDM). The majority of cases are TNDM, which resolve within a median of 18 months, and mostly (70%) are due to mutations in chromosome 6q24.[3] In contrast, almost 40% of PNDM are caused by mutations in the gene encoding the Kir6.2 subunit of the adenosine triphosphate (ATP)-sensitive potassium channel (KCNJ11).[4] The most common gene mutation reported in an Indian case series was the ABCC8 mutation.[5] Other reported mutations are in the genes encoding insulin promoter factor-1 (IPF1) and glucokinase (GCK).[6] GCK is a key regulator of glucose metabolism in pancreatic beta cells, and homozygous inactivating GCK mutations result in a complete deficiency of the glycolytic enzyme.

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We report a case of PNDM that was due to a novel mutation (Glu178Asp) in the GCK gene. To the best of our knowledge, this is the first Indian infant with a GCK gene mutation.

Clinical Description

A full-term female baby, product of a third-degree consanguineous union, was born to a 25-year-old primigravida by elective cesarean section under spinal anesthesia. The indications were oligohydramnios and intrauterine growth retardation (IUGR), as identified by ultrasonography. There

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were no maternal or environmental risk factors for sepsis immediately preceding the delivery. The antenatal period had been uneventful, except that the mother had contracted COVID-19 infection during the second trimester, which resolved with no major medical issues requiring hospitalization. In addition, the mother had been diagnosed with diabetes just before she conceived and required insulin throughout her pregnancy. Her blood sugars were well controlled with the last trimester HbA1c of 6%. There was no history suggestive of polyhydramnios. The baby's weight was 1880 g and the Apgar score was 8 and 9 at 1 and 5 min, respectively. The family history was significant [Figure 1]. The father also had DM, having been diagnosed at the age of 28 years, and on oral hypoglycemic agents for 3 years. The paternal grandmother and maternal grandfather, who were siblings, were also diabetic.

On examination, the baby was small for gestational age (SGA) with a birth weight of 1880 g (0.28 centile), length 45 cm (5.99 centile), and head circumference of 31 cm (0.94 centile). A Ponderal Index of 2.06 was indicative of symmetric IUGR. Vitals were stable, there were no apparent congenital malformations, and the systemic examination was normal. Breastfeeding was initiated successfully, and the baby was roomed in with her mother. Blood sugar monitoring was initiated as per hospital protocol for babies born to diabetic mother, and found to be >200 mg/dl, at 1 and 3 h.

Management and outcome

The causes that were considered for hyperglycemia were transient insulin deficiency commonly seen in SGA babies and the possibility of stress hyperglycemia due to unrecognized early-onset neonatal sepsis. The baby was shifted to the neonatal intensive care unit, where a sepsis screen and blood culture were sent, the baby was started on empirical antibiotics and intravenous 5% dextrose. The sepsis screen was negative. Hyperglycemia persisted throughout the 1st day of life, with venous values as high as 320 mg/dL, despite being on a glucose infusion rate of only 2.1 mg/kg/min. There was no acidosis, and the urinary ketones were negative. This prompted us to start an insulin infusion with rates adjusted according to the blood glucose levels. The baby became euglycemic at 0.04 IU/kg/h. Nasogastric milk feeds were started on the 2nd day and breastfeeding on the 3rd day (Hence the insulin requirement increased). Investigations were proceeding simultaneously. The abdominal ultrasound revealed a normal size pancreas, whereas the C-peptide levels for assessing pancreatic β cell function were low, 0.39 ng/ml (normal: 1.1–4.4 ng/mL). Further management was planned in consultation with a pediatric endocrinologist. The infant was gradually shifted from regular insulin to NPH insulin infusion and discharged on twice-daily injections (2 IU/kg/day), after being advised regarding regular blood sugar monitoring and home care.

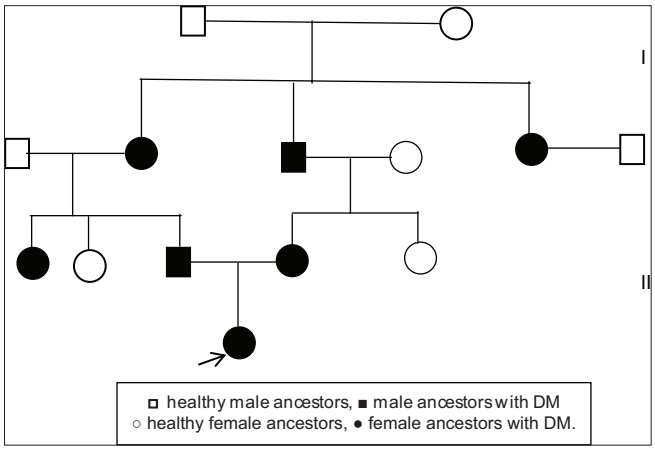

Figure 1: Three-generation pedigree chart of the index case

In view of the significant family history, consanguinity, and persistent hyperglycemia, a gene panel for MODY and neonatal diabetes was sent. This revealed a homozygous missense variation in exon 5 of the GCK gene (chr7:g.44189616T>G; depth: 562x), which lies in the hexokinase domain of the GCK protein. It is known to result in amino acid substitution of aspartic acid for glutamic acid at codon 178 (p. Glu178Asp). The mutation is autosomal recessive in inheritance and is associated with permanent neonatal diabetes. The parental genetic study was not done despite counseling due to financial restraints. The final diagnosis was NDM due to a mutation in the GCK gene.

The baby has been on regular follow-up since discharge. Initially, domiciliary blood sugar monitoring revealed intermittent hyperglycemia, despite the high dose of NPH insulin. Therefore, it was decided to give the baby a trial of a concurrent oral sulfonylurea (glibenclamide at 0.5 mg/kg/day). However, this proved to be ineffective in achieving good control. Finally, a long-acting insulin, Levemir (insulin detemir), was added at 3 months. Currently, she is 5 months old, weighs 6 kg, and is more or less maintaining normal blood sugar levels on this regime. There are a few areas of lipodystrophy at the injection sites. She has attained age-appropriate developmental milestones and her neurodevelopment examination is normal.

Discussion

Only a few cases of GCK-PNDM had been described globally. An exhaustive literature search could not identify any Indian case report with a GCK mutation. GCK is a key regulatory enzyme in glycolysis in the pancreatic beta-cell. It forms the rate-limiting step in glycolysis because of its low affinity for glucose and lack of feedback inhibition from its product, glucose-6-phosphate. This allows GCK to function as a glucose sensor, and control insulin release. Availability of excess glucose produces excess ATP, which causes closure of ATP-sensitive potassium channel (K-ATP). Closure of these channel causes membrane depolarization and calcium influx which, in turn, cause insulin secretion.[7] In cases of GCK mutation, though the K-ATP channel is normal, there is defective glucose sensing, resulting in insufficient ATP generation and nonclosure of the K-ATP channel. As GCK

controls insulin release, homozygous inactivating GCK mutations result in a more severe phenotype, presenting at birth as PNDM. Heterozygous inactivating mutations of the GCK gene are associated with GCK-MODY, also known as MODY2. Defective glucose sensing results in a higher set point for glucose homeostasis, causing mild, asymptomatic fasting hyperglycemia. In people with GCK-MODY, the prevalence of macrovascular complications is probably similar to that in the general population, and they do not develop significant microvascular complications even after long-standing mild hyperglycemia. Heterozygous activating GCK mutations have been associated with hypoglycemia. Therefore, identification of a GCK mutation has implications in the clinical course and clinical management of the disorder.[7] The severity of diabetes is directly related to the functional severity of the GCK mutation. Some mutations like that of R397 L result in a less severe phenotype that may respond well to sulphonylureas, whereas some mutations (i.e., of T228M) show less improvement.[6] In our case, sulfonylurea did not prove beneficial for the short duration for which it was given. Thus, besides the routine aspects of genetic counseling, establishing a genetic diagnosis in patients with PNDM is important for directing the course of pharmaceutical management.

Lessons learnt

- Multigenerational history of diabetes can be suggestive of a monogenic etiology
- Homozygous missense variation in exon 5 of the GCK gene (chr7:g.44189616T>G; Depth: ×562), which results in amino acid substitution of aspartic acid for glutamic acid at codon 178 (p.Glu178Asp) causes permanent neonatal diabetes mellitus
- This genotype did not respond to a trial of sulfonylureas in this infant.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Acute Intravascular Hemolysis in the Critical Phase of Severe Dengue

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Abstract

Background: Dengue and severe dengue have various hemorrhagic manifestations ranging from mild presentations such as petechiae, bleeding from injection sites, ecchymosis, and gum bleeding to severe presentations like major mucosal bleeding such as hematemesis, melena, menorrhagia, and concealed internal bleeding. Common causes of anemia in dengue are due to blood loss (secondary to thrombocytopenia and/or coagulopathy), transient suppression of the bone marrow, and rarely, hemolytic anemia. **Clinical Description:** We describe a 5-year-old boy who presented to us in the critical phase of severe dengue with features of capillary leakage and cola-colored urine. Salient investigation reports were anemia, thrombocytopenia, normal reticulocyte count, absence of coagulopathy, indirect hyperbilirubinemia, deranged transaminase, highly elevated lactate dehydrogenase, and low haptoglobin levels, and hemoglobinuria, suggestive of acute intravascular hemolysis (AIVH). Autoimmune and microangiopathic hemolytic anemia, malaria, ingestion of dyes, snake bite, Glucose 6 phosphate dehydrogenase deficiency, and incompatible blood transfusions were excluded. Thus, the final diagnosis was severe dengue with hemolytic anemia and AIVH. **Management:** Oxygen delivery by the Heated Humidified High-Flow Nasal Cannula, strict input/output charting, appropriate fluid therapy, and diuretic infusion were the mainstays of management in an intensive setting. The aim was to maintain ventilation, perfusion, balance hydration, achieve optimal urine output and prevent fluid overload. **Conclusion:** Clinicians should consider Dengue as a possible cause for AIVH in children with severe dengue and cola-colored urine.

Keywords: Acute Intravascular hemolysis, dengue fever, hemolytic anemia

Dengue is a common viral infection caused by four serotypes of the Flaviviridae family (DENV 1, DENV 2, DENV 3, and DENV 4). Affected individuals may be asymptomatic or exhibit a diverse range of multi-systemic clinical manifestations and complications.[1] The World Health Organization classifies the illness as "Dengue (with or without warning signs)" and "Severe dengue." The latter encompasses potentially lethal complications, due to plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment (hepatic, cardiac, or central nervous system). After an incubation period of 5–7 days, the course of illness comprises three sequential phases: A febrile phase (that may be biphasic and last for 2–7 days), a critical phase (starting with defervescence and lasting for 24–48 h), and a convalescent phase.

Hematological manifestations are common due to the existing thrombocytopenia and coagulopathy. These include petechiae, mucosal bleeds, hematoma formation, and severe bleeding manifestations such as hematemesis, melena, or intracranial bleeds.[2] Thus, anemia in dengue can result from blood loss or transient bone marrow suppression. There have been rare reports of adults presenting with hemolytic anemia,[3-7] but hardly in children/adolescents. After a literature search, we could identify a single description of acute intravascular hemolysis (AIVH) in a 17-year-old Sri Lankan boy in the febrile phase of dengue.[8]

We report a case of AIVH noted in the critical phase in a much younger boy. To the best of our knowledge, this has not been reported earlier from India.

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Clinical Description

A 5-year-old previously healthy, boy presented with high-grade fever for 6 days, associated with generalized malaise. On the 1st day of the fever, his parents had consulted a primary care physician who had prescribed some oral medication, the details of which were not available. On the 3rd day of fever, he developed loose watery stools and nonprojectile, nonbilious, vomiting. His oral intake became poor, though the frequency of urine output was unchanged, and color was normal. There was no difficulty in breathing, bleeding from any site, or rashes. The child was hospitalized and diagnosed and managed as severe dengue, based on a positive dengue Non-Structural Antigen 1 report with anemia, thrombocytopenia, and deranged liver function tests. He developed respiratory distress on the 6th day of fever, requiring oxygen support. He was referred to our center on day 6 for further management.

At presentation, the patient was afebrile, conscious, and alert. The heart rate was 54/min (sinus rhythm); respiratory rate 54/min with the use of accessory muscles of respiration; and noninvasive blood pressure recorded as 103/70 mm Hg (right arm supine position). Pallor and icterus were present. There were no skin rashes or lymphadenopathy. His weight was 15 kg (10th centile for age), height 109 cm (25th centile for age), and weight for height at 25th centile for age. Salient systemic examination findings were decreased air entry in both lung fields with no additional breath sounds, and soft hepatomegaly with a liver span of 8 cm. Dark cola-colored urine was observed on Foley's catheterization [Figure 1]. On retrospective history taking, we were unable to elicit recent travel, recurrent abdominal pain, ingestion of any substance, food, or medicine containing dyes known to change urinary color (other than those prescribed on the 1st day, though 6 days had elapsed). There was no history of any recent blood transfusion or surgery.

Investigations confirmed anemia, thrombocytopenia, hepatitis [Table 1], and a normal coagulation profile. A very high level of Lactate dehydrogenase (LDH), presence of 3–5 red blood cells/high power field (RBCs/HPF) on urine microscopy, and hemoglobin on urine spectrophotometry were indicative of hemolytic anemia secondary to AIVH. Further workup showed a normal reticulocyte count (1%), low serum haptoglobin levels (<30 mg/dl, normal range 40–280 mg/dl), and negative direct and indirect Coomb's test. Malaria was excluded by peripheral smear and rapid malaria antigen test. The qualitative test for Glucose 6 phosphate dehydrogenase (G6PD) was normal. No abnormal cells or evidence of agglutination was seen in the peripheral blood smear. The trend of salient hematological reports after admission is given in Table 1. The chest X-ray showed bilateral pleural effusion, whereas an abdominal ultrasound detected free fluid in the abdominal cavity. Serological tests for Hepatitis A and Hepatitis E were negative.

Management and outcome

The child was managed in the Pediatric Intensive Care Unit (for severe respiratory distress due to fluid overload. He was started on oxygen delivery by Heated Humidified High Flow Nasal Cannula (HHHFNC) and maintenance intravenous fluids. The amount of fluid was decided according to clinical assessment and urine output, the aim being the prevention of hemoconcentration (due to dengue) and renal shut down (due to intravascular hemolysis). Furosemide infusion (0.05 mg/kg/hour) was administered to induce diuresis and prevent acute kidney injury (AKI) due to hemoglobinuria. Renal parameters were monitored daily

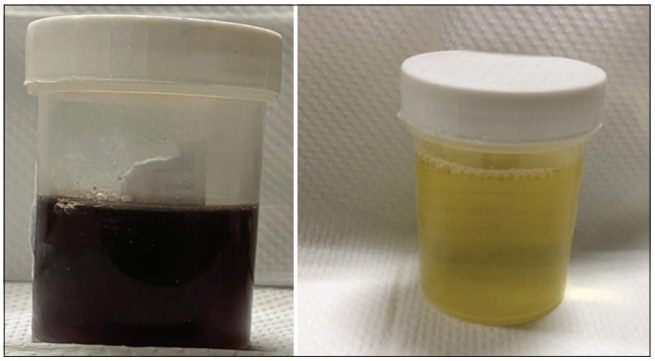

Figure 1: Urine samples of the patient on day 1 (left) and day 6 (right) of admission

Table 1: Laboratory parameters during the febrile and critical phase of dengue in the patient

Day of admission	1	2	3	4	5	6
Hemoglobin (g/dl)	7.6	11.8	10.4	9.2	5.5	9
TLC (10^3/microlitre)	21.77	29.35	37.97	42.73	18.58	17.15
Platelet (10^3/microlitre)	1.65	1.55	1.76	2.30	1.20	95
Total bilirubin (mg/dl)	2.2	2.5	3.8	-	-	1.6
Indirect bilirubin (mg/dl)	1.1	1.15	2.3	-	-	0.5
Aspartate transferase (U/L)	7654	15,118	7741	-	-	1987
Alanine transferase (U/L)	3936	3283	1908	-	-	1023
LDH (U/L)	>20,000	18,967	15,741	9566	-	3061
Serum creatinine (mg/dl)	0.30	0.40	0.50	0.35	0.35	0.30

LDH: Lactate dehydrogenase, TLC: Total leucocyte count

and remained normal. He received a packed red blood cell transfusion on day 1 of admission, due to fall in hemoglobin that was attributed to ongoing hemolysis.

Symptomatic improvement was seen by the 4th day of admission along with normalization of the urine color, and he was weaned off from the HHHFNC. However, another blood cell transfusion was required on the 5th day of admission, due to continuous fall in hemoglobin. Subsequently, his hemogram, liver function tests, and LDH levels started to normalize [Table 1]. He remained clinically stable and was discharged on request. The child was followed up twice, on day 13 and day 21 from the day of admission. He was clinically stable and reported normal urine color. Investigation reports on the last visit were hemoglobin of 8.9 g/dl, platelets 2.45 lakhs/mm^3, and LDH 511 U/L.

Discussion

The patient was a 5-year-old boy with severe dengue who presented to us in the critical phase with evidence of fluid leakage as evident by pleural effusion and free fluid in the abdomen. The continuing fall in hemoglobin level without any evidence of active bleeding, indirect hyperbilirubinemia, raised LDH, hemoglobinuria, and low haptoglobin levels were suggestive of AIVH. This is commonly caused by autoimmune hemolytic anemia, falciparum malaria, ingestion of dyes, snake bites, G6PD deficiency, microangiopathic hemolytic anemia, and incompatible blood transfusions. We were able to exclude these causes by history, physical examination, and relevant laboratory examination. Thus, we attributed it to severe dengue.

Very few cases of AIVH have been reported as a complication of dengue in children. The Sri Lankan boy with massive hemoglobinuria[8] was managed with forced diuresis and isotonic saline boluses in addition to maintenance fluid therapy. The type of fluid management will depend on which phase of illness the child is in. In the critical phase, the aim should be to maintain a fine balance between extravascular fluid overload and intravascular fluid depletion due to the leaky capillaries. The use of fluids and diuretics should be balanced to maintain circulating volume and simultaneously avoiding renal shutdown. During AIVH, erythrocyte lysis releases hemoglobin which binds to haptoglobin and is reabsorbed by the kidneys. Once the haptoglobin binding capacity gets exceeded, free hemoglobin appears in the urine imparting the typical 'cola' color to it. The accumulation of excessive ferric ions causes free radical formation, damage to the tubule epithelial cells leading to renal tubular toxicity and AKI.[9] If managed appropriately, the outcome should be favorable.

Lessons learnt

- Hemolytic anemia is a rare complication of dengue fever
- AIVH requires appropriate fluid management and the use of diuretics, according to the phase of illness
- In the critical phase, the therapeutic aim is to avoid fluid overload and prevent AKI.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Targeted Breast Milk Modification: A Low-Cost Feeding Option in Young Infants with Citrullinemia

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Abstract

Background: The management of urea cycle disorders (UCDs) needs use of nitrogen scavenger drugs and protein restricted special formulas. The latter is not easily accessible and expensive. Continued breastfeeding is poorly tolerated by most babies. In these circumstances, targeted breast milk modification can be lifesaving by reducing ammonia and preventing a catabolic state. **Clinical Description:** A term baby born by normal delivery was discharged at 48 h after successfully initiating breastfeeding. He developed lethargy, poor feeding, and seizures on the 4th day. Vitals were stable. Sepsis, hypoglycemia, hypoxic-ischemic encephalopathy, dyselectrolytemia, hepatic/renal derangement, structural brain anomalies, cerebral edema, and hemorrhage were ruled out. A UCD was suspected due to hyperammonemia without acidosis. Citrullinemia was established by elevated citrulline and no orotic acid. **Management:** Breastfeeding was stopped, nitrogen scavenger drugs started, and peritoneal dialysis performed. As specialized milk formula was unavailable, we started diluted breast milk mixed with corn starch and coconut oil to achieve protein restriction and provide appropriate carbohydrates, lipids, and energy. Dilution was gradually decreased. There was gradual improvement in sensorium with normalization of ammonia. The baby was well till 8 weeks but developed symptomatic hyperammonemia due to noncompliance with therapy. **Conclusion:** Targeted modification of breast milk may be the only viable option for feeding infants with UCD in extraordinary circumstances. However, its short- and long-term consequences need to be researched thoroughly.

Keywords: Breast milk, citrullinemia, neonate

Urea cycle disorders (UCDs) are rare inborn errors of metabolism. The availability of better screening and diagnostic facilities has resulted in increased detection nowadays. These disorders require early diagnosis and treatment with nitrogen scavengers and protein-restricted special formulas.[1] These protein-free formulas are expensive, and the high cost is a limiting factor in adequate management, especially in low- and middle-income countries.

We present a newborn who was diagnosed with citrullinemia, in whom we were unable to provide commercially available specialized formulae due to financial restraints. The aim is to share our experience in feeding the affected infant an indigenous modification of maternal breast milk using graded dilution and addition of cornstarch and coconut oil.

Clinical Description

A term male infant, born of a nonconsanguineous marriage to a primigravida mother, was delivered vaginally at a primary health-care facility. Antenatal period was uneventful. There was no history of any maternal sepsis setting or prolonged/precipitate labor. The baby cried immediately at birth, had a birth weight of 2.8 kg, and was discharged on the 2nd day of life after the establishment of breastfeeding. The baby developed lethargy, poor feeding, and multifocal clonic convulsions on the 4th day of life. The parents were migrant laborer's belonging to the lower socioeconomic strata.

At admission, the baby was lethargic, but the vitals were stable. On anthropometry, the weight was 2.7 kg, head circumference 34.2 cm, and length 48 cm. There was no evidence of dysmorphism, neurocutaneous markers, pallor, or

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icterus. The baby's cry, activity, and spontaneous movements were depressed, and there was minimal arousability. There was no cranial nerve involvement. Both pupils were constricted and reacted to light. The baby was hypotonic with depressed deep tendon and neonatal reflexes. Remaining systemic examination was normal. Investigations were planned to rule out the common causes of neonatal depression such as hypoglycemia, dyselectrolytemia, sepsis, renal, and/or hepatic derangement. The blood glucose, complete blood count, sepsis screen, liver, and renal function tests were normal. The cranial ultrasound did not reveal any abnormality. The arterial blood gas was normal, but serum ammonia and lactate were elevated, 885.9 µmol/L and 6.5 mmol/L, respectively. A differential diagnosis of an inborn error of metabolism with hyperammonemia was considered, possibly a UCD.

Management and outcome

Suitable investigations were ordered, and supportive management initiated. The baby was kept nil per orally (NPO), other than sodium benzoate (400 mg/kg/day), L-carnitine (200 mg/kg/day), thiamine (300 mg/day), riboflavin (100 mg/day), and Vitamin B_{12} (1 mg/day). Peritoneal dialysis was started with a short dwell time of 10 min. Parenteral nutrition was provided with 10% dextrose infusion (glucose infusion rate 8 mg/kg/min), lipids (3 g/kg/day), and a mixture of amino acids (0.5 g/kg/day). Elevated plasma citrulline levels of 1364.2 units/L on tandem mass spectrometry and absence of orotic aciduria on urinary gas chromatography-mass spectrometry established the diagnosis of citrullinemia. L-arginine (300 mg/kg/day) was added to sodium benzoate and carnitine. The serum ammonia level decreased to 230.2 µmol/L within 24 h of starting therapy. This decline was associated with a corresponding improvement in sensorium.

The parents were counseled about further workup and specific management. We were unable to get a gene mutation analysis done due to financial restraints. Specialized protein-restricted formula was not affordable. By the 10th day of life, it was decided to give the baby a trial of diluted breast milk mixed with corn starch and coconut oil, with energy and protein composition [Table 1] planned to be as close as possible to the commercially available formula that would provide appropriately high calories with minimal proteins. The pros and cons of this kind of feeding were discussed with the parents, and written informed consent was taken. The baby received gradual increment in feed volumes, calories, and proteins according to weight and tolerance. Clinical status and ammonia levels were closely monitored [Table 1]. Magnetic resonance imaging of the brain on day 12 of life revealed changes of hyperammonemic encephalopathy. The feed volumes reached maximal undiluted breast milk by day 34. No feed intolerance was observed and the serum ammonia levels continued to decline [Figure 1]. The baby was discharged on day 40 of life on exclusive breastfeeds with continuity of nitrogen scavenging medications. The weight was 3.1 kg, sensorium better, but mild appendicular hypotonia was present.

On follow-up at 8 weeks, the baby was on exclusive breastfeeds with normal ammonia levels. The baby had achieved social smile, but mild hypotonia persisted. At 3 months of age, the infant was re-admitted with vomiting for a day and lethargy for 8 h. On probing, it was elicited that the parents had stopped all medication for a week. On admission, vital signs were stable. The weight was 3.8 kg (<−3 standard deviation [SD]), length 58 cm (−2 SD), and head circumference 36 cm (<−3 SD). The baby was mildly neurologically depressed. The remaining examination was normal.

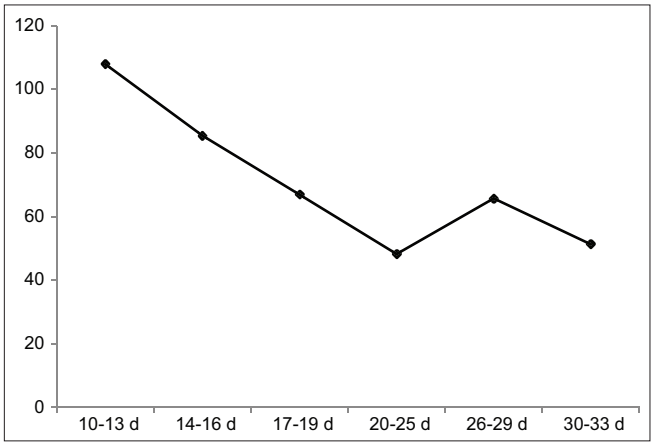

Figure 1: Trend of serum ammonia levels (umol/L) with therapeutic interventions

Table 1: Day-wise targeted modification of breast milk*

Day of life	Breast milk: Water dilution	Volume of milk/ water (ml/feed)	Coconut oil (ml)	Corn starch (g)	Carbs (g/oz)	Protein (g/oz)	Lipids (g/oz)	Calories (/oz)
10-13	1:3	1.5/4.5	0.5	0.5	3.11	0.08	2.55	32.7
14-16	1:2	4/8	1	0.75	2.16	0.10	2.63	26.89
17-19	1:2	8/16	1	2	2.79	0.11	1.55	25.41
20-25	1:1	16/16	2	1.5	2.15	0.14	2.26	34.09
26-29	3:1	39/13	2	1	2	0.20	1.87	26.09
30-33	4:1	48/12	2	2	2.48	0.22	1.78	27.38

*100 g corn starch powder: 88.4 g carbohydrate, coconut oil: 8.62 calories/mL. Special formula: 2.24 g carbohydrates/oz, 0.98 g protein/oz, 0.3 g lipids/oz, 20 calories/oz

The only metabolic abnormality identified was elevated serum ammonia (370 µmol/L). The infant was kept NPO for 48 h and nitrogen scavenger medications restarted. Feeds were re-introduced, following the earlier schedule. The infant improved and was discharged after 10 days. The parents were counseled to continue breastfeeding, the nitrogen scavenger medication and the need for regular follow-up. However, the baby was lost to follow-up.

Discussion

The primary aim of therapy of infants with UCD is to reduce ammonia rapidly and provide minimal protein to prevent endogenous protein catabolism. Prognosis depends upon early and aggressive management of hyperammonemia. Management includes protein cessation/restriction, intravenous fluid and ammonia, scavenging medications,[2-5] and dialysis (ammonia >500 µmol/L).[2] Enteral feeding is restarted after 48–72 h of stabilization, to prevent catabolism. Proteins are reintroduced when ammonia is <100 µmol/L. The total energy intake should be 120% (age-adjusted) with proteins at 1.4–2.1 g/kg/day.[2] However, proteins are re-instituted at 25%–50% of expected intake[5,6] and gradually increased.[3] If ammonia levels increase, special formulas are used, either in isolation or combined with natural proteins.

Further management requires specialized formulas, in addition to nitrogen scavengers. If not provided, there is a high risk of cognitive impairment, epilepsy, and death.[1] However, these are expensive, not easily accessible, or not affordable. The cost of a single 60 ml feed of targeted breast milk preparation used for this baby was 3.6 cents (2.5 rupees) in comparison to 1.28 USD (95 rupees) for specialized formula, almost a fifth of the daily per capita Indian income. In this case, the breast milk was initially diluted to reduce the protein content. Coconut oil was used to provide calories. Corn starch was the main source of carbohydrates. It is already being used in neonates for persistent hypoglycemia and glycogen storage disorders.[7] The concentration of breast milk was gradually increased till full undiluted breast milk feeding was reached.

Exclusive breastfeeding and nitrogen scavenging medications have been in used in some infants with UCD under strict monitoring, but it is poorly tolerated by many patients. That is why we considered using targeted breast milk modification following the principles of UCD management in this baby as the only available option. We could not find any previous similar reports of feeding on a literature search. Although as of now, this practice cannot be recommended as standard care, it may be considered as a viable option only in special circumstances, to tide over the metabolic derangement, and sustain enteral nutrition when there are no other alternatives. Although the level of ammonia was controlled in our baby, he developed microcephaly and the nutritional status was poor (though parental compliance was dubious). We were unable to monitor growth and development in this infant. Research on short-term and long-term implications of breast milk modification is warranted.

Lessons learnt

- Special formulas are expensive and inaccessible to many infants with inborn errors of metabolism due to unavailability or financial constraints
- Targeted breast milk feeding may be considered as special circumstances in infants who cannot afford these formulae, with close clinical and biochemical monitoring
- Short-term and long-term implications of this need to be established before it can be considered standard care.

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Conflicts of interest

There are no conflicts of interest.

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Congenital Midline Cervical Cleft – A Rare Neck Anomaly

A 3-month-old, boy presented with a painless neck lesion noted since birth. There were no associated redness, discharge, and difficulties in breathing or breastfeeding. The antenatal, natal, and postnatal periods had been uneventful. Examination revealed stable vital parameters and normal anthropometry. A midline linear cervical cleft, 30 mm in length and 7 mm in width, extended from the submental to the suprasternal area, with atrophic skin at the base. There was a 3 mm × 3 mm nipple-like projection at the cephalic end and a dry sinus tract at the caudal end directed toward the manubrium [Figure 1]. No other midline defects in the lower lip, tongue, oral cavity, jaw, or chest were identified. The ears were normal. Neck movement was not restricted. Systemic examination was normal. A clinical diagnosis of congenital midline cervical cleft (CMCC) was made based on the clinical phenotype. Ultrasonography of the neck confirmed a depth of 2 mm of the tract that had a blind ending. No other anomalies were detected. Abdominal ultrasonography and echocardiography were normal. The parents were counseled, and the child was kept under pediatric surgery follow-up for surgical correction.

CMCC is rare, constituting about 2% of neck anomalies. It is hypothesized to result from impaired midline fusion of the first and second branchial arches during embryogenesis. The three components differ histologically: the skin tag usually demonstrates normal skin; the cleft is lined by atrophic keratinized stratified squamous epithelium without any skin appendages, and the sinus tract is lined by pseudostratified squamous epithelium with seromucinous glands that often discharge. CMCC can be isolated; associated with clefts in the lower lip, tongue, mandible, sternum, thyroglossal duct cyst, bronchogenic cyst, ectopia cordis, and other intracardiac anomalies, or a component of Brachiootorenal syndrome. Neck contracture may result due to scarring and formation of a fibrous cord during healing. Treatment is surgical excision during infancy with closure of the defect by Z plasty to prevent contractures.[1,2]

Clinicians should be aware of the four differential diagnoses. Thyroglossal cyst is the most common, a remnant of the thyroglossal duct that normally obliterates by the 5th week of gestation. It appears as a fluid-filled swelling that moves with deglutition and protrusion of the tongue. This pathognomic feature is due to its relation with the hyoid bone but is difficult to appreciate in an infant. Occasionally, it may intermittently discharge the sinus. The tract of the thyroglossal duct anomaly is cranially directed, in contrast to a CMCC which is directed caudally.[1,3] Branchial sinuses and fistulae are the remnants of embryonic branchial cleft and pouches, usually of the third and fourth branchial arches. These present as cystic swellings or fistulae in the lower neck along the anterior border of the sternocleidomastoid muscle. They may have internal connections with the pharynx or pyriform sinus.[4] Dermoid cysts are superficial, subcutaneous masses or cysts that do not move with deglutition.

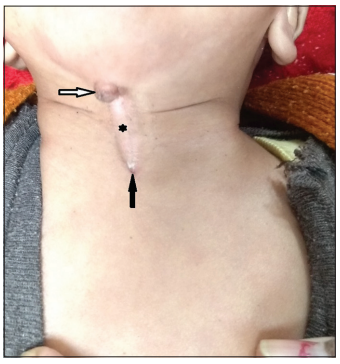

Figure 1: Image showing the frontal view of the congenital midline cervical cleft. A midline cervical skin defect extends from the submental to suprasternal area with atrophic pale skin at base (*). A nipple-like projection is seen at the cranial end (white arrow) and a sinus tract is present at the caudal end (black arrow)

Declaration of patient consent

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

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Conflicts of interest

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A Neonate Born with Natural Garment: Congenital Melanocytic Nevus

Monochorionic diamniotic twin girls were born to a primigravida at 34^{+2} weeks gestation via vaginal delivery. Both cried immediately at birth. The second twin was a girl with a birth weight of 1900 g. A large, black, skin lesion covering her back was noted at birth. Her twin and other family members had no similar lesions. Examination revealed a hyperpigmented nevus, measuring 13 cm × 13 cm, with well-demarcated margins, papular surface, and hypertrichosis [Figure 1]. Smaller hyperpigmented satellite lesions of variable size were present over the buttocks, right foot, left leg, and knee. A clinical diagnosis of giant congenital melanocytic nevus (GCMN), with "bathing trunk" distribution, was made. The cranial sutures and spine were normal. Systemic examination was unremarkable. Magnetic resonance imaging of the brain was normal. Parents were counseled regarding the nature, prognosis, and management of the disease.

The overall occurrence of congenital melanocytic nevus is 1%–3%, with slight female preponderance. Large or giant GCMN is reported to occur in 1:20,000 live births, with the variety "GCMN in garment" being even rarer, 1:500,000.[1] Lesions are classified with reference to the projected adult size:[2] small (<1.5 cm); medium (1.5–20 cm); large (>20–40 cm, >9 cm on the head and >6 cm on the body); and giant (>40 cm). These lesions are hypothesized to occur due to gain-of-function somatic mutations in either proto-oncogenes, BRAF V600 variant, or NRAS Q6. These affect the microtubule-associated protein kinase signal transduction pathway, leading to abnormal proliferation of embryonic melanoblasts. Apart from the significant cosmetic disfigurement, GCMN is associated with neurocutaneous melanosis (in 3%–10% of neonates at high-risk category i.e., with lesions >40 cm, multiple satellite lesions or >2 medium-sized lesions);[3] melanomas (in 2%–5% GCMN, particularly >60 cm or with satellite lesions);[4] or malignancies such as liposarcoma and rhabdomyosarcomas.

Management is individualized, the aim being close monitoring for malignancy and neurological involvement, cosmetic rehabilitation, and providing psychological support. Parents need to be counseled about the need for regular local checks of any change in color, texture, and/or size. Earlier, surgical excision was the mainstay to avoid malignant transformation. These included serial resection, excision followed by skin grafts, and tissue expanders followed by resection. However, nowadays, the role of surgery is no longer certain, considering the inability to remove the lesion in entirety, the risk of extensive postsurgical scarring, the absence of actual reduction in risk, especially since there are reports of malignancy occurring in surgically excised areas.[5] Less invasive procedures such as curettage, dermabrasion, and laser ablation are also being used. There are ongoing clinical trials with NRAS inhibitors such as trametinib in individuals with known NRAS mutations and some speculation regarding the use of endothelin-1 receptor antagonists.

Figure 1: Giant congenital melanocytic nevus over the back measuring 13 cm × 13 cm with satellite lesions over the buttocks and thighs

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.

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Clinical and Electroencephalogram Correlation of Self-Limited Epilepsy with Autonomic Seizures

A 2-year-old, developmentally normal, boy presented with multiple seizure-like events over 10 days. These episodes were described as brief (20–30 s), vacant stares, associated with impaired awareness, hypersalivation, retching, vomiting, tongue thrusts, and pallor of the face and body. A few episodes exhibited tonic posturing of the upper limbs [Figure 1 and Video 1 (video available from: *https://www.ipcares.org/articles/2021/1/4/images/IndianPediatrCaseRep_2021_1_4_271_331377_sm3.mp4*)]. Other aspects of history were normal. There was no dysmorphism or neurocutaneous markers. Neurological examination was normal. Cranial Magnetic Resonance Imaging (epilepsy protocol) was normal. The drug-induced sleep electroencephalogram (EEG) revealed multifocal epilepsy with bilateral occipital predominance [Figure 2]. A diagnosis of Self-Limited Epilepsy with Autonomic Seizures (SeLEAS) or "Panayiotopoulos syndrome" was made, based on semiology and EEG findings. Seizures stopped within 72 h of starting sodium valproate.

SeLEAS is a relatively frequent, benign epileptic syndrome characterized by predominant autonomic symptoms and/or focal onset motor seizures. The former include retching, emesis, changes in color (pallor, flushing, or cyanosis), pupillary dilatation, hypersalivation, cardiorespiratory, and thermoregulatory alterations.[1] Clinicians should be aware of this entity as these events are frequently misdiagnosed as acute encephalitis, syncope, migraine, cyclic vomiting syndrome, motion sickness, sleep disorder, or gastroenteritis.[2] Interictal EEG shows occipital spikes. Multifocal spikes with high amplitude sharp-slow wave complexes can also occur at various locations.

Figure 1: The seizure semiology was a vacant stare with impaired awareness associated with hypersalivation, retching, vomiting and tongue thrusting, and pallor of the face and body, lasting for 20–30 s. There was no postictal drowsiness

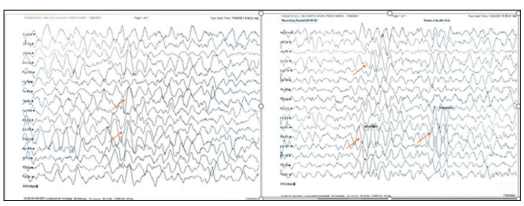

Figure 2: The interictal sleep electroencephalogram record shows frequent sharp wave, spike and slow wave (1–3 Hz, 300–500 microvolt) discharges arising from O1 and O2 with spread to adjacent electrodes, accentuated during photic stimulation. There are independent frequent sharp wave discharges from F3, F4, P3, and FP3 suggestive of multifocal epilepsy with bilateral occipital predominance

Seizures will stop in most children within 2–3 years of the first episode. The risk of developing epilepsy in adulthood is similar to the general population. Anticonvulsant therapy (oxcarbamazepine, valproate, and levetiracetam) are indicated when seizure frequency is high.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given her 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 identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Lipoid Pneumonia: Fifty Years of Unmasking an Unusual Cause of Pneumonia

Lipoid pneumonia (LP) is a rare form of pneumonia caused by inhalation or aspiration of lipids/oils of animal or plant origin. In the last 50 years, LP resulting from various cultural, medical, and behavioral practices has been reported in literature worldwide, in all age groups. A peak was noted between 1987 and 2006; however, with improved understanding and awareness of this entity, there has been a decline in its incidence. Due to the nonspecific presentation, diagnosis is often delayed or missed in children. We selected this case report from 50 years ago, as it is an important and entirely preventable pediatric cause of persistent pneumonia and interstitial lung disease (ILD).

Clinical Case Description

The case report by Bakshi *et al*.[1] describes a 3-month-old female child who was apparently well till 1 month of age. The infant presented with a history of recurrent episodes of fever, vomiting, and diarrhea associated with marked irritability for 1.5 months. Past, antenatal, perinatal, and family history was noncontributory. General physical examination was normal. Salient systemic examination findings included firm and nontender enlargement of the liver and spleen; 5 cm and 7 cm below costal margin, respectively. Respiratory examination revealed reduced breath sounds on the right side.

Blood investigations were normal, except for mild anemia and high ESR (55 mm). Chest radiography showed dense opacity on the right upper and middle zone. The tomography report described it as a mass in the posterior mediastinum. The skeletal survey and bone marrow examination were inconclusive. The differential diagnoses of posterior mediastinum mass considered were ganglioneuroma, cyst, teratoma, and gut duplication. Surgery revealed a solid mass involving the right upper and lower lobes, for which right pneumonectomy was done. Histopathological examination found inflammatory granulomas with large masses of sudanophilic material. The baby died due to postoperative complications. Autopsy revealed extensive pneumonia, a fatty liver, and reactive hyperplasia in the spleen. The final diagnosis was foreign body granuloma in the lung due to lipid aspiration or LP. On reviewing the history, it was elicited that the infant had been fed "ghee" daily from the age of a month due to some social custom. The authors hypothesized that the hepatosplenomegaly was the reticuloendothelial response to the foreign body granuloma formation.

Brief Historical Review

LP has been reported in the literature since 1925, when it was first associated with chronic use of laxative- and oil-based nasal drops. It has been described under different names such as paraffinoma, cholesterol pneumonia, and lipid granulomatosis, each denoting the association with inhalation or ingestion of oily substances. The exact incidence of LP is still not known. Initially, it was usually reported in children with defects in deglutition or neuromuscular diseases due to increased chances of aspiration, but there are several case reports in healthy individuals as well. In most of the earlier cases, diagnosis was established either on surgically resected specimens or autopsy. Treatment was based upon individual experience.

Advances in the Last 50 Years

We briefly discuss various aspects of LP that have become clearer in the past decades.

Risk factors

Besides the aforementioned causes, the most causes were due to the use of home remedies such as oily nasal drops, feeding animal fat (like "ghee" in this case) to establish regular bowel habits, or transnasal administration of medicines for coughs and colds. Medical causes include Lorenzo's oil in the management of adrenoleukodystrophy,[2] and more recently with a ketogenic diet for management intractable seizures.[3] A systemic review by Marangu *et al*.[4] observed that out of 44 studies, 25 reported co-infection cultured from blood or respiratory tract secretions. The most common infection (6 studies) was nontuberculous mycobacteria (NTM). Other infections noted included *Branhamella catarrhalis*, *Pseudomonas*, *Acinetobacter*, *Klebsiella*, and common respiratory viruses.

Clinical presentation and diagnosis

Children with LP may present acutely with fever, cough, and respiratory distress or with nonspecific symptoms that are insidious in onset and depend upon the degree of exposure to lipid/oil. Physical examination is usually normal, although dullness on percussion, crackles, wheezes, and/or rhonchi may be present. In long-standing progressive disease, physical findings related to chronic hypoxia such as clubbing may develop.[5] Blood investigations are usually normal, unless a coinfection exists, in which case there will be leukocytosis. Once a history compatible with exposure to lipids/oils is certain, the diagnosis can be

confirmed by demonstration of intra-alveolar lipid and lipid laden macrophages in the sputum or on bronchoalveolar lavage (BAL).

Radiologic features

The findings of suspected LP on a chest radiograph are neither specific nor diagnostic. Patients who present acutely may show homogenous dense opacities, often with air bronchograms and sometimes a fine, "spun glass" appearance. These changes may be seen as early as 30 min and in most cases by 24 h of acute exposure. Those with chronic symptoms may have ground-glass or dense opacities (as seen in consolidation) that involve one or more segments, typically with peribronchovascular distribution and involving the lower lobes.[5] A computerized tomographic (CT) scan of the chest may reveal diffuse airspace/ground-glass opacities with basal/lower lobe predominance. Less frequent findings are fatty attenuation, interstitial septal, thickening/crazy-paving appearance, expansile pneumonia, and nodules. CT can detect areas of fat attenuation as low as −30 HU. Recently, by using advanced fat saturation techniques, magnetic resonance imaging (MRI) has been utilized to identify fat depressed signals diagnostic of LP that are found in the middle of the lobe, or within the consolidation and/or nodules and get missed on CT.[5]

Treatment

The optimal treatment of LP is still unknown. Avoiding risk factors that cause exposure to lipids and supportive care is the mainstay of current management. The use of anti-inflammatory agents such as steroids has been reported by some authors, but there is lack of clinical trials to validate this. There are a few reports of successful treatment with intravenous immunoglobulin.[4] Mycobacterial infection must be excluded before immunosuppression. Other modalities include repeated lung lavage and surgical resection of the involved segment.

Prognosis and outcome

LP is usually indolent, if recognized early, and the risk factors modified. In patients with chronic symptoms and delayed diagnosis, the disease can be persistent and difficult to treat. Though patients show clinical improvement, radiological signs may persist. Mortality is reported inconsistently.[4,5]

To conclude, LP is a frequently missed diagnosis in children because of nonspecific clinical-radiological presentation and lack of knowledge about the various risk factors for aspiration or inhalation of oils/fats. A high index of suspicion should be kept in any child presenting with unexplained pneumonia, and history should be taken for exposure to lipid-containing substances. LP is easily preventable if we increase awareness among the general population and professional colleagues about this entity and modify our cultural and medical practices.

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Bird Fancier's Lung Disease in a Child with Chronic Respiratory Illness

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Bird fancier's lung is a type of hypersensitivity pneumonitis and rare interstitial lung disease in children. It has 3 forms of presentation viz. acute, subacute, and chronic. Here we present a child with chronic hypersensitivity pneumonitis secondary to pigeon exposure. A 12-year-old boy belonging to a family of pigeon breeders developed cough and dyspnea for two years. On evaluation, he had features of interstitial lung disease with pulmonary arterial hypertension. The diagnosis was confirmed on lung biopsy which showed features of chronic hypersensitivity pneumonitis. The child was managed with oral steroids, oral sildenafil and advised to avoid further exposure to pigeons, to which he responded. Clinicians will benefit from obtaining a detailed environmental history and making diligent efforts to identify the inciting agent and prevent further exposure.

Hypersensitivity pneumonitis (HP) is a chronic respiratory disease in children. It is a condition caused by exposure to various inhaled agents such as agricultural dust, bio-aerosols, fungal, bacterial, or protozoan microorganisms, and certain reactive chemicals. The two major inciting allergens are bird (avian) allergens and inhaled particles derived from fungi. The diagnosis is often missed due to its rare occurrence, subtle symptoms and signs, and poor awareness among physicians. Here, we discuss the clinical approach to a child with chronic respiratory illness, who was subsequently diagnosed as a case of HP, secondary to pigeon exposure.

Clinical Description

A 12-year-old male child from a rural background presented to our institution with cough and intermittent episodes of low-grade fever for 2 years. The cough was dry, nonparoxysmal, more during waking hours, and absent during sleep. There was no associated wheezing. The fever was of moderate grade (albeit never documented), appeared for a few hours several days at a time, and not associated with any other symptoms. He had developed breathlessness during the last 6 months. Initially, it was on exertion; however, by 2 months before presentation, it had progressed to occurring at rest. There was decreased appetite and loss of weight for 2 months. There was no history of any swelling, facial puffiness, noisy breathing, palpitations, or fainting. There was no significant medical history before this illness. No one in the family had tuberculosis (TB). Since the onset of symptoms, the child had received multiple antibiotics, nebulization with bronchodilators, and a complete course of empiric anti-tuberculosis therapy. He was the fifth-born child of a nonconsanguineous marriage and a student of class V, with normal development history. His father was a farmer. There were no pet animals in the household.

At admission, the child had signs of respiratory failure with heart rate of 132/minute, respiratory rate 42/minute, intercostal retractions, and transcutaneous oxygen saturation of 84% in room air. His weight was 32 kg (−1.04 Z score) and height was 148 cm (−0.37 Z score). On general examination, there was pallor and grade 3 pandigital clubbing, but no cyanosis (on oxygen), significant lymphadenopathy, pedal edema, or elevated jugular venous pressure. Throat, ear, and nasal cavity examinations were normal. Chest examination showed symmetric shape and expansion, centrally positioned trachea, and normal percussion notes in all areas. Bilateral crackles and wheezing were heard on auscultation. The second heart sound was loud but not palpable. There was absence of parasternal heave, splitting, or any murmur. Examination of other systems was normal. The child was stabilized with oxygen delivered through nasal prongs and intravenous fluids. Broad-spectrum antibiotics were started empirically, and a posteroanterior chest radiograph was ordered.

What clinical differential diagnoses can be considered?

The clinical phenotype is that of a chronic respiratory illness with clubbing and probable pulmonary hypertension. Thus, the differentials that should be considered include complicated pulmonary TB, human immunodeficiency virus (HIV) infection, and acquired childhood interstitial lung disease (ILD). ILD could be due to environmental exposure, i.e. HP or systemic causes such as sarcoidosis, connective tissue diseases, anti-neutrophilic cytoplasmic antibody associated, or cystic fibrosis. Though less likely, cytomegalovirus or fungal infection can also be considered. A hyperimmune state like Langerhans cell histiocytosis would be kept lower down, the points against this being the chronic duration of symptoms and absence of other clinical indicators. Diagnoses that could be excluded clinically at this point were acyanotic congenital heart diseases with left-to-right shunts, aspiration syndromes, major congenital lung or airway malformations (late presentation), and primary immune deficiency disorders (normal growth with the absence of recurrent infections and nonrespiratory symptoms).

What are the salient features in the chest X-ray?

The X-ray appears well positioned with adequate exposure [Figure 1]. Visualization of only five intercostal spaces bilaterally indicates hypoinflation. Diffuse reticulonodular opacities are visible in both lung fields. The cardiac silhouette is normal, but the pulmonary bay is not visible. The pleural spaces, trachea, bones, and soft tissues are normal. These radiographic features and the clinical background suggest ILD of childhood onset. However, disseminated TB, cytomegalovirus infection, and causes of secondary immunodeficiency must be excluded.

Investigations

Complete blood count showed normal hemoglobin (15.6 g/dl), total leukocyte count (11.5 × 10^9/L), and platelet count (313 × 10^9/L). The differential count showed 60% neutrophils, 28% lymphocytes, 10% eosinophils, and 2% monocytes. The absolute eosinophil count was 1.15 × 10^9/L and ESR 10 mm. The tuberculin skin test was nonreactive. Induced sputum specimens were negative for TB on smear and GeneXpert. HIV serology was nonreactive.

On account of peripheral eosinophilia, eosinophilic lung diseases were also considered. Total serum IgE level was elevated (2400 IU/L). Stool examination did not show parasitic ova or cysts. Serology for helminthic infestations was negative for *Ascariasis*, *Filariasis*, *Strongyloides*, and *Trichuris*. Echocardiography ruled out structural heart disease and confirmed moderate pulmonary artery hypertension (PAH). Spirometry could not be performed as the child was breathless even at rest.

What should be the next line of investigations?

Ideally, a flexible fiberoptic bronchoscopy should be done for bronchoalveolar lavage (BAL) analysis. However, the child was too unstable for such an invasive procedure requiring sedation and analgesia. Therefore, computed tomography (CT) scan of the thorax was planned.

What are the salient findings in the computed tomography scan of the thorax?

The contrast-enhanced CT scan [Figure 2] showed bilateral diffuse ground-glass opacities with lingular bronchiectasis and dilated pulmonary artery. Mild cardiomegaly and mediastinal lymphadenopathy were noted. These features were suggestive of (but, not pathognomonic) of ILD with secondary PAH, but the specific type was not discernible.

What should be done next to determine the diagnosis?

We decided to broaden the workup for known causes of diffuse ILD with peripheral eosinophilia and elevated IgE, such as chronic eosinophilic pneumonia and HP. Specific tests for *Wuchereria bancrofti*, *Toxoplasma gondii*, *Toxocara canis*, *Trichinella*, and *Echinococcosis granulosus*, were negative. A nonreactive skin prick test for *Aspergillus fumigatus* hypersensitivity and normal *Aspergillus*-specific IgE levels ruled out allergic broncho-pulmonary aspergillosis. Despite the relatively unstable condition of the child, we proceeded with

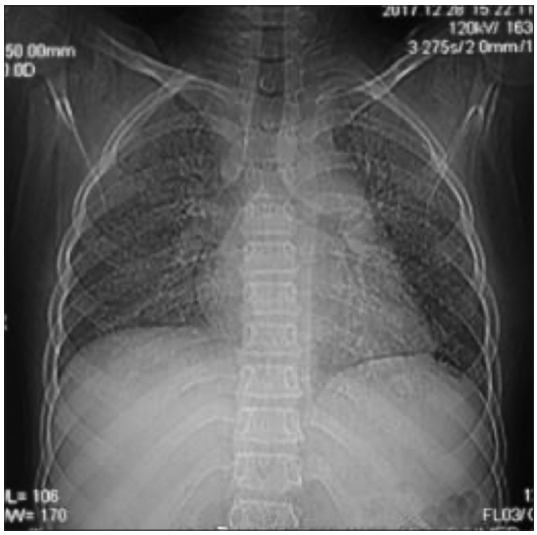

Figure 1: Chest X-ray showing hypoinflation with bilateral reticulonodular opacities

fiberoptic bronchoscopy (after counseling the parents and taking all precautions and high-risk consent) to reach a diagnosis. This showed normal airway anatomy and absence of lingular bronchiectasis. BAL revealed 230 cells with lymphocytic predominance but no eosinophils. Thus, eosinophilic lung diseases were no longer considered likely. Microbiologic examination for bacterial, mycobacterial, fungal, and atypical infections (*Mycoplasma*, pneumocystis) were negative.

Since the only differential that remained was HP, we decided to revisit the clinical history. Probing to identify potential causes of hypersensitivity uncovered the fact that pigeons were being bred at home for a couple of years, with occasional active involvement of the child. Based on this lead, IgE for avian antigen was ordered, but it was negative. Thus, no other option remained, but to perform an open lung biopsy under general anesthesia with high-risk consent. This revealed fibrosis with peribronchiolar mononuclear infiltrates and well-formed epithelioid granulomas, highly suggestive of chronic HP [Figure 3].

Management and outcome

The child was started on oral prednisolone (1 mg/kg/day) and oral sildenafil (2 mg/kg/day) for the PAH. Over the next 3 weeks, his O_2 requirement improved significantly, and he could be weaned off it within 4 weeks. Dyspnea improved from New York Heart Association (NYHA) Class 4 to NYHA Class 3 at the time of discharge. The family was advised to avoid further exposure to the pigeons. On follow-up, the child showed further improvement of respiratory symptoms, and hence, steroids were tapered and stopped over 8 weeks.

Discussion

This case highlights the importance of environmental and occupational exposure to allergens in children with chronic

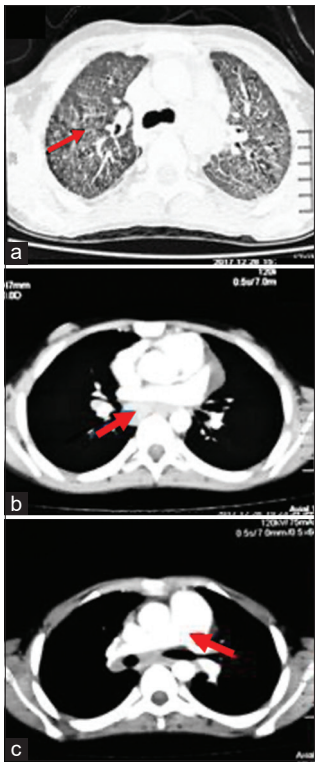

Figure 2: High-resolution computed tomography chest showing bilateral diffuse ground-glass opacities (a), Mediastinal lymphadenopathy (b), and dilated main pulmonary artery (c) Depicted by red arrows in the respective panels

respiratory symptoms. Though uncommon, isolated chronic pulmonary manifestations with features of ILD should prompt the clinician to consider HP. Childhood onset ILD is of three types: (i) related to exposure/environmental insults; (ii) systemic disease processes; and (iii) primary lung parenchyma dysfunction. Since exposure-related lung diseases are less common in children compared to adults,[1] pediatricians may miss making the diagnosis.

HP is an immune-mediated ILD that predominantly involves the distal lung. It occurs due to repeated exposure to specific antigens, both organic and nonorganic. In children, the most common etiology is bird antigen, especially that of pigeons. The pathogenesis is very complex, including immune complex-mediated (type 3) and delayed hypersensitivity (type 4). Children usually present with cough, dyspnea, and cyanosis and are often misdiagnosed and managed as poorly controlled bronchial asthma. When compared with adults, anorexia and weight loss are more pronounced.[2] There are no well-defined diagnostic criteria for children, unlike for adults.[3] Therefore, the diagnosis is usually based on typical symptoms, clinical signs, history of exposure, consistent radiological findings, lymphocytosis on BAL analysis, characteristic histopathological features, and clinical improvement after elimination of the antigen. Our patient displayed all of these features.

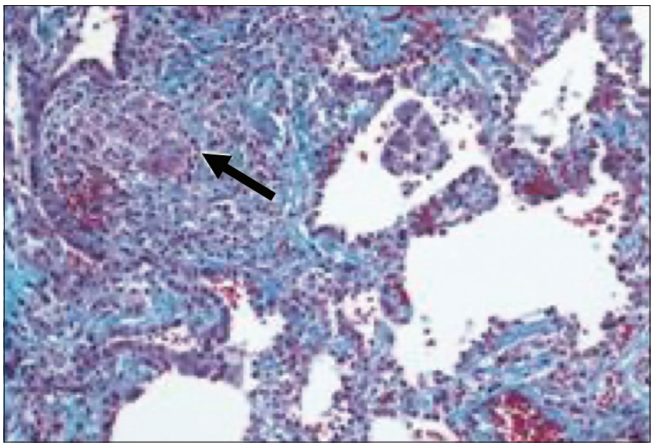

Figure 3: Histopathological section of the lung tissue showing well-formed epithelioid granuloma and mononuclear infiltrates highlighted by the black arrow

BAL may show lymphocytic predominance (>20%) but can be normal as well. A low lymphocyte CD4:CD8 ratio is suggestive of HP, but this is nonspecific and insensitive, especially since children can normally have a low CD4:CD8 ratio.[4] High-resolution CT findings include ground-glass opacities (reported as 40%–93% in various studies), traction bronchiectasis, micronodules, honeycombing, and mediastinal lymphadenopathy.[5] These findings may correlate with the duration. Air trapping mosaicism is seen in acute subtypes; ground-glass opacities in both acute and chronic forms; and fibrosis, interstitial thickening, and traction bronchiectasis in chronic HP. Characteristic histopathological features of granulomatous interstitial pneumonia include a triad; chronic inflammatory infiltrates along small airways, diffuse interstitial infiltrates of chronic inflammatory cells, and scattered small nonnecrotizing granulomas.[6] The index case exhibited all three, but one should note that this is not found in all cases.

Most children have acute to subacute presentations. Very few cases have been reported with chronic forms.[2,7,8] The primary modality of treatment is total avoidance of the inciting allergen and systemic corticosteroids. Earlier, the treatment is started, better the outcomes. The prognosis is more favorable compared to adults, and mortality is rare.

Declaration of patient consent

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Forensic Files

Scald injury in Children: Innocent Bystander or Herald of Abuse

Burns are defined as thermal injuries due to exposure to flame, hot liquids, chemicals, electricity, or radiation. Worldwide, burns represent the third-most common cause of fatal injury in children after traffic accidents and drowning.[1] Scalds, or burns due to hot liquids, account for half to two-thirds of all burns in young children.[1] The most common agent implicated in scald injuries is hot water (51%–60%), globally. In India, scalds are also due to hot milk, oil, porridge, tea, coffee, or sambhar/daal. The nature of liquid influences the severity of the burn, with injury from ghee, oil, or any fat being deeper due to the high latent heat and viscosity.[2]

Young children are highly susceptible due to their innate curiosity, impulsivity, and injury-prone behavior. Due to thinner skins, they suffer more damage than adults, and at lower temperatures. Apart from the mortality of 5%, severe pain and distress may result in long-term physical and psychological impairment. Scalds are mostly accidental and occur at home, usually in the kitchen or bathroom. Being preventable, it is important to focus on appropriate first aid, timely referral to a burn's unit, and parental education regarding preventive strategies. However, intentional scald injuries are commonly seen in child abuse, accounting for 5.3%–14% of pediatric burn admissions.[3]

Pediatricians should be able to suspect, identify, and manage such cases efficiently, not only to decrease morbidity but also to fulfill their medico-legal responsibilities. Timely management using a multi-disciplinary team approach, and reporting abuse to competent authorities is mandatory. We aim to sensitize our readers to salient aspects of pediatric scald injury through a true, but the anonymized case.

Case Report

A 2-year-old male child was brought to the emergency department of our hospital with alleged history of tea being accidentally spilt over his right ear at home in the kitchen about 4 h back. The boy had been playing and had bumped into his grandmother, who had been holding a cup of freshly brewed tea. The child immediately started crying due to the pain. Before being brought to the hospital, the affected area had been washed with cold water. There was no history of significant medical issues or hospitalizations.

According to hospital protocol, the resident on duty registered a medico-legal case, informed the institutional police post, and started evaluation after taking informed consent from the father**.** The history of postscald hearing loss was not apparent. The boy's vitals, general condition, and level of consciousness were normal. There was a superficial

erythematous burn over the ventral aspect of the right pinna, with a small blister on the outer curvature of the pinna. Areas of ulceration, bleeding, oozing, or pus discharge were absent [Figure 1]. An otorhinolaryngologist ruled out the ear canal and tympanic membrane involvement. According to the Lund and Browder Chart, the total body surface area (TBSA) of the burn was <1% and being of partial thickness, it was classified as a minor burn. The pediatric surgeon dressed the wound with silver sulfadiazine, and prescribed an oral antibiotic for 5 days, a pain killer, and daily dressing. At discharge, the parents were counseled about when to return and advised to visit the hospital's "Burns" out-patient department.

Let's ask the experts

Q. What are the typical characteristics of a scald injury?

Mechanisms

Injuries due to spillage leads to splash burns which are nonuniform in shape and distribution, and of variable depth. Immersion injuries are more uniform and deeper. A less common injury is due to moist hot steam like that erupting from a pressure cooker.

Pattern

Scalds are characterized by marked superficial erythema with blister formation and result in partial-thickness burns. The depth, outline, and appearance of the injury depend upon the age of the patient, type of agent, mechanism, duration of contact, and type of first aid provided.

Distribution

Spill burns usually involve the front part of the body, mostly the face, neck, and upper limbs. Immersion injuries frequently affect the hands, buttocks, and lower limbs.

How do contact burns differ from scald burns?

In contrast, a contact burn is caused by dry heat, resulting from brief or prolonged direct contact with extremely hot solid objects like irons, stoves, or electrical fixtures. They cause deep dermal or full-thickness burns with the outline corresponding to the shape of the hot object. The lesion appears blackened, is minimally painful, and frequently requires surgical intervention.

Q. How are scald injuries classified in children, on the basis of body surface area and depth?

The severity of scalds is assessed on the basis of depth (or layers of skin involved) and size, or the percentage of TBSA affected. Wilson's classification as first-, second-, and third-degree or superficial, partial thickness or full-thickness burns is similar in children and adults. However, in newborns and children, the commonly used "Rule of nine" to determine the extent of TBSA affected is not applicable due to different body proportions (i.e. larger heads and smaller limbs). The Lund and Browder chart takes the age-dependent variation in surface area of different parts of the body into account [Figure 2]. A crude method is the "Rule of palm," whence the child's extended palm is considered 1% TBSA. Accurate measurement is also essential for calculating fluid requirements during management.

Q. What are the risk factors for accidental scald burns?

Risk factors identified in various studies across the world include younger age, nuclear families, overcrowded households, lower socioeconomic conditions, and children with special needs.

Q. How can scald injuries be prevented?

Scald burns are preventable by the adaptation of stringent child safety practices. These include not drinking/holding hot liquids with children in one's lap, keeping utensils holding hot liquids out of the reach of children, filling cold water before

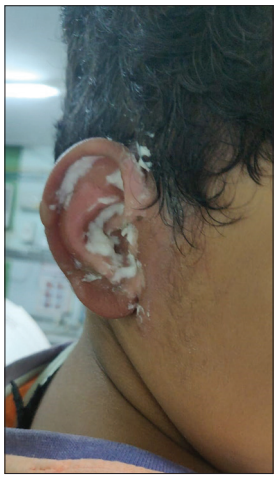
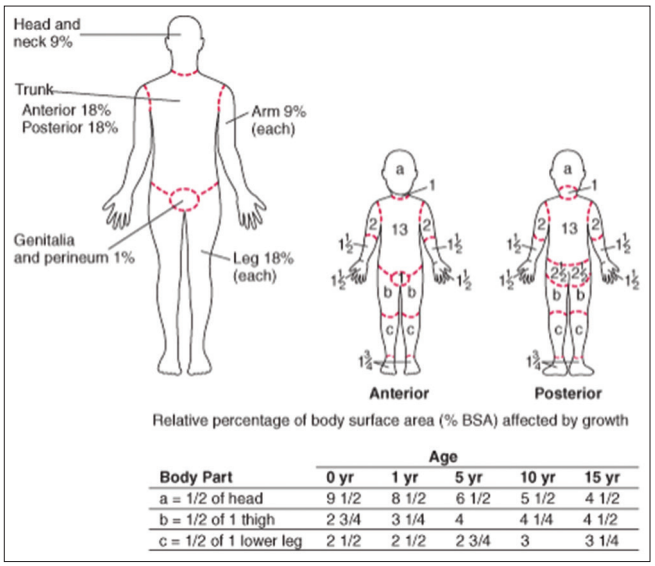


Figure 1: Scald burn of right ear pinna with blister on the outer curvature and evidence of silver sulphadiazine application



Relative percentage of body surface area (% BSA) affected by growth

Body Part	Age 0 yr	1 yr	5 yr	10 yr	15 yr
a = 1/2 of head	9 1/2	8 1/2	6 1/2	5 1/2	4 1/2
b = 1/2 of 1 thigh	2 3/4	3 1/4	4	4 1/4	4 1/2
c = 1/2 of 1 lower leg	2 1/2	2 1/2	2 3/4	3	3 1/4

Figure 2: Lund and Browder chart for calculation of affected total body surface area in children

Table 1: Differentiation between unintentional (accidental) and intentional (abusive) scalds[6]

Characteristic	Accidental Scalds	Abusive Scalds
History	Reasonable and plausible	Changing, unclear, and inconsistent
Agent	Usually nontap water (hot beverages/water used in cooking)	Majority caused by hot tap water
Mechanism	Predominantly as spill injury with few immersion injuries	Forced immersion injury, most commonly associated with bathing
Distribution	Mostly involves the head, neck, trunk, and upper extremities	Mostly feet and bilateral lower extremities. Bilateral involvement of the buttocks, lower back, and perineum are significantly associated with abuse
Pattern	Usually irregular margins with variable depth, asymmetric with lack of glove and stocking distribution.	Sharply demarcated burn margin with uniform burn depth, usually full-thickness, symmetrical with circumferential/glove and stocking distribution
Uniformity	The initial point of contact deeply burned with decreasing severity as liquid flows down the body	No splash marks and creases and opposing surfaces are spared
Associated features	Absent	Other marks of injuries/fractures, previous healed injuries, fearful child, associated neglect or growth faltering, history of burns, and lack of parental concern

hot water in the bathroom, and setting the water thermostat to <50°C.[1,4]

Q. What are the roles and responsibilities of the treating physician?

The general principles of the management of a child presenting with scald burns include the following-

a. Assessment of the child's airway, breathing, circulation, disability, state of consciousness, and status of exposure, immediately within contact.
b. Performing a thorough evaluation to determine relevant history (how, when, where, the agent, first aid received, and sociodemographic factors), salient examination (vital parameters, any inhalational or other injuries), and local inspection (site, depth, distribution, extent as TBSA, and any secondary changes).
c. Supportive care (i.e. fluid management and nutritional support) as per standard protocol
d. Pain assessment and management using age-appropriate dosage and nature of analgesics
e. Wound management aimed at rapid healing, wound cleansing, debridement, and dressing. In most cases of minor scalds, topical silver sulfadiazine is an effective remedy.
f. Psychological care and support to the child and family to overcome the emotional trauma.

Q. What are the pointers toward intentional scalds that pediatricians should be aware of?

Child-related high-risk factors of intentional scalds include young child, chronic illness, girl child, unwanted child or child misbehavior. Parental risk factors are teenage pregnancy, poverty, illiteracy, alcohol or substance abuse, domestic violence, or nonbiological caregiver. Indicators that point toward possible abuse are: Delay in seeking medical care; the history that keeps on changing or is inconsistent with the nature of the injury or developmentally impossible; attributing the injury to another child; an unrelated adult bringing the child for medical attention; other indicators of physical abuse; or prior history of abuse.[5] Table 1 depicts characteristics of lesions that help in differentiating between abusive and accidental burns.[6]

Legislature-Child abuse protection laws

Considering intentional burns as a dangerous weapon of offense, it has also been included in Section 326 of the Indian Penal Code, which deals with acts voluntarily causing grievous hurt by using dangerous weapons or means. Under this section, the use of fire or any heated substance as a weapon of offense is punishable by imprisonment or/and fine as indicated.

The World Health Organization defines "Child Abuse" as a violation of the basic human rights of a child. It constitutes all forms of physical, emotional ill-treatment, sexual harm, neglect or negligent treatment, commercial or other exploitation, resulting in actual harm or potential harm to the child's health, survival, development or dignity, in context with a relationship of responsibility, trust, or power. The Ministry of Women and Child Development is primarily responsible for child rights and protection. Other bodies include the National Commission for Protection of Child Rights (2007), which enquires, investigates, and recommends action against perpetrators of child abuse and neglect; Child Welfare Committee; and Integrated Child Protection Scheme (2009). The four core laws concerning child protection are: (i) Juvenile Justice Act/Care and Protection (2000, amended 2015); (ii) Child Marriage Prohibition Act (2006); (iii) Protection of Children from Sexual Offences Act (2012, amended 2019), and; (iv) Child Labor Prohibition and Regulation (1986, amended 2016). CHILDLINE (1098) is a 24 × 7 emergency telephonic helpline, which helps in linking children reporting abuse or neglect with rehabilitation services.

Through this case, we have tried to highlight the management of a commonly encountered, yet totally preventable injury in

children. It is important for the frontline physician to be aware that both the child's medical and psychological care needs to be addressed while being on the lookout for the possibility of abuse.

Declaration of patient consent

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

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Child Health in the Hinterland

A Premature Baby with Respiratory Distress in a Rural Primary Health Center: Role of Technology in Newborn Care

Over the last two decades, the place of childbirth in India has shifted from homes to hospitals: while in 2004–2005, 60% of all childbirths were at home, in 2018–2019, more than 80% of childbirths in 18 of the 22 Indian states took place in a health facility. This shift was noted in rural as well as urban areas. While the newborn mortality rate (NMR) has declined in the same period, the magnitude of reduction is not proportionate to the increase in institutional births.[1] Insufficient improvement in the quality of maternal–newborn care is probably the reason for this inadequate decline in NMR.

Much has been said about the value of technology in improving newborn care. Indeed, technology has a huge potential to improve the quality of care for the three major leading causes of deaths in this vulnerable age group in India: neonatal sepsis, asphyxia, and low-birth weight. However, such technology is often developed for application in hospitals and well-resourced

settings and may not be easy to deploy or use in reality in primary care settings.[2]

Basic Health Care Services (BHS) runs a rural primary health center (PHC) in Dungarpur district of South Rajasthan as a public–private partnership. This PHC serves a total population of 25,000, the majority of whom (80%) belong to a scheduled tribe. A male family member has migrated to the city for labor from almost 60% of the households. The nearest referral hospital is 60 km away, and it takes a motorized vehicle about 2 h to travel this distance due to the poor condition of the roads.

The PHC is managed by a medical doctor, four nurses, qualified as general nurse midwives, a laboratory technician, a pharmacist, and a cleaning staff. The PHC staff can connect with the specialist doctors, including a pediatrician by telephone at all hours. About 30–40 childbirths are conducted in the PHC every month, about one-third of whom are low-birth weight.

We present the narrative of a baby who was born prematurely in this PHC and developed respiratory distress within 1 h of birth. Through this case, we aim at highlighting the value of appropriate, low-cost technology that, when deployed at scale, can lead to saving many newborn life in low-resource primary care settings. We further discuss the characteristics of technological solutions that are appropriate for such settings and emphasize the need for developing and deploying these solutions.

Case Study

Nisha (*name changed*), a 20-year-old woman presented to the PHC at 34-week gestation with spontaneous labor pains. She was a primigravida mother who gave a history of receiving four antenatal care visits in the village where her in-laws resided. Her spouse is a migrant laborer based in Ahmedabad. As is the custom, she had come to her parent's home for childbirth, which was in a village lying in the catchment area of our PHC. The pregnancy had been uneventful, and she continued to perform heavy work at home and farms during pregnancy. She had taken some iron–folic acid and calcium supplements during pregnancy, but her compliance was not adequate. When she presented to us during labor, she weighed 53.5 kg, and her height was 144 cm. Her hemoglobin was 8 g/dL.

Nisha's labor progressed normally, with the fetal heart rate (as monitored by a fetal Doppler), staying normal throughout. However, when the baby girl was born, she did not cry immediately. The attending staff resuscitated the baby as per standard protocol, and she started crying after a few minutes. The birth weight was 2271 g and the baby was placed on skin-to-skin contact with her mother for kangaroo mother care (KMC). The baby was noted to have tachypnea, chest in-drawing, and grunting; though perfusion was maintained, there was no cyanosis and the baby was moving her limbs actively. However, the condition continued to worsen, and 30 min after birth, pulse oximeter revealed oxygen saturation (SpO_2) of 88%.

We made a clinical diagnosis of prematurity with severe respiratory distress, possibly hyaline membrane disease. Referral to a higher center was categorically ruled out by the mother and her female attendants, due to the absence of any a male kin member. Hence, we started teleconsultation with a neonatologist. In the meantime, the team started the baby on O_2 at 1 lpm, using an O_2 concentrator and nasal prongs. They also administered maintenance intravenous (IV) fluids and IV antibiotics. The blood sugar levels remained within normal limits. Respiratory distress continued with SpO_2 fluctuating below 94%, despite receiving O_2 and increasing the flow rate up to 4 lpm.

It was decided to use indigenously prepared continuous positive airway pressure (CPAP) to deliver O_2 [Figure 1]. Nasal prongs were connected to a three-way cannula. Tubing from one end of the cannula was connected to the O_2 concentrator, while a glass bottle filled with 10 cm of water was attached to the other end [Figure 2]. The depth of tubing in the water determined the CPAP pressure being provided.

After CPAP with 4 l of oxygen was started, the baby's saturation stabilized around 96% and respiratory rate normalized to around 54/min within 2 h. Over the next few hours, the baby became comfortable and stopped grunting, and we were able to progressively decrease the oxygen flow rate. After 24 h, the baby had a respiratory rate of 50/min, did not have any intercostal retractions, and was maintaining

Figure 1: Simultaneous administration of indigenous continuous positive airway pressure and kangaroo mother care to the baby in the primary health center

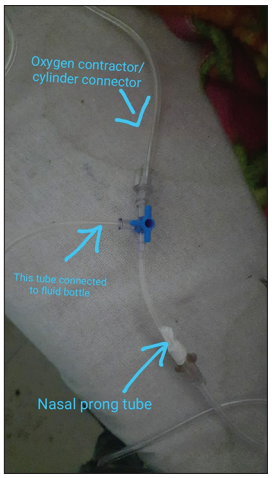

Figure 2: Components of the indigenous continuous positive airway pressure

SpO_2 above 95% on room air. The mother had continued to provide KMC throughout and had started breastfeeding when the baby was stable. Antibiotics were continued during hospital stay. On day-3, we discharged the baby, encouraging mother to continue exclusive breast feeding (EBF) and KMC at home.

The auxiliary nurse midwife (ANM) and accredited social health activist (ASHA) worker visited the mother and baby on regular intervals at home. They supported continuity of providing KMC and EBF. Throughout the first 4 weeks after birth, the mother and maternal grandmother alternated in providing KMC for 8–10 h per day. At the 6 weeks visit, the baby weighed 3350 g and was thriving.

Discussion

As enunciated in the Alma Ata declaration, appropriate technology made universally available is one of the important characteristics of PHC. Despite its promise, much of the available technology is not actually appropriate, especially in low-resource settings. For example, a radiant warmer that requires regular power supply will not be helpful if the power supply is erratic. In other cases, the skills required to operate the said technology can be imparted only after extensive training and, that too, in specialized settings, e.g., the use of intermittent positive pressure ventilation. Further, the costs of the technology being considered may be prohibitive, or maintenance may be expensive and unavailable.[3] Therefore, many options of available technology remain unused or underused.

In contrast, the four technology-based solutions cited in this case are examples of the appropriate use of technology in low-resource settings. Small, portable pulse oximeters are inexpensive, easy to use, and critical in the assessment of respiratory distress. Oxygen is lifesaving for many patients in PHC settings, where referral to the next level of care may not be feasible, will be expensive, and may be too late. Oxygen concentrators are easy to use and low cost alternatives to heavy oxygen cylinders. However, their use requires regular power supply, which may be challenging in some settings. This can be overcome by models that are charged and operate on battery. In our PHC, we have limited power backup and a few O_2 cylinders for backup. Indigenous CPAP is another simplified solution to the common problem of severe respiratory distress that can be life-saving, especially when managed by a skilled team. KMC is the simplest intervention that demonstrated a huge impact on newborn survival, growth, and bonding between mother and baby.[4] It only requires a healthcare worker to train, support, and empower family members to participate in the care, development, and survival of their babies.

This case study illustrates the value of appropriate technology in saving newborn lives. However, much of healthcare technology is not appropriate in many low-resourced primary healthcare settings, due to expense, difficulties in deployment or use, and dependence on uninterrupted power, high-speed internet, or personnel with specialized skills. Pediatricians, primary care professionals, and technologists should come together to develop and deploy simple, affordable, and usable technology options that would help us inch closer toward the dream of primary healthcare for all, especially vulnerable populations who need it the most.

Declaration of patient consent

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

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World Health Organization, Division of Child, Adolescent, Maternal and Reproductive Health has supported the project to integrate KMC within the PHC that we (BHS, www.bhs.org.in) run as a public–private partnership.

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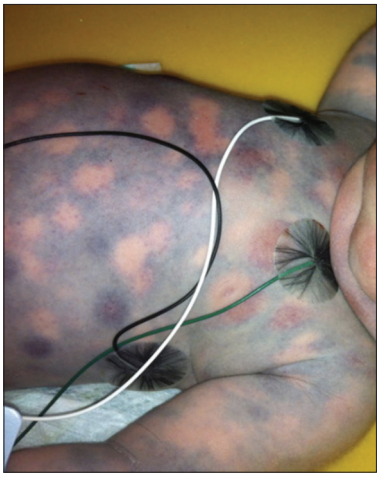
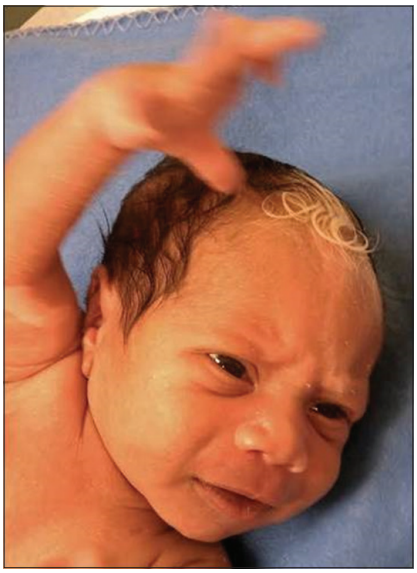
Neonatology Quiz for Pediatricians

Neo-Quiz 4

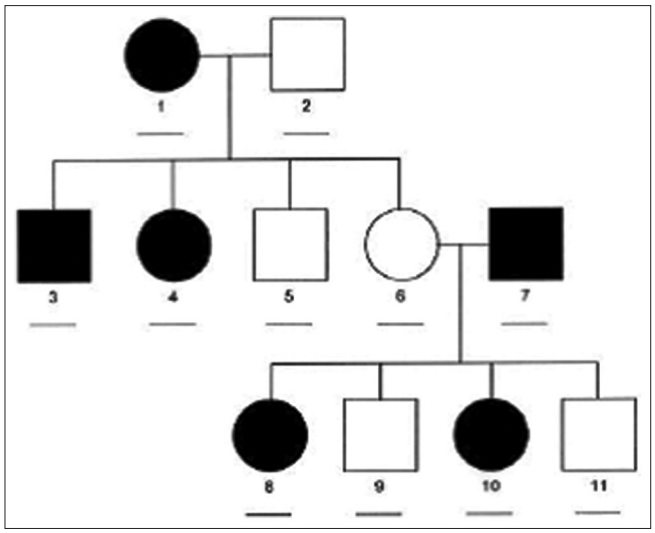
1. During an online expert consultation session, a general practitioner was sent the summary a 2-day-old boy with rashes [Refer to the figure below]. The baby was born at term with a birth weight of 2 kg. The discharge summary recorded normal vitals and abnormal heart sounds. What is this rash? What is the most likely diagnosis?



2. A 3-day-old boy has an unusual appearance [Refer to the figure below]. Both the baby's eyes are of different color and he is nonresponsive to loud sounds. What is the most likely diagnosis?



3. A baby boy is born to an insulin dependent diabetic mother. The presence of abdominal distension and initial inability to pass stools (which had subsequently improved) led the doctor to investigate for Hirschsprung's disease. However, the rectal ganglion cells were normal. What other condition should be considered?
4. Identify the inheritance pattern depicted in the following figure.



5. Name a glycogen storage disease which is also a lysosomal storage disease
6. What is the stomach capacity of a neonate at birth?
7. Which component of breastmilk is effective against *Entamoeba histolytica*?

Declaration of patient consent

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Dr Watson's Clinical Mystery

Clinical Approach to a Febrile Young Infant with Hepatosplenomegaly Using the Principle of Occam's Razor

In the prepandemic era, a 2-month-old girl presented to the hospital with refusal to feed for 1 day. Her parents gave a history of fever for a few hours daily for a week, that had never been documented. She also had gradually progressive abdominal distension for the same duration. There was no history of vomiting, loose stools, jaundice, bleeding from any site, rashes, seizures, lethargy or excessive crying, cough, or difficulty in breathing. The urinary and stool patterns were unremarkable. Before her illness, the baby was predominantly being breastfed but also given diluted formula milk by bottle. Her feeding had become poor for a week and almost nil for a day. She had received some medication from a practitioner for 3 days, the nature of which was unknown.

The baby was hospital born to an unrelated couple at 36 weeks gestation by vaginal delivery with a birth weight of 2 kg and normal Apgar scores. On the second day of life, she developed jaundice for which she received phototherapy for a day and was discharged. The antenatal period had been uneventful with quickening perceived at 4 months. The 28-year-old mother had history of an unexplained stillborn at term and a 2-month spontaneous abortion. There was no other contributory family history. The baby had been vaccinated at birth and 6 weeks.

The baby was normothermic with stable vital parameters. The weight was less than 3rd percentile, but length and head circumference were normal. Pallor was present. The anterior fontanelle was at level and no icterus, rashes, petechiae, ecchymoses, edema, or unusual facies/overt congenital anomalies were noted. The upper abdomen appeared full without any visible distended veins. Firm hepatosplenomegaly was present with liver 3 cm below costal margin (span

Table 1: Application of the 2004 hemophagocytic lymphohistiocytosis clinical trial diagnostic criteria in the index patient

Diagnostic criteria	Patient
Fever ≥38.5°C for more than 7 days	Present
Splenomegaly	Present
Pancytopenia (at least 2: Hemoglobin <9 g/dL, platelets <100,000/μL, ANC <1000/μL)	Present
Increased triglyceride levels (>265 mg/dL) and/or fibrinogen <150 mg/dL)	Present
Tissue hemophagocytosis (bone marrow, spleen, lymph node, or liver)	Present[#]
Low or absent NK cell activity OR reduced/absent surface expression of NK cell perforin and/or CD107α (lysosomal associated membrane protein 1)	Not done
Ferritin >500 ng/mL (levels >3000 ng/mL more indicative of HLH	Present
Soluble CD25 (sCD25) or soluble IL-2 receptor α (sIL-2R) >2400 IU/mL	Not done
Elevated CXCL9*	Not done

[#]This was done postmortem, *Some authors include this as the ninth criteria (5/9 to be met). ANC: Absolute neutrophil count, HLH: Hemophagocytic lymphohistiocytosis, sIL-2r: Serum-soluble interleukin-2 receptor, IL-2: Interleukin-2

8 cm) and spleen 5 cm below costal margin. Ascites was not appreciated and bowel sounds were normal. Although cry and spontaneous movements and neonatal reflexes were preserved, they appeared depressed. Cardiovascular and respiratory systems were normal.

Dr. Watson: There is no clinical indicator of a surgical cause. The clinical phenotype is an acute febrile illness and hepatosplenomegaly (HSM), so the etiology is probably infectious. It may be sepsis, but I must exclude malaria, urinary tract infection, and meningitis, the usual causes of fever in a young infant. Pending the baseline test reports, I will start intravenous fluids and empirical parenteral broad-spectrum antibiotics that will cover community-acquired microbes. The organomegaly is a bit too firm than usual for an infant though.

The hemogram displayed low hemoglobin (5.5g/dL), decreased absolute neutrophil count (704/mm^3), thrombocytopenia (26 × 10^9/L), and a reticulocyte count of 2.5%. The peripheral smear was normal, apart from the decreased leukocyte and platelet populations, and there were no toxic granules, indicators of hemolysis, or abnormal cells. The C-reactive protein was elevated (32 mg/L). The only biochemical abnormalities found were in the liver function tests; SGOT 125U/L, SGPT 33U/L, PT 21.8 s, APTT 52.1s, and INR1.8 s. D-dimer levels were normal. Investigations for malaria were negative. Urine microscopy was normal, as were cerebrospinal fluid (CSF) cytology, gram staining, and biochemistry (the lumbar puncture was done after platelet transfusion).

Dr. Watson: Hmm. She has HSM, transaminitis, and pancytopenia. Can it be hypersplenism resulting from portal hypertension with secondary sepsis? Or an infantile malignancy like a neuroblastoma or an embryonal tumor? An ultrasonogram is non-invasive and I can get it done while I await the blood, urine, and CSF culture reports.

The abdominal ultrasonogram confirmed hepatosplenomegaly with normal echotexture. The portal vein diameter was normal. There were no calcifications or lesions in any organ or mesenteric lymphadenopathy. All three cultures were sterile after 48 h.

Dr. Watson: Sherlock always says I should use the principle of Occam's razor and look for a single simple explanation rather than multiple, complex assumptions. I need to think of an infantile-onset disorder that would explain the triad of fever, HSM, and pancytopenia. The first differential may still be infectious- maybe a congenital TORCH or Human Immunodeficiency Virus infection; the second an infiltrative disorder of the bone marrow by a hematological malignancy (acute lymphoblastic leukemia?), Hemophagocytic lymphohistiocytosis (HLH), or a storage disorder like Gaucher disease type 2.

The TORCH immunoglobulin M panel for toxoplasmosis, rubella, cytomegalovirus, and herpes viruses was nonreactive, as was the maternal HIV status. Bone marrow aspiration exhibited hypercellular marrow with erythroid hyperplasia, normal maturation of myeloid series, and megakaryocytes and absence of any abnormal cells. Ferritin levels were high (2000 ng/ml), triglycerides levels elevated (792 mg/dl), and fibrinogen low (93 mg/dl).

Dr. Watson: Five of the eight diagnostic criteria of HLH are satisfied in Table 1. I must start HLH directed treatment right away. I will order a Whole Exome Sequencing (WES) as well.

Two weeks had elapsed by the time the diagnosis was made. The baby's condition had deteriorated considerably, by then. The parents were counseled about the grim prognosis and the necessity and risks of the HLH-2004 treatment protocol. After sending appropriate cultures, the baby was empirically started on the next line of intravenous antibiotics (meropenem and vancomycin) and an antifungal (caspofungin), to minimize the possibility of a nosocomial infections flaring up with immunosuppression. The treatment was initiated with dexamethasone and oral cyclosporine. Supportive care (cryoprecipitate and fresh frozen plasma) was provided as required. However, the baby continued to deteriorate (hence, etoposide could not be given) and she succumbed within 18 days of admission. The parents agreed to a postmortem liver biopsy that demonstrated evidence of hemophagocytosis. The WES report confirmed a PRF1(-) gene mutation with homozygous variation in exon 2 and c. 386G > C (p. Trap129Ser).

Dr. Watson: This mutation is the most common cause of Type 2 Familial Hemophagocytic lymphohistiocytosis (FHL). Even though we lost this baby, we can now offer prenatal testing

for the next pregnancy. I must ensure that the family receives proper genetic counseling.

Discussion

Every pediatrician knows how difficult ascertaining the etiology of a patient with HSM can be, given the heterogeneous causes, and the multiple clinical phenotypes involving permutations and combinations of pallor, jaundice, lymphadenopathy, etc. Then, there are other dimensions that need to be factored in; age of onset, duration, presence or absence of fever, etiological yield, invasiveness, and cost of the multitude of tests, etc. One must employ an individualized, logical, and sequential clinical approach. This is a situation that requires the principle of Occam's Razor. Initially developed for mathematics, its use has extended to philosophy, science, and the field of clinical medicine. When an event has more than one explanation, consider the one that requires the simplest or fewest assumptions. This is what Dr. Watson used to arrive at a clinical diagnosis of HLH, and then establish etiology as FHL. However, in the less than Utopian Indian settings, availability of tests and limited financial resources are major challenges to this process.

HLH is an aggressive and life-threatening autosomal recessive syndrome resulting from mutations in the PRF1, STX11, UNC13D, or STXBP2 genes. It affects one in 100,000 children, with the highest incidence in those less than 3 months. The underlying pathophysiology is a hyperimmune state which renders cytotoxic T-lymphocytes and natural killer cells incapable of lysing macrophages. These in turn, produce increased cytokines such as tumor necrosis factor-α, interferon-ϒ, and interleukins that generate the fever and cause extensive multiorgan destruction.

Clinical manifestations are usually nonspecific, with fever and HSM. Investigations can provide a clue and a high index of suspicion should be kept when there is pancytopenia, which presents from the onset in the majority.[1] This occurs due to two mechanisms; hematopoietic suppression by elevated cytokines or hemophagocytosis by overactivated macrophages.[2] However, this may not be evident in the early phases of disease and may necessitate repeated bone marrow/tissue examination.[3] Biomarkers include hypertriglyceridemia (cytokines suppress lipoprotein lipase), increased ferritin (secreted by macrophages), and reduced fibrinogen (increased release of plasminogen activator leading to hyperfibrinolysis).

According to the HLH-2004 trial diagnostic criterion,[4] molecular diagnosis for children is confirmatory by homozygosity or compound heterozygosity for any of the HLH-associated mutations. In adults, the criteria include heterozygosity of one of the genes with consistent clinical findings or five of the eight/nine findings given in Table 1. It is important to remember; however, that these diagnostic criteria were established for the stringent settings of clinical trials. In reality, treatment should not be delayed if they are not satisfied given the high mortality of HLH, and the fact that patients may be too ill to undergo biopsies or tests may not be available. In these situations, modified criteria may be used for diagnosis: three of four clinical findings (fever, splenomegaly, pancytopenia, or hepatitis) and the presence of at least one abnormal immune marker (hemophagocytosis, increased ferritin, hypofibrinogenemia, or absent/very decreased NK cell function).

The 2004 trials advocate early initiation of chemotherapy and immunosuppression for 8 weeks with dexamethasone, cyclosporine, and etoposide.[5-9] These may induce remission, as indicated by resolution of fever, decrease in spleen size, reduced ferritin levels, increased platelet counts, and normalization of fibrinogen. Hematopoietic stem cell transplantation (HSCT) is indicated in familial, persistent, or recurrent disease.[6,7] Prognosis is better when treatment is initiated early and in older children.[7-9] There are two studies of Indian children with HLH. The first[8] included 43 children (mean age 46 months) who were treated with corticosteroids (67%), intravenous immunoglobulin (64%), cyclosporine (33%), and etoposide (15%). The overall 2-year survival rate was 76%. The second study[9] included eight infants (mean age 7 months) who received management as per the 2004 HLH protocol. Of the five who received only induction, four died and one abandoned therapy. One of the two who underwent HSCT survived, while the last one was on the waiting list at the time of publication.

To conclude, a high index of suspicion of HLH should be kept in infants with fever, HSM, and pancytopenia and timely investigations sent. Molecular diagnosis is confirmatory, but as far as possible treatment should not be deferred for genetic or immunological testing, as the mortality rate is very high. Nonetheless, every attempt should be made to identify the underlying mutation so that prenatal testing can be offered.

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News Excerpts

Uncommon Causes of Allergies in Children

The incidence of allergies has been increasing globally, especially those pertaining to food and environmental allergens. This has been attributed to reasons like the cross-reactivity of allergens, increased travel, and rising levels of pollution, among many others. In this section, we shall discuss three interesting, but uncommon allergic manifestations in children.

Irahara M, Nomura I, Takeuchi I, et al. Pediatric patient with eosinophilic esophagitis and pollen-food allergy syndrome. Asia Pac Allergy 2020;10:e28.

This case describes an 8-year-old Japanese boy with a history of intermittent episodes of vomiting since the age of 2 years. The child had undergone tonsillectomy when he was 4 years following the suspicion that tonsillar hypertrophy was the cause of his vomiting, but the symptoms persisted. Episodic rhinorrhea and nasal congestion that were more in the winter and spring began after he turned 5 years old. At the age of 7 years, the child developed episodes of a feeling of 'itchiness' of the lips and throat, following the vomiting. It was noted that this occurred immediately after eating certain fruit such as kiwi, cherry, and apple. A positive family history of allergies in his parents was elicited and he was referred for evaluation and elimination of allergens when he was 8 years old.

The boy was 125.7 cm tall (–0.1 standard deviation [SD]), and weighed 25.6 kg (–0.2 SD). The remaining examination was unremarkable. There was a significant elevation of total immunoglobulin E (IgE) levels (215 IU/mL), particularly for antibodies specific for birch, apple, kiwifruit, peaches, and walnuts (>0.35UA/mL). The skin prick test (SPT) for fruits and nuts (raw kiwifruit, raw and heated peach, raw cherry, walnut, and hazelnut) revealed a positive wheal (≥3 mm in diameter). A diagnosis of Pollen food Allergy Syndrome for apple, kiwifruit, and cherries was made. Since raw and heated antigens caused positive results only for peach, it suggested the possibility of different sensitization routes for apple, kiwifruit, and cherry, vis-à-vis peach. The SPT was not be followed by an oral food challenge with nuts and peach as per usual protocol, as the parents did not give consent. However, the aforementioned items were completely eliminated from his diet. The vomiting did not resolve.

An esophagogastroduodenoscopy was performed after 11 months. This showed longitudinal furrows and esophageal rings in the mid to lower esophagus, eosinophilic infiltration in the stratified squamous epithelium of the mid esophagus and marked lymphoid follicles in the lower esophagus. The diagnosis was changed to Eosinophilic Esophagitis. The child

was started on oral esomeprazole (20 mg/day), following which his symptoms improved significantly, as did the repeat endoscopy findings.

Ballardini N, Nopp A, Hamsten C, et al. Anaphylactic reactions to novel foods: Case report of a child with severe crocodile meat allergy. Pediatrics 2017;139:e20161404.

A 13-year-old boy presented to the pediatric emergency following an anaphylactic reaction after ingesting crocodile meat (brought by his father, a professional chef, to prepare an exotic meal). After taking the first bite, the child developed itchiness in the mouth and throat, facial urticaria, conjunctivitis, angioedema, chest tightness, and breathing difficulties. The child had been diagnosed with chicken meat allergy since he was 5 years of age and followed a poultry-free diet. When he was 7 years old, he had an anaphylactic reaction after accidental intake of turkey, and an adrenaline autoinjector was prescribed.

The parents had immediately administered intramuscular adrenaline and β-2 agonist inhalation at before bringing him to the hospital. On hospitalization, salient examination findings were facial urticaria, periorbital angioedema, bilateral redness of the sclera, laborious breathing but no bronchospasm. The child became stable within 4 h and was discharged. As there were no previous reports of allergic reactions to crocodile meat in literature, the authors hypothesized that α-parvalbumin, a specific chicken meat allergen, may also be expressed in crocodile tail meat and/or the presence of IgE cross-reactivity between the two.

Das L, Ward MG. Case 1: A 12-year-old girl with food allergies and an acute asthma exacerbation. Paediatr Child Health 2014;19:69-70.

A 12-year-old girl, who was a known case of bronchial asthma, presented to the emergency department in the winter, with a sudden feeling of suffocation associated with bluish discoloration of the lips. She had been having an acute exacerbation (increased work of breathing, cough, and wheezing) for 3 days. The episode was preceded by symptoms suggestive of a mild upper respiratory tract infection. The patient reported increased requirement of inhalation with her prescribed short-acting bronchodilator, and incomplete response, compared to previous episodes. She had been compliant with her medication and had not had an exacerbation for the previous 6 months. At presentation, she had an oxygen saturation of 85% in room air, respiratory rate of 40 breaths/min, increased work of breathing and decreased air entry, bilaterally. She received salbutamol, ipratropium, intravenous steroids, and magnesium sulfate immediately, after which the child improved. The chest radiograph revealed hyperinflation.

Causes for the sudden worsening were probed for. History of symptoms of hypersensitivity (wheezing, dyspnea, and pruritis) was elicited on ingestion of certain food items (peanuts, chickpeas, and lentils) and seasonal exposure to grass and pollens. The parents reported that she had been demonstrating a depressed mood associated with reluctance and anxiety related to going to school for some time. There was no history indicative of substance abuse. Further probing revealed that she was being bullied at school for several months, primarily due to her food allergies. Three days earlier, her classmates had smeared peanut butter on her schoolbook and her symptoms had got triggered after she handled it.

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Wonder

Editor's comment: The genesis of this book was a life-changing incident that occurred in the life of R. J. Palacio. She had gone somewhere with her young son when they came across a girl with an atypical face, and he became scared and started crying. The author felt that removing her son would be the best option in a difficult situation, but her decision only resulted in inadvertently upsetting the girl and her family. As providence would have it, Palacio chanced upon the song "Wonder" by Natalie Merchant. The lyrics and the incident became her muses and she started writing the book. Do listen to it, if you can.

Doctors have come from distant cities, just to see me,

Stand over my bed, disbelieving what they're seeing;

They say I must be one of the wonders of God's own creation.

And as far as they see, they can offer no explanation…

Incidentally, the book was published in 2012, while the movie was released in 2017.

Wonder by R J Palacio

What's better a movie or a book? A book, I guess. Because it lets your mind drift into the world of the story and lets you see the characters and feel their emotions like you were one of them. Well, I saw the movie, "Wonder," first and that gave faces to the beings I imagined reading through the book. And I'll stick to my answer, books are definitely better than the movie, any day.

"*You can't blend in when you were born to stand out*" says the soothing blue cover of the first book by R. J. Palacio. It carries an animated half face of a boy with oddly placed eyes and ears, and no more features to see. I guess the animator found it easier to draw it like that for the main character, who is a child with a craniofacial malformation and genetic syndrome that the author doesn't name throughout the book.

August Pullman or Auggie, as everyone calls him, takes you through his thoughts and experiences as he joins school for the first time at the ripe old age of 10 years. Born with a complicated facial deformity (I read somewhere that Auggie has Treacher Collin's syndrome), he spent a good amount of time in his first few years; in and out of hospitals, undergoing several surgeries to correct the facial deformities, being fed through tubes while he recuperated and undergoing multiple plastic surgeries to make his face more acceptable to the world. But Auggie doesn't seem to have "felt" the surgeries as much, as he was affected by the astonishment, shock, and even fear that always accompanied the glances given to him by the rest of the world. With his lovable sense of humor, Auggie describes the people he has met and how they reacted to him, while he coolly goes on with his life. He introduces you to every member of his family, including his dog Daisy, in a way that makes you feel you have become a part of his life. Auggie is like just any other 10 years old with a fetish for anything that revolves around "Star Wars" or science. His handling of people's behavior though, is way beyond his age.

The book is described in chapters written in first person in a distinctive style that reflects the distinctive personality of the narrator. It takes you through the minds and thoughts of not just Auggie, but his sister, his friends and classmates. This type of portrayal helps you understand how each one feels about the fact that Auggie has a complex genetic syndrome, and how that knowledge affects their relationship with him. As he is directly joining middle school without any prior experience of the intricacies of school life, the school director arranges a preschool welcome with three children handpicked to be his buddies and show him around. Each of them is an individual with different reasons for being his buddy, and with different thoughts and reactions to Auggie and his face. At some point, the book transposed me back to my own school experiences of being the victim of bullying, and how it still affects me on my 1st day anywhere; a new institution, a new workplace or even just meeting new people for the first time. Paradoxically, it was actually refreshing to relive those days and I did what I've always wanted to do, read the minds of the friendliest and nastiest kids in my class.

As paediatricians, one gets to see children with problems and special needs that we know they will live with for the rest of their lives, and one thinks "*let's accept that the universe hasn't been kind to ….*" as someone says in relation to Auggie in the book. We sympathise with the family and what we think they suffer. As a third person and a doctor, one tends to forget that they are just as normal as the rest of us, apart from the medical issues that complicate the way society sees, and behaves with them. The World Health Organization describes "handicaps and disabilities" as more of a social disease than an individual's disease in themselves. If this concept has been difficult for you

to understand so far, reading "Wonder" will definitely help you experience it. The book does its bit to help you understand that children with complex syndromes need empathy and compassion rather than simply sympathy.

The high points of the book are Auggie's mature and brave reactions to the comments that come his way from people that don't matter to him, and those that do. And not only that, it helps you understand what it feels to be his friend, his mother, his sister, his sister's boyfriend, his sister's best friend and anyone else, whose life Auggie has touched by his mere presence. The author has a wonderful and warm style of writing. Though this is Palacio's first book, it comes as no surprise that it has sold more than a few million copies, and became a best seller. I'll recommend this to be read by every paediatrician who feels that it is not just important to treat children with special needs but equally critical to understand what goes on in their minds, because I strongly believe that "healing goes way beyond treating!"

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I Wear the Mask, It Does Not Wear Me (Out)!

In "The three musketeers," Athos, Porthos, and Aramis planned the rescue of Phillipe, an unfortunate member of the royal family who had been wrongly imprisoned by his identical twin, the brutal King Louis XIV, and forced to wear an iron mask. One of their concerns was that the tribulations Phillipe had faced might have permanently scarred his soul for the worse. However, when they finally managed to liberate him after a series of tumultuous events, Phillipe declared "I wear the mask, it does not wear me!" That statement has stuck tenaciously onto me since I was 12 years old, and first read the book. Little did Alexandre Dumas realize in the 1800s that these words would hold a whole new meaning, a little more than two centuries later. However, the essence remains the same. Circumstances and situations around us will change (and not always for the better), but we would be expected to remain strong, resilient, and positive. It is in this context that I am inspired to relate three incidents in my life that revolve around this theme.

My smartphone pinged at 6.15 am. I opened one bleary eye to focus on the picture of the unknown sender – "Do you remember me doctor?" I snapped to attention as the eyes looked very familiar. The rest of the face in the image was masked, as is everybody else for more than a year now. Racking my memory's deepest recesses was to no avail. After a brief moment, I heard a second ping. This time viewing an "unmasked" picture caused realization to finally dawn, and I felt a sharp stab of pain in my heart. It was the mother of a neonatal patient from years ago, who happened to be a burn victim. Her lower face, neck, and torso were a mangled mess of a scar. She had painfully endured the stolen glances of strangers, muted comments of passers-by, and ostracization from even her own family, ever since an accidental domestic cooking gas explosion had changed her life forever at the tender age of 22 years. "I walk free now doctor; I am not the only one who has to cover my face. I am the same as everyone else around me." She followed it up with an emoji that brought a smile to my face, and made my day.

It was a routine outpatient service day, barring the fact that I was wearing my N95 mask. A family walked in with a jaundiced baby, comprising the parents and an overly enthusiastic grandmother who monopolized the entire conversation. It irked me no end that the parents seemed completely disinterested in the proceedings. I wanted to explain the chances of rising jaundice over the next few days and the need for close follow-up, to the parents directly. When I pointedly turned toward them and began my usual barrage of medical jargon, the grandmother interrupted. "Doctor," she said, "they are both deaf-mute, but they can lip read. You will have to remove your mask and speak slowly and deliberately." Suitably chastised, I moved away to a safe distance, removed my mask, and started my explanation to the now very attentive young couple. There is always another side to every story!

In 2007, I ventured to appear for my first postdoctoral entrance examination for super specialty training in neonatology. Outside the hall were innumerable aspirants, all of whom were competing for the only two seats in the country. There I bumped into an old schoolmate, who introduced me to his wife. She was clad in the traditional burqa with a veil that left only her eyes uncovered. All I could see were two palpebral fissures. It made me wonder how I would recognize her again if we ever met without her husband being present. Retrospectively, that seems to be a skill that we have all been forced to learn. In fact, it has now become difficult to recognize people whom you met for the first time in the COVID era, when they are sans their masks!

All is not lost, hang in there!

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My Memorable Patient

Physicians often get nostalgic when they are asked to write or talk about a memorable patient. More often than not the patient is a rare case or a rare presentation of a common disease. It is not quite uncommon to come across loads of columns titled memorable patients in various medical journals. In my short pediatric practice, I have come across umpteen patients who put me up in a dilemma as to the diagnosis but my memorable patient is a 6-year-old girl who taught me how to live, more importantly she taught me how to be grateful to god. I call her Miss X.

Life for a pediatric resident can be quite tough at times. Unearthly working hours, stress, constant bickering of seniors, it's maddening to say the least. If you are have done your residency from a government medical college, you would agree with me that it is an extremely tough world down there.

It was one of those bright sunny mornings when I was called to attend upon Miss X. I had a bad start to the morning the bathroom tap had gone dry leaving me dry (the privilege of being a in a government hostel where living conditions are pitiable to say the least). In my foulest of moods I went to attend the patient. I had to take her history, fill in her case sheet, plan the relevant investigations and present it to the unit chief who would send me to the gallows if I make a single mistake. Luckily for me, Miss X had been to various hospitals before and had a thick folder of case reports and investigations. In my blackest mood I went to the X's bed, she was propped up reading an Amar Chitra Katha. Being a voracious reader myself, I am quite partial to those who read and my mood brightened up for here was a child who was interested in reading. Before I could mumble a hello, she said hello doctor I am 6 years old, have blood cancer and I am going to die soon. I was in a daze struck by the gravity of her medical illness. For the next hour or so I was in a trance listening to every word she had to say. She was in great pain the cancer had spread across her body making even talking difficult.

Miss X was a good student, she wanted to become a doctor. She had lot of friends who shared her Amar Chitra Kathas and watched Tom and Jerry with her. She had lost her golden hair due to the long chemotherapy sessions. At the end of our conversation I could only mumble a thank you and wish her all the best. In the tea club, the chief dwelled upon the case and declared it as a terminal one. She died in the night.

Miss X taught me one of the most important lessons a doctor could learn. Patients especially kids always do not need the state of art of technology, expensive medicines, fancy lab tests they need someone who has the willingness and patience to listen to them, someone who believes in their dreams however, silly they may be, someone who lends an ear, someone with whom they can share their trivial secrets, someone who can understand their pain, someone who gives them time.

Another point I think our residency programs lack is, though they make us think a lot, take correct decisions but somewhere down the line the Humane touch is getting lost under the huge workload of never ending labs, case histories, review meetings.

I wish we could teach our residents that sometimes apart from the armentarium of medicines, kids do need someone who puts a hand across their shoulder and say You would be fine, don't worry, I would be your Albus Dumbeldore, I would wave my magic wand and everything would be okay. After all we do require some magic in our life don't we?

All what is needed is to see with the eyes of another, listen with the ears of another and feel with the heart of another. If we can find a way where we all bring in a bit of empathy into our practice our children would be in a happier world.

Miss X taught me all of these. Thank you for being there Miss X.

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