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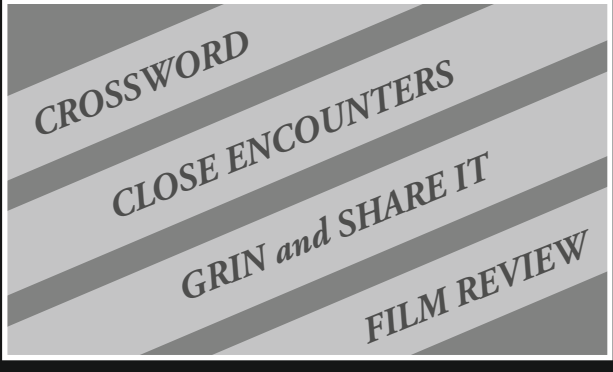

HIGHLIGHTS OF THIS ISSUE

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Indian Pediatrics Case Reports

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Contents

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What is so Special about *Indian Pediatrics Case Reports*?

In recent months, several senior- and middle-tier faculty members expressed interest in sending their cases to our journal. This was not to increase their number of publications, but because they felt that the quality of our case reports was "pretty good" and wanted to share their own experiences. They were not referring to the medical condition being discussed but rather the style of presentation in the Journal. Personally, I feel there are many reasons for this, but the most important one is positive ongoing collaboration between the author and the editorial team. Let me dissect each step of the editorial process, which cumulatively contributes to make *Indian Pediatrics Case Reports* (IPCaRes) special.

The fact that our Journal is dedicated to case reports (CRs) means that the permissible word count, number of tables and figures, etc., are more liberal than journals intended primarily for publishing research. As of now, around 90%–95% of our journal space is for case series, CRs, case videos, and case images. In contrast, only 0%–5% space is assigned for CRs in research journals. That translates to higher likelihood of acceptance for publication if the article has sufficient merit, despite us being a quarterly journal. Therefore, the time interval between acceptance and publication also becomes less, when compared to the research oriented journals.

More important, the USP of the editorial team is to try to ensure that each CR gets written impeccably. All the dimensions expected in a case presentation are covered; history (presenting complaints, history of present illness, history, etc.), clinical examination (vital signs, anthropometry, and general physical and systemic examination), synthesis of clinical information (to appreciate the clinical phenotype), and enumeration of differential diagnoses in order of likelihood, with rational justification. We insist that the authors elaborate upon the rationale used to plan investigations and eliminate contenders at each step until the final diagnosis is reached. This is followed by a description of the management and outcomes. The grand finale is the "pearls" that the treating team has gleaned from the case and which they feel should be shared with the readers. Pretty old school, right? Although you would expect any pediatrician to be able to do this, nothing can be further from the truth.

Allow me to digress for a moment. Recently, we conducted the "sent-up examinations" for our 3rd-year postgraduate students. All the examiners had the common grouse that the residents were unable to present a decent history and examination. I have heard similar complaints aired by colleagues in other institutions. Competency in clinical skills and presentation is slowly fading out. Add to that the poor(er) writing skills of our tech-savvy younger generation who can type a WhatsApp message bi-dexterously but struggle with framing an organized paragraph. This deadly combination contributes to the usual sub-optimal quality of the initial draft.

Hence, where do we come in? At the risk of sounding immodest, over the last 15 months, after having sifted, sieved, and edited numerous submissions, we have developed the ability to envision the end product at the outset. Compare it with the way a sculptor can picture the finished statue in the block of untouched marble. Therefore, we do not give up until the manuscript reaches the high standard that we have set for our journal. After many author-editorial team hand-holding cycles of appraisal, feedback, and correction (by mail and telephone), an article emerges that is not only of scientific merit and educational, but also a pleasure to read. A few authors who admitted to submitting to IPCaRes because they were rejected by more reputed journals have gratefully acknowledged the transformation to their work after our mentorship. We provide nurturing care, for early authorship development, and that is what makes our Journal special!

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Conflicts of interest

There are no conflicts of interest.

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Case Series

Home-based Early Intervention for Children with Neurodevelopmental Disorders by Community Therapy Providers Supported by a Specialized Mobile Application in Purulia, West Bengal

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Abstract

Background: Neurodevelopmental disorders (NDD) are a major global public health problem, particularly affecting children from the lower- and middle-income countries (LMICs). In India, nearly 2.3 million children below 6 years of age have some developmental disability, of whom many live in rural and semi-urban areas with minimum access to early intervention services. We attempted to reach out to such a population at their doorstep with affordable care and management through home-based early intervention (HBEI) programs provided by local field level workers (hitherto referred as community therapy providers [CTP]). A group of local youth, with a short training on NDD and EI methods, have been providing regular, weekly therapy sessions to the afflicted children at the latter's residence, under constant virtual guidance and monitoring by specialists, with the help of a mobile application. The children were initially screened and assessed by our specialist team, who assigned the therapy program and demonstrated the techniques to the CTPs. **Clinical Description:** We are sharing a series of 8 cases, ranging from cerebral palsy to Global Developmental Delay and speech delay, who have received HBEI for 3–5 months, to demonstrate the impact of the program. **Management and Outcome:** The children have shown improvement in all domains with the intensive and regular services. Moreover, empathy, concern, and inclusion of parents in therapy sessions rejuvenated the families. **Conclusion:** Provision of HBEI through field workers may be a cost-effective solution to the formidable problem of childhood disability among the under-privileged rural community. The electronic tracking system has proved very useful in remote monitoring.

Keywords: Childhood disability, home-based early intervention, mobile application

Neurodevelopmental disorders (NDD) and childhood disability are major public health problems globally, particularly in lower- and middle-income countries (LMICs). Both are closely associated with malnutrition and poverty, one aggravating the other, thereby leading to a vicious cycle, with increasing magnitude of burden. A recent community-based multi-centric study conducted in India in 2018 revealed an average prevalence of 12% of neurodevelopmental disabilities among 2–9-year-old children.[1] It is estimated that nearly 2.3 million children in India below 6 years of age have some form of developmental disability.[2] Proper management of NDD calls for a sustained multi-disciplinary approach involving various trained professionals. Many children with special needs live in rural and semi-urban areas and have restricted access to early intervention services. They are therefore largely undetected, identified late and/or poorly reported. These marginalized families face multiple barriers, which commonly include dearth of rehabilitation centers within easy travelling distance, long and difficult commutes to the available ones, loss of daily wages for each visit that affect adherence to follow-up, and high costs associated with availing specialized services in the private sector.[2] All these factors hinder early detection and timely intervention. Despite the launch of the Rashtriya Bal Swasthya Karyakram, District Early Intervention Centers (DEIC) are still not operational in many districts across the country. Thus, many children with neglected developmental delay culminate into irreversible, disabling conditions.

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Our organization provides services to under-privileged children with NDD through a home-based early intervention (HBEI) program in a rural block in Purulia, West Bengal. The terrain is difficult for travel, and the nearest district hospital is 30 km away. Our team of specialists (developmental pediatrician and experienced therapists) recruited graduates residing in the area and provided them with 7-day training in child development. This included knowledge and practical skills pertaining to developmental milestones, identification of red flags, administration of the modified Trivandrum Development Screening Chart, and common successful home-based strategies that we were using in early intervention**.** Following this, they were given the nomenclature of "Community Therapy Providers" (CTP). A team comprising of the experts and trained CTP conducted a developmental screening camp for children under 6 years of age in designated blocks in Purulia. This resulted in the identification of 122 children who were screen positive, out of which 76 families consented to being enrolled in the HBEI program. They underwent detailed assessment by the developmental pediatrician that involved clinical evaluation and the use of the following tools: The Gross Motor Function Classification Scale,[3] a five-level classification system for children with cerebral palsy (based on the current gross motor abilities and limitations in gross motor function), and Functional Assessment Checklist for Programming,[4] which is an activity-based checklist that identifies a child's strengths and weaknesses and is used for deciding individualized education program placement for children with cognitive impairment. Based on these, individualized intervention plans were formulated for 3 months. All details (demographic, assessment scores, goals, and the HBEI plan) were entered into a specialized mobile phone application, namely, Mobile Village-Based Rehabilitation–Early Intervention (mVBR-EI).[2] This tool devised by the Amar Seva Sangam (ASSA) also has built-in facilities for scheduling and monitoring follow-up visits. The application is used by all team members and enables the CTP to remain connected with the team leader and various specialists. Thus, this helps in maintaining high standards of intervention.

Each CTP was allotted 20–25 children with a clinical diagnosis and structured HBEI program, the details of which were demonstrated hands-on. The CTP adhered to the plan by carrying out weekly sessions of 30–90 min each at home with active parental participation, taking their concerns and limitations into account. The rendered services and performance of the CTP were remotely monitored by the experts through the mVBR-EI mobile application. The children were re-evaluated by the specialists every 3 months, and the next set of goals and intervention planned according to the progress made, thus maintaining continuum of the management [Chart 1].

The aim of this case series is to sensitize pediatricians to the benefits, challenges, and impact of "family centered home-based care" for families of children with special needs in difficult circumstances. Evidence-based intervention based on a comprehensive assessment is provided by CTP, supported by mobile technology and remote direction by specialists. Although this strategy cannot replace intervention delivered by qualified multi-disciplinary professionals, it serves to bridge a major gap in the provision of regular, structured management for vulnerable populations, when no other options are available.

Figure 1: SRM before and after HBEI. HBEI: Home-based early intervention

Clinical Description

We present the brief clinical information, diagnosis, and management of five children with special needs who were identified from the aforementioned camp. The details of assessment, goals, and intervention plans assigned by the experts before the onset of HBEI are given in Table 1.

Case 1

SRM, an 18-month-old girl, had a history of delayed acquisition of developmental milestones since early infancy. She was unable to hold her head and could not sit without support. She had been born at home, and there was a history of delayed cry at birth. The nutritional status was normal. The clinical phenotype was predominantly motor delay with spasticity and no visual or hearing impairment and the diagnosis was evolving cerebral palsy. The child was enrolled in our program when the parents expressed inability to go to the DEIC for further management. After HBEI was provided across 12 home visits [Table 1] and active parental participation, the child has progressed to standing with support and playing with toys [Figure 1].

Case 2

SM, a 5-year-old boy, presented with inability to walk, lack of interest in surroundings, difficulty in following commands, and performing activities of daily living (ADL). There was a history of hospitalization for severe postnatal hyperbilirubinemia. The child had not received any treatment, primarily because the family hailed from a very remote area. Salient examination findings were truncal ataxia and increased adductor tone. His vision was normal. A hearing could not be assessed, but he was responsive to sounds made at a normal conversation level. A clinical diagnosis of ataxic cerebral palsy with cognitive impairment was made. After 15 weekly sessions of HBEI [Table 1], the child has started walking with minimal support and can even walk a few steps without support. He has started responding to stimulation and engaging in interactive play. On our instruction, the parents have procured orthotic shoes and constructed indigenous walking bars, which have been beneficial.

Table 1: Case summaries of individual cases with goals and therapy plans

Initials, age and sex	Diagnosis	Initial goals set for 3 months and specific therapy plan	
SRM, 1.5 years, girl	Evolving CP GMFCS V	To attain head control and sitting without support To use hands in the midline	Holding child up with neck support making her sit in a corner with support promoting handling things with hands Placing him prone over a bolster and dangling objects from above Hip and knee flexion exercises to promote crawling
SM, 5 years, boy	Ataxic CP FACP 59.6% GMFCS III FACP 59.6%	To improve balance while sitting and walking To enhance pencil grip To increase vocabulary To promote imitation	Sitting with thighs abducted (on the bolster/potty-seat), walking on drawn footprints and by using rails Throwing a ball and joining dots Story-telling and encouraging group play and pretend play
AB, 5.5 years, boy	Spastic diplegic CP FACP 42% GMFCS IV	To maintain sitting posture without support To manipulate large objects with both hands To increase gesture use To utter a few consonants To interact and play with family members	Physical exercises, maintaining sitting posture with support, encouraging the prone position and crawling with truncal support Clapping both hands Encouraging visual tracking Offering colorful and sound producing toys
RP, 6 years, boy	Intellectual disability FACP 18.87%	To improve eye-hand coordination To increase attention span To participate more in ADL To play more meaningfully	Promoting interactive play Matching and coloring activities involvement in simple domestic chores Story telling Promoting to and fro communication
HB, 6.5 years, girl	Intellectual disability FACP 44.2%	To decrease drooling To utter more consonants To identify common objects and at least 1 color To follow 2-step simple commands To start finger feeding and participate more in ADL	Oral exercises promoting blowing and pursing of lips Tactile stimulation with dough Play based activities to improve object identification, social interaction and eye hand coordination Recognition of shapes and colors Allowing messy feeding by self

FACP scores is given as the percentage of overall skills compared to what is expected for age. ADL: Activities of daily living, GDD: Global developmental delay, CP: Cerebral palsy, GMFCS: Gross motor function classification system, FACP: Functional assessment checklist for programming

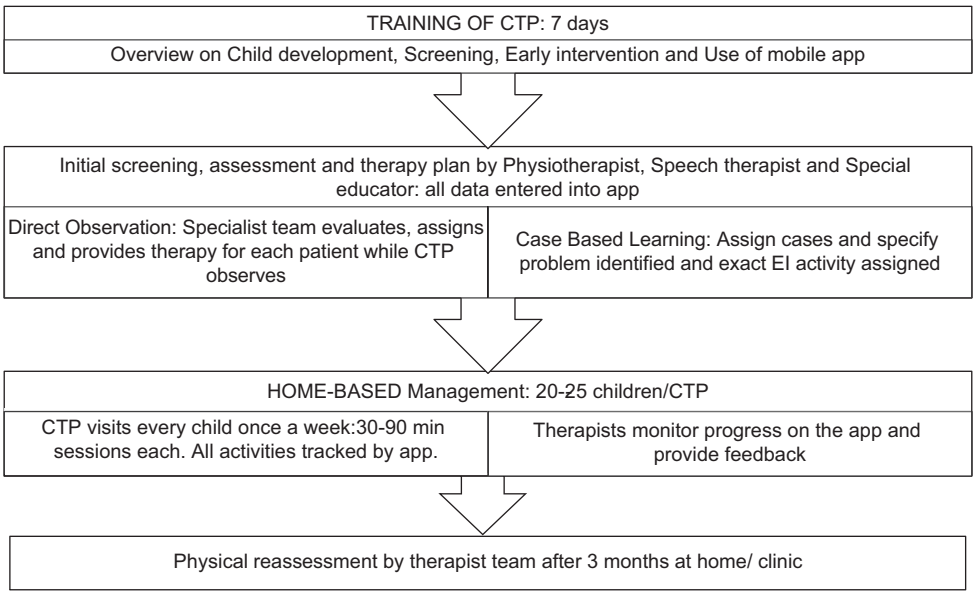

Chart 1: Flow diagram of program implementation

Case 3

AB, a 5.5-year-old boy, was identified with decreased movement of limbs, drooling, and generalized tonic–clonic seizures that occurred once or twice a month. The child had partial head control; was unable to reach for objects; was nonverbal with poor use of gestures; and displayed interest in others. However, it was noted that he was always kept in bed, and family members hardly interacted with him while taking care of his basic needs. The perinatal history was significant; prolonged hospitalization for prematurity, low birth weight, and birth asphyxia. Despite having multiple medical problems, the child had never received any treatment due to financial and logistic constraints. Hypertonicity was marked in the lower limbs. No visual or hearing impairment was noted.

Figure 2: HBEI in progress. HBEI: Home-based early intervention

A diagnosis of spastic diplegic cerebral palsy with cognitive impairment and seizure disorder was made. The child was started on antiepileptic drugs. The CTP initiated customized therapy [Table 1]. After 17 weekly home-based sessions, the child has shown marked improvement. He can sit up independently, stand with one handheld, and has developed good hand grasp. He has become more interactive and tries to play with toys. However, despite repeated counseling, family involvement remains suboptimal.

Case 4

A 6-year-old girl, HB, presented with age-inappropriate understanding, play, and behavior; parallel to that of a 3-year-old. The child was nonverbal and displayed profuse drooling. Parents had noted the problems from the 2nd year of life, for which they had consulted local practitioners, but had eventually given up when there was no improvement. Hearing and vision were apparently normal. Post assessment, our clinical impression was Intellectual disability [Figure 2]. The parents were unable to go to the DEIC due to 3 younger children at home with no one else to supervise them. The weekly therapy plan [Table 1] was provided by the CTP who involved the parents in play, ADL, and speech training while laying emphasis that all family members should interact with the child at every possible opportunity. After 3 months, the drooling had decreased, her speech had evolved to 2–3 meaningful words, and she can recognize two colors.

Case 5

RP, a 6.5-year-old boy, was identified with a developmental delay since infancy. As he grew older, it became apparent that there was no locomotor impairment, but his slow understanding caused difficulties in following instructions and his performance in ADL. Although he liked toys (albeit his interest had appeared late), he lacked age-appropriate play and had a short attention span. The child was shy and withdrawn, but there were no stereotypic behavior or overt sensory issues. The parents had never sought medical advice for his problems. A diagnosis of intellectual disability with autistic traits was made, pending a hearing assessment and formal assessment for autism spectrum disorder. His parents were taught how to play with the child and involve him in ADL [Table 1]. Following 18 sessions, the child has become more interactive, is engaging in group play and has been enrolled in the local school.

Discussion

We started running a weekend development clinic in Purulia in 2011, where our team offered free, voluntary service. It was observed that though initially there were many patients, almost two-thirds of them dropped out after a few visits due to the various aforementioned reasons. It was felt by all concerned that providing home-based therapy by people residing in the community would probably be a more viable solution. That is how the present program was conceived and came into existence. The main challenge was provision of high-quality therapy by the grass-root workers that required diligent monitoring by specialists. This was achieved by partnering with a community-based rehabilitation program in South India launched by a nongovernment organization, ASSA,[2] and adopting mVBR-EI by all members of our team.

HBEI programs for children with NDD have been implemented in various LMICs in several ways. Community-based rehabilitation with parent-based interventions is practiced in more than 90 countries.[5-7] A few HBEI programs by community workers are being implemented in India, Bangladesh, and Vietnam.[8-10] The majority of these programs target cognitive delays, communication, and psychosocial disorders rather than motor disabilities such as cerebral palsy. The probable reason for that is because the latter requires more specific training, and unsupervised parental intervention programs alone may not be beneficial.

The uniqueness of our program is that: (i) trained CTPs deliver structured therapy programs at the beneficiary's home and involve family members in the process; (ii) impairments in multiple developmental domains are addressed, and (iii) a mobile application is used for quality control, thereby assuring standardized service delivery, but at a much lower cost.

The CTP has created a positive impact on the lives of the beneficiaries. These children had been living with their challenges unattended to, due to a lack of awareness about available services and logistic issues. Their families were burdened with poverty, illiteracy, and the fear of social taboos associated with disability. In these circumstances, the CTP offers a beacon of hope by listening to their unique problems, offering continuous customized need-based care, and involving them in the process and decision-making. For example, for a busy village mother promoting self-feeding skills in a child with hemiplegic CP is more important than learning how to hold a pencil. The empathy and concern shown by the CTP who belonged to their community created a major socio-emotional connect which had a positive impact on the families. Although improvement has been documented in all these children (and many others), we have observed that the post intervention improvement has been most marked in younger children, which reiterates the importance of early detection and timely intervention.

Our approach focuses on increasing parental awareness and their hands-on involvement in activities directed at skill

development. This has resulted in a positive behavioral change among family members. We choose to focus our interventions around Dr. Rosenbaum's famous 'F-words[11] (*Function, fitness, family, friends, fun and future*): Attention is paid to enhancing "**f**unctionality" of the child; increasing ability to socialize with "**f**riends" and "**f**amily;" promoting physical and mental "**f**itness;" enhancing the scope for enjoyment and having "**f**un" (for the entire family); and allowing parents to look forward to a brighter "**f**uture." Nonetheless, the most apparent limitation of our program is that despite the use of technology and meticulous monitoring by experts, the services provided by the CTPs cannot be expected to be absolutely on par with services offered by professionals. Research aimed at evaluating the long-term impact of our program is required to determine the utility of our program.

Lessons learnt

- Provision of home-based early intervention through Community Therapy providers (CTP) may be a cost-effective solution for regular service delivery to children with special needs belonging to under-privileged and rural communities
- The local origin, familiarity and empathetic attitude of CTP make them highly acceptable by these families
- The mobile app tracks and records all activities by the CTP which can be easily monitored and remotely supported by the specialists which helps in quality control.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for 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 Series

Last-mile Delivery of Early Childhood Development Services: The Role of Community Health Workers in Dadra Nagar-Haveli District

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Abstract

Background: India has the dual challenge of a high prevalence of developmental delay and disabilities in early childhood and a paradoxical underutilization of available intervention services due to limited accessibility and acceptability by their families. Early Childhood Development (ECD) services delivered by community health workers (CHWs) ensure its last-mile delivery to every household. IIts acceptability is improved by including evidence-based, culturally, and contextually sensitive approaches as is done in the International Guide for Monitoring Child Development (IGMCD). The IGMCD is a tool that monitors and supports the development of children under 3 years of age and also enables provision of early intervention services when required. The IGMCD, recognizes caregiver strengths and priorities and helps to build a rapport between caregivers and providers. **Clinical Description:** We describe six children and their families from Velugam, Dadra-Nagar Haveli district, who received ECD services from CHWs who used the IGMCD package. These cases highlight how the CHWs used the IGMCD package to identify developmental delays, health and psychosocial risk factors to development and provide strategies to caregivers to support their children's development. **Management:** The CHW used individualized strategies to promote responsive caregiving and enhance opportunities for early learning. In addition, the IGMCD package reinforces health, nutrition, and ECD-directed messages that are provided at the Anganwadi centers. **Conclusion:** Children and families in underserved communities can receive comprehensive ECD services through CHWs who are trained to deliver the IGMCD.

Keywords: Community health worker, developmental monitoring, early childhood development, International Guide for Monitoring Child Development

Early childhood development (ECD) includes cognitive, physical, language, socioemotional, and motor development of children until 8 years of age.[1] The World Health Organization (WHO) and other partners launched the Nurturing Care Framework (NCF) with various levels of support according to developmental status: "universal" for typically developing children, "targeted" for those at high risk of delay, and "indicated" for children with Developmental Difficulties (DD).[2] Caregivers, service providers, and policymakers from sectors like health and education are key stakeholders in ECD and play an important role in helping children access services in keeping with their needs.

The high prevalence of DD in children in India warrants ECD-directed services that are free or inexpensive, easily accessible, and acceptable.[3] Existing programs such as the Rashtriya Bal Swasthya Karyakram and Integrated Child Development Services have successfully addressed health-related concerns of children with special needs. However, they face multiple challenges in the provision of services. These include restricted access, disproportionately fewer number of District Early Intervention Centers (DEIC) – every district in India does not have an operational DEIC yet, shortage of trained multi-disciplinary personnel, and decreased utilization due to the lack of awareness or issues emerging from the necessity of multiple visits.[4] Since this scenario is common in many lower- and middle-income countries (LMICs), working models to overcome these barriers that have been

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proposed and successfully implemented, include integration of service delivery with primary health care and "developmental monitoring" of young children by community health workers (CHWs).[5] This evidence-based, culturally sensitive strategy is different from conventional "developmental screening," which focuses primarily on identifying children at risk of DD, by virtue of "failing" a developmental screening test. In contrast, the process of monitoring helps to track and support the development of all children, extending beyond finding an aberration, and empowering caregivers by building their nurturing skills.[6,7]

The International Guide for Monitoring Child Development (IGMCD) is a developmental monitoring tool that has been standardized and validated in Indian children under 3 years of age. It comprises three key components: (1) monitoring (2) supporting and (3) providing early intervention. The "monitoring component" helps in tracking child development in seven domains (gross motor [GM], fine motor [FM], expressive language [EL], receptive language [RL], relating, play, and self-help [SH] skills), understanding the caregiving environment at home, and identifying the presence of protective and risk factors related to health and psychosocial factors that positively and negatively affect ECD, respectively. Typically developing children are expected to attain all milestones in the age interval that corresponds to their completed age [Figure 1]. A delay is inferred if the child does not attain one or more of the given milestones on or before the interval corresponding to their completed age.

The "supporting component" enables a trained CHW to provide learning opportunities that are developmentally and culturally appropriate. These are by giving supportive messages that emphasize noticing and building on the strengths and interests of the child, and being responsive to them.[8] Thus, it includes two components of NCF: responsive caregiving and providing opportunities for early learning.[2] The "early intervention" component simplifies the WHO International Classification of Functioning, Disability, and Health framework to apply family-centered and community-based early intervention for children with DDs.[8]

Our organization trains CHW employed by community-based organizations (CBOs) to use the IGMCD package. We partner with CBO working on maternal and child health and education in marginalized communities with limited resources and a high prevalence of factors detrimental to ECD, i.e., poverty, low parental literacy, anemia, malnutrition, and social problems such as alcoholism. Every CHW is educated till high school, has prior experience of working with children and families, and belongs to the community which they serve.[9]

INTERNATIONAL GUIDE FOR MONITORING CHILD DEVELOPMENT (GMCD)

DEVELOPMENTAL DOMAINS AND QUESTIONS	9-11 MONTHS	12-14 MONTHS	Need for Support
"Just as it is important to follow Ayesha's physical health and growth, it is important to follow and support her development. Children's brains develop most rapidly during the early years. It is useful to monitor their development and to see if there are any areas that need extra support. You know your child best. Let's talk for 5-10 minutes about her development. By development I mean, learning, communicating, understanding, relating to people, moving body, using hands and fingers, and also hearing and vision. **1. Caregiver's concerns. I'd like to first ask you, do you have any concerns about Ayesha's development in any of these areas?"** ☐ **No** ☐ **Yes** **What are caregiver's concerns?** *Listen to caregiver's concerns and tell caregiver you will come back to the concerns when you have learned about all domains of development.* **"Now I will ask you about how Ayesha is developing in all of these areas. Please give me examples of what she does in her daily life."**			
2. Expressive language. "How does Aisha let you know when she wants something? What kind of sounds, gestures does she use?"	☐ **Repeats syllables ("da-da")**	☐ **Has one meaningful word** ☐ **Uses arm or hand to point to people or objects**	
3. Receptive language. "How does she show you that she understands when you talk to her? For example how does she react when you tell her where is daddy? Where is ball? Come here!"	☐ **Understands names of familiar people (mummy, daddy, sister)**	☐ **Understands verbs/action words (come, take, stop)** ☐ **Understands names of objects (ball, toy)**	
4a. Gross motor (large movements). "Tell me about her movement, like holding and raising her head, sitting, walking."	☐ **Sits without support**	☐ **Pulls to stand holding on to objects** ☐ **Stands alone momentarily** ☐ **Walks holding onto objects**	
4b. Fine motor (fine movements). "How does she use her hands and fingers, like holding objects?"	☐ **Picks up small objects (like pieces of food) using pincer (thumb and index finger) aided by other fingers**	☐ **Picks up small objects using pincer (thumb and index finger) only**	
5. Relating. "How does Ayesha relate to or show interest in people she knows? What does she do to engage them? How is her eye contact? " *Wait for caregiver to respond, then ask:* **"How does she relate to strangers?" "How does she show that she knows they are strangers?"**	☐ **Shows recognition of stranger in some way (may turn away from strangers in anxiety, caution, shyness, fear, or may stare for prolonged time)**	☐ **Spontaneously seeks to share enjoyment and interest with others (cuddles caregiver, kisses, inspects toy together)**	
6. Play activities. "Tell me about Ayesha's play. How does she play with people, with objects or toys?" Ask if needed: **"What playthings/toys does she have, how does she play with them?"**	☐ **Looks for toys/objects that disappear** ☐ **Inspects toys/objects with curiosity, looks at some detail** ☐ **Imitates gestures during play (clapping hands, making face)**	☐ **Initiates game "peek-a-boo"** ☐ **Inspects how toys/objects work (how wheels turn, doll moves, bells ring, lights turn on)**	
7. Self-help activities. "What kinds of things does she do for herself, like eating?"	☼ **Children in this age range may not be expected to attain self-help milestones**	☐ **Uses fingers to feed herself (knows that it is food and feeds herself)**	
8. Nurturing care environment. "Thank you for telling me so much about Ayesha's development, you know her so well. Now please tell me about her daily life. "What do you and your family do at home, in your daily life to help her develop, learn, communicate?" *Listen to what the caregiver is telling you. Prompt by asking: "What do other family members and friends do with her?" Support caregivers by acknowledging and praising all their efforts. Provide ideas from the "GMCD Support Card" or "I Learn with You" if necessary.* **9. Developmental risks. "Sometimes caregivers may have a lot going on. For example, they may feel overwhelmed, stressed or depressed, there may be financial problems or illness in the family, and caregivers may find it hard to support their child's development. Are there such or other difficulties in your family situation?"** *Listen with empathy and identify psychosocial risk factors.* **10. Planning for interventions and follow-up. "What are some ideas or plans you have to support Ayesha's development despite these difficulties? At this early age when development is so important, what could you, your family, friends and community do to help her develop?"** *Support caregivers' efforts. If caregivers do not have ideas or plans, tell them you would like to talk further with them about these. Provide your feedback on the GMCD and plan follow-up together with the caregiver.*			
©Ertem IO, Ankara University. The GMCD is to be used only by providers who have completed the GMCD Provider Training Program given by licensed GMCD Trainers and have obtained a GMCD Provider Certificate. The GMCD cannot be used for research without completing the GMCD Researcher Training Program and obtaining a GMCD Researcher Certificate.			

Figure 1: The developmental domains, questions, examples of age ranges, and milestones of the International Guide for Monitoring Child Development

We present six cases that highlight the importance of psychosocial stressors in ECD and have been managed by CHWs employed by the CBO. Both CHWs are from Velugam, Dadra-Nagar Haveli district. This village has 894 children under the age of 6 years (2011 census). The literacy rate is 54.95%, and most adults are daily wage laborers on farmlands.[10] Health care and the supplemental nutritional needs of this population are met by the primary health center. A DEIC situated 20 km away, is the nearest facility providing early intervention to children with DD. Since a visit to the center means missing a day's work, it proves to be a major deterrent for most families. No other ECD promotive services were available to the community before the introduction of the IGMCD package. The CHWs who have been trained to use the IGMCD package monitor the development of all the children under the age of 3 years in the community. The local anganwadis provide them with the list of households with children under the age of 3 years. Children identified with developmental delay receive weekly visits, whereas typically developing children are monitored on a monthly basis. We aim to sensitize our readers to the positive impact that even a simple strategy provided by trained CHWs can have in an under-resourced community.

Clinical Description

Each summary and Table 1 include brief details of the child and family: delays identified on IGMCD, health and psychosocial stressors, intervention initiated by the CHW at home, and changes that were observed in the developmental status and home environment after 6 months.

Family 1

The GM domain was primarily affected in this 2-month-old girl. The CHW recognized that though motivated, the caregivers were overburdened by farm and domestic work, and child-rearing responsibilities of the other children. The IGMCD support component was used to provide simple strategies like keeping an eye on her while the mother was doing her work and providing stimuli like colorful homemade toys to get her to reach out and grasp them.

Family 2

This 10-month-old (corrected age used) boy who had been born preterm and belonged to an extremely poor background

Table 1: Case-wise comparison of provision of the International Guide for Monitoring Child Development package and changes observed 6 months after initiation

Age and sex	Domain-wise delays (IGMCD)	Protective factors	Risk factors	Developmental status at 6 m follow up	Changes seen at home
Family 1 2 months girl	GM: Unable to raise the head in prone Unable to move hands/legs while supine	H: EBF, uses ICDS for suppl. nutrition and meals PS: Family concerned about child's needs and prioritizes education	H: Nil PS: Older sibling has developmental issues	GM: Able to stand without support	Active involvement in responsive caregiving
Family 2 10 months* boy	GM: Sitting with support EL: Use of vowels and consonants	H: Nil PS: Active participation of mother in all interventions	H: Preterm, LBW PS: Extreme poverty, food insecurity	GM: Can stand without support EL: Uses few single words and gestures	Enhanced caregiver knowledge of child developmental and early intervention
Family 3 13 months girl	EL: Repeated syllables used FM: Immature pincer grasp Play: shakes or throws toys	H: Regular Anganwadi Visits PS: Nil	H: PEM PS: Less interaction with sibling	EL: Uses single words FM: Holds crayons to scribble Play: Imitates	Active involvement of elder sister
Family 4 16 months girl	EL: Vocalization and pointing to communicate	H: Using ICDS services PS: Aunt reads books to the child	H: PEM PS: Denial of developmental delay, gender bias, and domestic conflict	EL: Uses few single words and gestures	More developmental stimulation provided by aunt. Parents still nonsupportive
Family 5 27 months boy	EL: Used only gestures (point and nod)	H: Nil PS: Mother education Level class X	PS: Mother's awareness of developmental poor. the child delay is not considered significant	EL: Uses many single words and gestures	The mother sought help for elder son with poor school performance
Family 6 36 months boy	GM: Difficulty in head control and rolling over FM: Palms fisted, EL: made vowel-consonant sounds RL: Turns toward sounds Play: responds to sound of rattle	H: Seeks medical help. Neonatal hospitalization for 21 days. Taken to DEIC where diagnosed as cerebral palsy	H: PEM PS: Elderly caregivers who are alcoholic and unable to go to DEIC due to financial restraints	GM: Sits with support FM: Brings hands to mouth EL: Babbles RL: Can recognize a few names Play: Mouths toys	Caregivers more motivated to provide developmental stimulation and nutritional status has improved

*Corrected age used. IGMCD: International Guide for Monitoring Child Development, DEIC: District Early Intervention Centre, EL: Expressive language; FM: Fine motor, GM: Gross motor, H: Health; IGMCD International Guide for Monitoring Child Development; m month; PS: Psychosocial, RL: Receptive language, ICDS: Integrated Child Development Service, EBF: Early Breast Feeding, PEM: Protien Energy Malnutrition

displayed delays in GM and EL. The CHW recognized risks such as the remote location of their house and food scarcity. She also recognized the caregiver's willingness to support the infant's development and connected her with the Accredited Social Health Activist worker for the provision of nutritional support. The IGMCD support component was used to suggest simple strategies to promote development (e.g., the use of everyday opportunities and homemade toys to increase interaction with the infant).

Family 3

This 13-month-old girl was identified with delays in EL, FM, and play as well as the presence of malnutrition. The CHW recognized and reinforced the caregiver's commitment to her daughter's growth and development, including her efforts to obtain nutritional aid from the Anganwadi worker. She also noted risks within the home environment such as limited opportunities for exploration and learning. The CHW taught the caregiver to make sound-producing toys that the child liked and used them to teach her words [Figure 2]. Although the child showed improvement, she was lost to follow-up when the family relocated to another village.

Figure 2: A community health worker demonstrating strategies from the IGMCD support card to the caregiver. IGMCD: International Guide for Monitoring Child Development

Family 4

The 16-month-old girl had a delay in EL. The CHW recognized several risk factors that were adversely affecting her development such as malnutrition, gender discrimination, marital discord revolving around the absence of a son, and repeated pregnancies in the attempt to get one. The caregivers had not sought medical attention for the child despite noticing her language delay and had stopped sending her to the Anganwadi after a younger sibling was born. The CHW collaborated with the Anganwadi worker and the dual efforts of both succeeded in motivating the caregivers to resend PJ to the Anganwadi. The CHW taught the child's aunt to notice and capitalize on the child's interest in books by making books at home and using it to help the child recognize and name pictures. The CHW also encouraged the aunt to model the use of words everytime the child used gestures. An attempt was also made to gently and gradually alter the parents' attitudes.

Family 5

This 27-month-old boy displayed a significant delay in EL. The CHW recognized that although his mother refused to acknowledge his delays (believing that he would eventually start speaking like other family members), she nonetheless

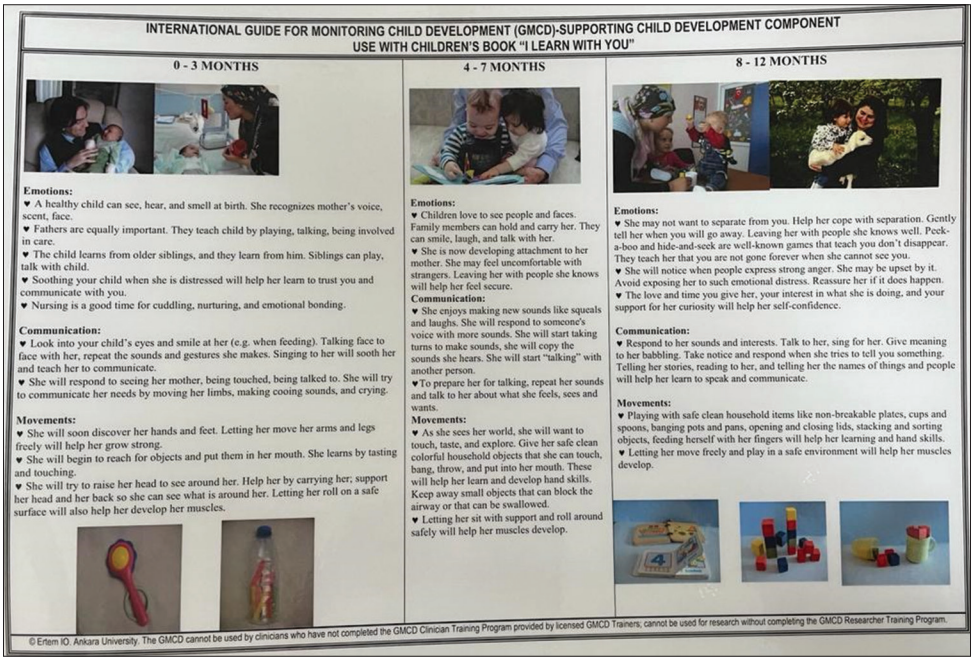

Figure 3: The IGMCD Support Card. IGMCD: International Guide for Monitoring Child Development

prioritized his learning. Instead of challenging her beliefs, the CHW invested her efforts in building a rapport with the mother by suggesting activities that the mother considered useful and demonstrating the effect of using simple words such as "de" during daily interactions with her son. A major breakthrough was made when the mother confided her concerns regarding the poor scholastic performance of her elder child and sought the CHW's assistance in tackling that as well.

Family 6

This 3-year-old boy was particularly challenging due to his family circumstances. His parents had abandoned him and resided in a different city. The child was being reared by his elderly grandparents in the village. The child had been diagnosed with cerebral palsy at the district hospital at 9 months of age (the neurological sequelae of significant neonatal events). He also had malnutrition. Although they tried to look after him as best as they could and tried to feed him, they were unable to take him to the DEIC for intervention due to financial constraints, problems with commuting, and their own struggles with alcohol abuse. The CHW demonstrated strategies to provide developmental stimulation at home and improve nutrition [Figure 3].

Discussion

We know that home-based parenting interventions based on responsive caregiving practices and delivered by trained CHWs positively impact cognitive, motor, and language outcomes for children in many LMICs.[11] However, relatively little is known about factors that can sustain these gains. It is likely standardized delivery of an evidence-based, accessible, and acceptable ECD service will contribute to the sustainability and scalability of these positive outcomes. The IGMCD package is ranked highly for accuracy and feasibility of use.[12] By using open-ended questions, the CHW can discern which standardized milestones have been attained. Additional probing questions are used to elicit more information when needed. The tool elicits critical information related to caregiving practices at home, as well as risk and protective factors that can significantly influence ECD related to their interlinkages with health and psychosocial dimensions. Descriptors such as "strengths" and "areas needing extra support" are used instead of stigmatizing terms such as "pass" or "fail" while sharing results with caregivers. When a delay is identified, the identified risk factors are addressed, the delayed domain is supported, monitoring is repeated during follow-up, and community-based early intervention is added, as warranted. The rapport that gets established between the caregivers and CHWs enable them to discuss strategies to overcome factors that have been identified as detrimental to ECD with the family, in a nonconfrontational manner. Monitoring enables longitudinal follow-up and support of a child's and family's well-being and progress. This helps to build trust among caregivers. In addition to developmental monitoring and building responsive caregiving practices, the IGMCD package is used to reinforce the health, nutrition support, and ECD-directed messages that are being provided at the Anganwadi centers.

A standardized training program equips providers to learn about prevention, early identification, and planning of individualized intervention, which ensures consistent quality.[6] The IGMCD package is freely available for use once the users are trained. Clinicians from over 30 LMICs have been trained and 13 countries have national-level trainers.[13] The IGMCD package has been included in the preservice training of health providers and the national child health monitoring system in Azerbaijan and Turkmenistan. In India and Guatemala, not-for-profit organizations like ours have incorporated it into community home visit programs.[6] A randomized controlled implementation trial is currently exploring the effectiveness of the IGMCD package in rural settings in these two countries.[14]

Our case series demonstrates that the delivery of IGMCD by trained CHWs has a positive impact on the community, especially in vulnerable populations. With standardized training support, the CHWs were able to use IGMCD to reliably identify developmental difficulties and offer services and support in keeping with the locally available resources and family circumstances. The CHWs in our case series benefited from posttraining support to administer the IGMCD as recommended. This may have to be built into the training time for CBOs considering the use of the package in their communities. Truly, a comprehensive package such as the IGMCD presents an immense opportunity to take ECD services to the last mile in our country, where significant disparity in access to health-care services exists.

Lessons learnt

- Integration of evidence-based ECD services with primary health care will improve its accessibility
- Culturally and contextually appropriate ECD services that focus on responsive caregiving and providing opportunities for early learning, while recognizing the strengths of the caregivers will increase acceptability among them.
- Developmental monitoring enables the promotion of development, prevention, early identification, and intervention for developmental delay and disabilities, and is preferable to developmental screening in all settings and especially in resource-poor settings like India.

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.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

Atypical Kawasaki Disease with Polymyositis and Panniculitis: Case Report and Review of Literature

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Abstract

Background: Kawasaki disease (KD) is a medium-vessel vasculitis that commonly affects young children. Many atypical presentations that differ from the classical phenotype have been described. **Clinical Description**: A 3-year-old boy presented with acute onset refusal to walk due to severe pain in both lower limbs for 8 days. This was accompanied by fever for 7 days. Significant findings included diffuse tenderness of bilateral thighs and leg muscles, probable normal joints, and absence of rashes, edema, significant lymphadenopathy, organomegaly, or paralysis. He had a hemoglobin of 10.6 g/dL, neutrophilic leukocytosis, and normal platelet count (384×10^9/L). He was started on intravenous cloxacillin, assuming polymyositis or acute osteomyelitis. Radiographs, ultrasonography, and bone scan of the lower limbs revealed normal bones and joints. However, magnetic resonance imaging detected patchy hyperintensities in multiple muscles, though muscle-specific enzyme levels were normal. The fever and pain persisted and investigations for other differentials (including classical KD) were inconclusive. At the end of 2nd week of illness, atypical KD was suspected, when he developed periungual skin peeling with increasing erythrocyte sedimentation rate and platelet counts. **Management:** The diagnosis was confirmed by echocardiogram proven left main coronary artery dilatation. He was started on intravenous immunoglobulin. Since fever persisted, a second dose was administered, following which defervescence occurred and his symptoms subsided. **Conclusions:** Atypical KD should be considered in a fever of unknown origin when diagnostic criteria of classical KD are not satisfied. Polymyositis and panniculitis are uncommon atypical manifestations.

Keywords: Atypical Kawasaki disease, intravenous immunoglobulin resistance, polymyositis; subcutaneous nodules

Kawasaki disease (KD) is a medium-vessel vasculitis that commonly affects children <5 years of age.[1] The clinical spectrum of KD varies from complete KD (the typical presentation) to incomplete and atypical forms, which often pose as a diagnostic challenge. The typical manifestations of complete KD in the 1st week of illness include fever for at least 5 days, bilateral nonpurulent conjunctivitis, cervical lymph node enlargement, redness of the lips and tongue, erythema or edema of the palms and soles, and a polymorphous rash.[1] Children who present with fever of the same duration but with fewer physical criteria are considered to have incomplete KD.[2] Although the terms incomplete and atypical KD are used interchangeably, atypical KD refers to the presence of manifestations that are not commonly seen in the complete or incomplete phenotypes, i.e., renal impairment, facial nerve palsy, gastrointestinal manifestations, and testicular swelling.[2]

We report a child who presented with pain in both lower limbs and fever, whose initial provisional diagnosis was myositis/osteomyelitis, but further workup established the diagnosis of atypical KD. A literature search revealed very few cases of atypical KD presenting with polymyositis.[3-5] This report serves a dual purpose, adding evidence to expand the clinical repertoire, as well as providing a brief review of the heterogeneous presentations of atypical KD.

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Clinical Description

A 3-year-old boy was brought to our hospital with pain in both lower limbs for 8 days and fever for 7 days. Apparently healthy before presentation, he went to bed symptom-free, and awoke in the morning with diffuse pain that was restricted to only both lower limbs. It was severe enough to result in him refusing to walk, though there was no loss of movement. The next day he developed fever, moderate in degree, and not

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associated with chills or rigors. There was no history of local swelling in either lower limb, or warmth, redness, or stiffness of his ankles, knees, or hips. There was no history of any rash, cough, coryza, sore throat, breathlessness, or palpitations. There was no history of preceding trauma or bleeding from any site, progressive pallor, loss of weight or appetite. Bowel and bladder habits remained unchanged, though he had difficulties in squatting. His sensorium was normal, though he was irritable due to the pain. There was no history of similar complaints in the past or of history suggestive of previous cardiac or gastrointestinal involvement, or exanthematous illness. He was the second born to nonconsanguineous parents, and the family history was not significant. He had a smooth perinatal transition, was developmentally normal, vaccinated as per the national immunization schedule and was receiving an appropriate diet.

At the time of admission, he was febrile (38.5°C), with tachycardia (pulse rate of 136/min), and normal respiratory rate (28/min), blood pressure (between 50th and 90th centiles), and capillary refill time (<2 s). Anthropometry was appropriate for age with weight for age, height for age, and weight for height between 0 and-1 Z scores. Pallor, icterus, clubbing, pedal edema, and significant lymphadenopathy were absent. There were no rashes, petechiae, or ecchymosis; mucosa of the oral cavity, lips, and tongue was normal. The Bacille Calmette-Guérin scar appeared normal. Musculoskeletal examination revealed diffuse tenderness over bilateral extensor aspects of the thighs and legs, without erythema, swelling, or increased temperature of the joints. Localized joint tenderness or restricted range of motion of any joint was difficult to ascertain as the child cried whenever any part of the lower limb was touched. Local examination of the spine was normal. The motor component of the central nervous system examination (CNS) of the lower limbs revealed normal bulk, but the gait, power, tone, and deep tendon reflexes could not be precisely assessed due to the marked pain and tenderness. The remaining CNS, cardiovascular, respiratory, and abdominal examinations were noncontributory.

Since the clinical phenotype comprised acute-onset musculoskeletal involvement, of bilateral lower limbs with fever, the possibility of an infectious, inflammatory, or autoimmune etiopathogenesis was considered. Table 1 lists the differential diagnoses that were included based on the clinical phenotype at admission: acute polymyositis, acute osteomyelitis, septicemia, septic arthritis/reactive arthritis, and acute rheumatic fever (ARF).

Management and Outcome

Preliminary investigations revealed an elevated erythrocyte sedimentation rate (ESR) of 105 mm at 1-h, neutrophilic leukocytosis with total leukocyte count (TLC) 25 × 10^9/L, a differential count of 75% neutrophils (N), 15% lymphocytes (L), 6% eosinophils (E), and 4% monocytes (M), mild anemia (hemoglobin 10.6 g/dL), normal platelet count (384 × 10^9/L), and a peripheral smear displaying normocytic normochromic red blood cells with absence of atypical or malignant cells. Since this favored the acute infectious differential diagnoses of acute polymyositis or acute osteomyelitis, he was empirically started on intravenous cloxacillin and oral ibuprofen, pending further investigation reports. The roentgenograms of femur, tibia, and fibula were normal (though done on day 9 of illness). The absence of joint effusion on ultrasonography of the hip, knee, and ankles excluded any form of arthritis. Magnetic resonance imaging (MRI) of the lower limbs showed diffuse patchy areas of hyperintensities in all the muscles of the thigh, involving all the compartments [Figure 1]. However, the levels of serum creatine kinase (CK) and lactate dehydrogenase (LDH) were normal; 35U/L (normal range: 5–130 U/L) and 145 IU/L (normal range: 150–500 IU/L), respectively. Since radiographs cannot conclusively exclude acute osteomyelitis when performed early, a Technetium-99 bone scan was undertaken and proved to be normal. Liver and kidney function tests showed no evidence of organ dysfunction. Two blood cultures sent within a 24-h span were sterile. The diagnostic criteria of classical KD and Jones criteria for ARF were applied but were not satisfied. Since the acute infectious etiologies were ruled out, and the symptoms were still persisting, we started considering other diagnoses that would match the evolving clinical phenotype [Table 1]. A normal bone marrow examination ruled out hematoreticular malignancies and other infiltrative disorders. A negative serum anti-nuclear antibody test and the absence of uveitis excluded systemic-onset juvenile idiopathic arthritis (SOJIA). Although less likely, we even ruled out the possibility of an acute pain crisis associated with sickle cell anemia by a negative sickling test.

By the end of the 2nd week, the child developed periungual desquamation in the child's toes, though redness of lips, strawberry tongue, conjunctival congestion, edema of the dorsal aspect of hands and feet, rash, and significant lymphadenopathy were absent. Other new findings noted were painless, subcutaneous nodules on the extensor aspect of the left forearm and the shin of the right leg, the biopsy of which revealed panniculitis. Repeat laboratory parameters revealed increasing leukocytosis (TLC 35.25 × 10^9/L with 73% N, 18% L, 5% E, and 4% M), thrombocytosis (690 × 10^9/L),

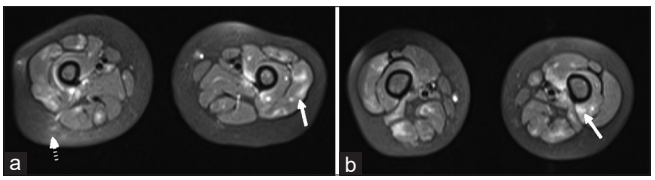

Figure 1: MRI of lower limbs (a) and (b) showing diffuse patchy areas of hyperintensities noted in all the muscles of thigh involving all compartments (white arrow). Few patchy hyperintensities also noted in the subcutaneous tissues in posterior aspect of right thigh and medial aspect of left thigh (white doted arrow). MRI: Magnetic resonance imaging

Table 1: Differential diagnoses considered based on the timeline of illness

Diagnosis	Points in favor	Points against
At admission (early second week of illness)		
Acute polymyositis	Diffuse pain in the lower limbs. Neutrophilic leukocytosis Patchy areas of hyperintensities in all the muscles of thigh on MRI	Muscle specific enzymes like serum creatinine kinase and lactate dehydrogenase were within normal limits
Acute osteomyelitis	Diffuse pain in the lower limbs. Neutrophilic leukocytosis Difficult to localize any specific site of bony involvement as the child cried whenever he was touched	X-ray, MRI and Technetium-99 scintigraphy lower limb were normal
Septic/reactive arthritis	Diffuse pain of the lower limbs. Difficult to localize any specific joint involvement as the child cried whenever he was touched	No joint swelling, warmth, or redness. USG and MRI of joints were normal with no evidence of effusion
Septicemia	Young child with persistent moderate to high grade fever and no localizing signs or symptoms Neutrophilic leukocytosis	Two blood cultures sterile No biochemical evidence of organ dysfunction or organomegaly
Acute rheumatic fever	High grade fever Difficult to localize any specific joint involvement as the child cried whenever he was touched	Unusual to present at the age of 3 years Jones criteria not satisfied
Classical KD*	Fever for >7 days with no other possible explanation. Elevated ESR 105 mm at 1 h (on 8th day of illness)	Diagnostic criteria not satisfied Platelet 384×10^9/L on 8th day of illness
Lymphoreticular malignancies	Persistent moderate to high-grade fever for more than a week. Elevated total count (25×10^9/L)	No atypical cells in blood and bone marrow examination were detected
Sickle cell anaemia	Anemia present with Hb 10.6 g/dL Possibility of acute pain crisis	Presence of fever Sickling test was negative
SOJIA	Difficult to determine tenderness or pain on motion as the child cried whenever he was touched	No evidence of joint involvement, duration <6 weeks No rash/lymphadenopathy/uveitis or organomegaly. ANA negative
In the late 2nd week of illness		
Atypical KD	Persistent fever Periungual desquamation of toes Rising ESR and platelet counts Left main coronary artery dilatation in ECHO	Only polymyositis No typical findings of KD, i.e., conjunctival congestion, cheilosis, strawberry tongue, edema, and significant cervical lymphadenopathy
Multisystem Inflammatory Syndrome in Children	Fever >3 days Elevated ESR. ECHO showing coronary artery abnormalities	No rash, shock, hypotension, coagulopathy, or gastrointestinal symptoms. RT-PCR and Covid antibodies for COVID-19 negative

*Suspected at the end of the 2nd week of illness, when the child developed periungual desquamation in toes, thrombocytosis (690×10^9/L), and dilatation of coronary artery detected on ECHO. MRI: Magnetic resonance imaging, USG: Ultrasonogram, RT-PCR: Reverse transcriptase-polymerase chain reaction, ESR: Elevated inflammatory markers, SOJIA: Systemic-onset juvenile idiopathic arthritis, ANA: Anti-nuclear antibody, ECHO: Echocardiogram, KD: Kawasaki disease

and further rise in ESR (120 mm at 1-h). At this point of time, the possibility of atypical KD and multisystem inflammatory syndrome in children were considered [Table 1]. Reverse transcription polymerase chain reaction, as well as antibodies for coronavirus disease- 2019 were negative. An echocardiogram revealed a thin rim of pericardial effusion and dilatation of the left main coronary artery (LCA) with 2.55 Z (normal cut off <2 Z score) as apparent in Figure 2a and b, thereby satisfying the diagnostic criteria for atypical KD [Table 1].

Hence, the final diagnosis of atypical KD was established on the 13th day of illness. As per standard protocol, he was started on intravenous immunoglobulin (IVIg) in a single dose of 2 g/kg with aspirin (75 mg/kg/day). Since there was no defervescence within 72 h of the first dose, a second dose of IVIg was tried. Following this, the fever subsided, the limb pain gradually resolved over the next 4 days, and by the 5th day the child had become ambulatory. He was discharged on low-dose aspirin (5 mg/kg/day). On follow-up, 4 weeks later, he remained symptomless. However, since repeat echocardiography showed persistent dilatation of the LCA, clopidogrel (1 mg/kg/day) was added to the low-dose aspirin.

Discussion

KD is an important cause for acquired heart disease in children,[6] presumed to be triggered by a respiratory illness in genetically predisposed individuals. It is the most common vasculitis in children, with a predilection for involving the coronary arteries. Complications include coronary artery dilation and aneurysm in 25% of untreated patients and 4%

with treatment.[5] The diagnosis of KD is established by a set of clinical criteria, which many infants and young children may not satisfy, as in this case. It is important to recognize that the terms "incomplete" and "atypical" KD does not imply that the disease is milder than classical KD. On the contrary, these children can often have devastating coronary sequelae as the diagnosis and treatment usually get delayed. We established the diagnosis and initiated specific therapy 5 days after hospital admission, which was the 13th day of illness. Musculoskeletal involvement as the primary manifestation of KD is uncommon, and rarely reported. In this child, the diagnostic dilemma arose once we excluded the common acute infectious causes. Although it is known that the onset of systemic symptoms can precede arthritis in SOJIA, nonetheless, the diagnosis cannot be made without evidence of joint involvement. Both KD and SOJIA are inflammatory disorders that share common triggering agents and immunologic pathways. Interestingly, coronary dilation has also been reported in SOJIA.

A literature search identified cases with a similar presentation. Singh *et al*. reported a 10-year-old boy suspected to have

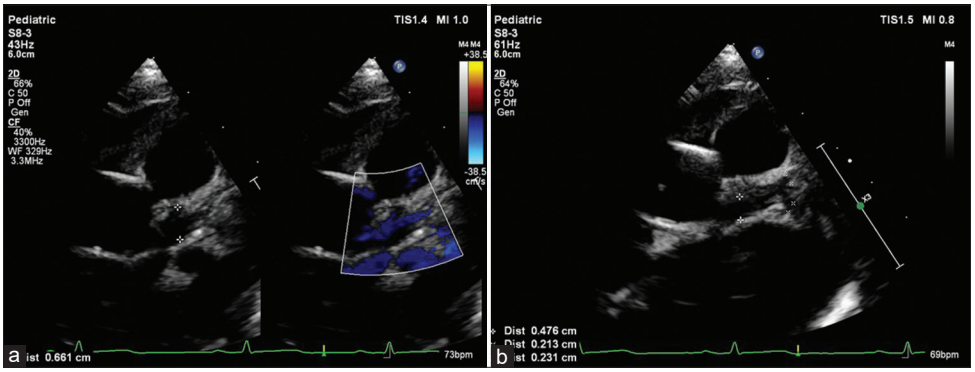

Figure 2: (a and b) Parasternal short axis view showing dilated LCA with a focal aneurysm measuring 6.61 mm in color compare mode. (b) Parasternal short axis view showing dilated LCA (4.76 mm) bifurcating into left anterior descending (2.31 mm) and left circumflex artery (2.13 mm). LCA: Left main coronary artery

Table 2: Comparison of case reports of Kawasaki disease with myositis

Study	Age, gender	Main complaint	Initial diagnosis	When KD diagnosed	Additional features	Cardiac evaluation	Treatment given
Vigil-Vázquez *et al*.[3]	7 years*	Fever, abdominal pain	Iliopsoas myositis	3rd week of illness	Signs of peritoneal irritation, shock	ECHO-coronary dilatation	IVIg Aspirin, IV Methyl-Prednisolone, Infliximab
Gama *et al*.[4]	8 years, boy	Sore throat, fever, abdominal pain	Infectious mono-nucleosis	2nd week of illness	Respiratory paralysis	ECHO-coronary aneurysm	IVIg Aspirin
Koutras[5]	1.5 years, boy	Fever, irritability, conjunctivitis	KD	1st week of illness	Proximal weakness, dysphonia Dysphagia	ECG ST-T changes	Aspirin
Anjani *et al*.[11]	10 years, boy	Fever, rash, scrotal swelling	TSS, Juvenile Dermatomyositis	3rd week of illness	Proximal weakness	Normal	IVIg, Aspirin, IV Methyl prednisolone
Lee *et al*.[13]	6 years, girl	Fever, cough, rash, sore throat	Drug-induced rash	2nd week of illness	Left calf myositis	Normal	IVIg Aspirin
Sugie *et al*.[14]	3 years, boy	Fever, rash, cervical lymphadenopathy	KD	2nd week of illness	Diffuse muscle weakness in all extremities	ECHO-coronary dilatation	Aspirin
Lin *et al*.[9]	8 months boy	Fever, edema, rash	KD	1st week of illness	Orbital muscles	ECHO-coronary dilatation	IVIg Aspirin
Agarwal *et al*.[15]	10 years girl	Fever, rash, cervical lymphadenopathy	KD	1st week of illness	Muscle weakness of hip extensors	Normal	IVIg Aspirin
Present case	3 years boy	Limping, irritability	Poly-myositis, OM, SOJIA	2nd week of illness	subcutaneous nodules	ECHO-coronary dilatation	IVIg Aspirin

*Gender is not mentioned in the case report. ECHO: Echocardiogram, ECG: Electrocardiogram, IV: Intravenous, IVIg: IV immunoglobulin, KD: Kawasaki disease, OM: Osteomyelitis, SOJIA: Systemic-onset juvenile idiopathic arthritis, TSS: Toxic shock syndrome, ST-T changes: ST segment and T wave changes

acute osteomyelitis, who was later diagnosed with KD.[7] KD presenting with myositis has been reported as early as 1980.[8] This child had clinical polymyositis, MRI evidence of extensive muscle involvement, but the typical elevation of muscle-specific enzymes CK, LDH, and SGOT that is commonly seen in infectious myositis, was absent. This may possibly be explained by the fact that the levels were done in the premuscle necrosis stage, and the timely administration of IVIg prevented it from progressing to the necrotic stage when the enzyme elevation is seen. A summary of the few other cases of KD presenting with myositis that we found on a literature search is given in Table 2. The common manifestations were fever and muscle pain. The other associated complaints were diverse, such as orbital cellulitis,[9] respiratory paralysis and dysphagia,[4,5] and erythema nodosum in a 3-year-old girl with KD[10] (as in this case). The initial diagnoses considered by the treating physicians before establishing a diagnosis of KD included infectious mononucleosis, viral polymyositis, adverse drug reaction, and juvenile dermatomyositis.[11]

About 10%–20% of KD may not respond to the first dose of IVIg (IVIg resistance) and require a second dose, like in our child. It is likely that host genetic factors, such as polymorphisms in the Fc gamma receptors, play a role in both the response and resistance to IVIg.[12] It has been observed that patients who are initially IVIg resistant are at increased risk of developing severe coronary artery abnormalities. Resistance to the first dose of IVIg was also reported in a few cases of KD with myositis.[3] These children were noted to have persistent coronary dilatation on follow-up, as in this case.

Our case deserves special mention for two reasons: first, for the atypical presentation with polymyositis and cutaneous vasculitis; and second, the presence of IVIg resistance with persistent coronary dilatation. Atypical KD can closely mimic many diseases, thereby posing diagnostic dilemma even to the most astute clinicians. Thus, a clinician should keep a high index of suspicion of atypical KD in the setting of persistent fever, elevated inflammatory markers, and absence of any other plausible explanation.

Declaration of patient consent

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

Lessons Learnt

- KD can present with isolated painful myositis in its early stages
- Panniculitis can be rarely associated with KD
- In a child with "Fever of unknown origin," KD should always be considered as one of the differential diagnoses, especially when the clinical diagnosis is not clear, or the investigations and the clinical course do not support any specific diagnosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

The Role of Behavioral Phenotyping in Establishing a Diagnosis of Pseudo-Angelman Syndrome

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Abstract

Background: Behavioral phenotypes are observable patterns of behavior present in certain genetic syndromes that have distinctive social, linguistic, cognitive, and motor profiles. These may play an important role as pointers toward certain genetic disorders. The recognition of aberrant behavior is important for therapeutic targeting by behavioral modification strategies and medication. The repertoire of behavioral constellations is exhaustive, but common manifestations include aggression, self-injury, autistic features, and a happy demeanor comprising excessive smiling and outbursts of laughter without any preceding triggers. **Clinical Description:** We describe the approach that was used to establish diagnosis in a boy with a happy disposition, cognitive impairment, and seizures, the firstborn of a couple desiring genetic counseling for their second 7-week pregnancy. After deep phenotyping (identifying overt and concealed dysmorphism, assessment of vision, hearing, behavior, and cognition), a syndrome search was performed by a geneticist using suitable handles. The clinical phenotype of the proband was then matched with the generated list of disorders. The most likely diagnosis Angelman syndrome (AS) was excluded by negative specific genetic testing. Chromosomal microarray identified 2q23.1 microdeletion that is associated with pseudo-AS. Prenatal diagnosis at 16 weeks revealed an unaffected fetus. **Management:** There is no cure for this syndrome. Affected children benefit from symptomatic intervention provided by a multidisciplinary team including clinical geneticists, pediatricians, pediatric neurologists, developmental pediatricians, and various professional therapists. **Conclusions:** Behavioral phenotypes aid in establishing diagnosis in certain genetic disorders. A happy disposition coupled with intellectual disability should prompt the clinician to involve a geneticist in management, even if overt dysmorphism is not apparent.

Keywords: Behavioral phenotype, genetic disorder, happy demeanor, MBD5, microdeletion, pseudo-Angelman syndrome

Behavioral phenotypes are observable patterns of behavior that are present in certain genetic syndromes and have distinctive social, linguistic, cognitive, and motor profiles. These behavioral characteristics may act as pointers toward a specific genetic diagnosis. In addition, they also have a profound impact on the quality of life of the caregivers due to the significant disruption caused at home and outside. For instance, Lesch–Nyhan disease is a monogenic X-linked condition characterized by self-mutilation, aggressiveness, impulsiveness, etc., which can be very difficult for parents to handle. A well-known behavioral phenotype is the one associated with Down syndrome. Although these children are generally cheerful and sociable, they can also display autistic behavior, hyperactivity, obsessive–compulsive behavior, psychosis, etc., Diagnostic dilemmas arise when several syndromes have similar behavioral manifestations. In these cases, a step-by-step logical approach needs to be employed to arrive at the final diagnosis, just as would in a child with hepatosplenomegaly and short stature, which can be caused by multiple etiologies. Deep phenotyping of certain genetic syndromes can aid in deciding the direction of genetic testing, thus saving precious time and costs.

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In this case report, we describe the diagnostic approach that was undertaken in an undiagnosed child with cognitive impairment, epilepsy, neurological abnormalities, and unusual behavior whom we had the chance to encounter. After deep phenotyping, we established a diagnosis of pseudo-Angelman syndrome (AS) due to MBD5 haploinsufficiency. There are very few cases reported globally, and to the best of our knowledge, this is the first one to be reported from India.

Clinical Description

A healthy nonconsanguineous married couple was referred to the genetics department of our institute for reproductive

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counseling for their second pregnancy (7 weeks gestational age). They had a significant family history of their firstborn, a 7-year-old boy, having cognitive impairment and behavioral problems since early childhood and epilepsy since the age of 3 years. Although the child had been taken to multiple professionals, a clinical diagnosis had still not been made. The expectant couples' primary concern was whether their next child would be similarly affected. It was decided that we would attempt to establish a diagnosis based on the clinical phenotype and plan genetic testing (as warranted). The feasibility of a prenatal diagnosis would hence be explored accordingly.

The mother reported an uneventful antenatal period in her first pregnancy, with normal perception of quickening and subsequent fetal movements. A boy was born at term through a normal vaginal delivery and he cried immediately at birth. Records showed that at birth, the weight was 2.8 kg, head circumference 36 cm, and length 51 cm, all within normal limits. The perinatal period was normal. Concerns regarding the delayed acquisition of developmental milestones began when it was noted that he still did not hold his neck at 6 months of age. Elicitation of attainment of other milestones that the parents could remember in various domains were as follows: sitting without support at 11 months, standing with support at 24 months, and independent walking at 30 months (gross motor); pincer grasp at 18 months and ability to feed himself independently at 7 years; bisyllables at 30 months and two-word phrases at 4 years (language). The social milestones were also delayed, but the parents were unable to remember specific details. However, regression was not reported in any domain. Currently, at 7 years, he was able to run and speak in short sentences but not tell a story. His social interaction corresponded more with that of a younger child. He had not been sent to school due to his decreased ability to understand and follow instructions and atypical behavior (laughing aloud without reason, hyperactivity, and repetitive hand movements). There was no history of self-injurious behavior or aggression toward others. The child had still not attained a regular sleep pattern which was evident by significant nocturnal awakening and excessive daytime sleepiness. According to the parents, his hearing and vision were apparently normal.

At 3 years of age, he had experienced the first episode of generalized tonic–clonic seizures, which was not associated with fever, trauma, or any infectious illness. Consequently, he had three more episodes till the age of 5 years. He was currently seizure-free for almost 2 years on levetiracetam at 20 mg/kg/day. There was no significant history of any other significant medical illnesses. A three-generation pedigree was obtained, which showed no significant family history [Figure 1a]. The child was immunized for age.

Vital parameters were stable. His weight was 15.6 kg (−3 standard deviation [SD]), height 113 cm (−1.78 SD), head circumference 49 cm (−1.64 SD), and body mass index 13.2 (<5th centile). Facial dysmorphism can be appreciated in Figure 1b and c, which included a narrow forehead, medial flaring and sparseness of the lateral eyebrows, a prominent nasal bridge, anteverted nares, long and smooth philtrum, thin vermilion border, and hypodontia. Significant neurological findings were generalized hypotonia, in the presence of normal power, and normal deep tendon reflexes. There was no ataxia or gait disturbances. The rest of the systemic examinations were normal. The clinical phenotype was that of a dysmorphic child with intellectual disability and epilepsy. Since there were no "dysmorphic handles" pathognomonic of any particular definite or probable syndrome after the preliminary evaluation, we planned subsequent "empirical" workup according to the three main features, intellectual disability/possibly autistic features, epilepsy, and dysmorphism. Investigations and referrals were planned accordingly.

Management and Outcomes

Thyroid function tests were normal; thyroid-stimulating hormone 2.5 mU/L, and thyroxine (T4) levels 1.2 ng/dL. Magnetic resonance imaging of the brain and electroencephalogram were normal. Ultrasonography (abdomen) and echocardiography did not reveal any concealed congenital anomalies. Structured assessment of vision and hearing assessments did not reveal any impairment.

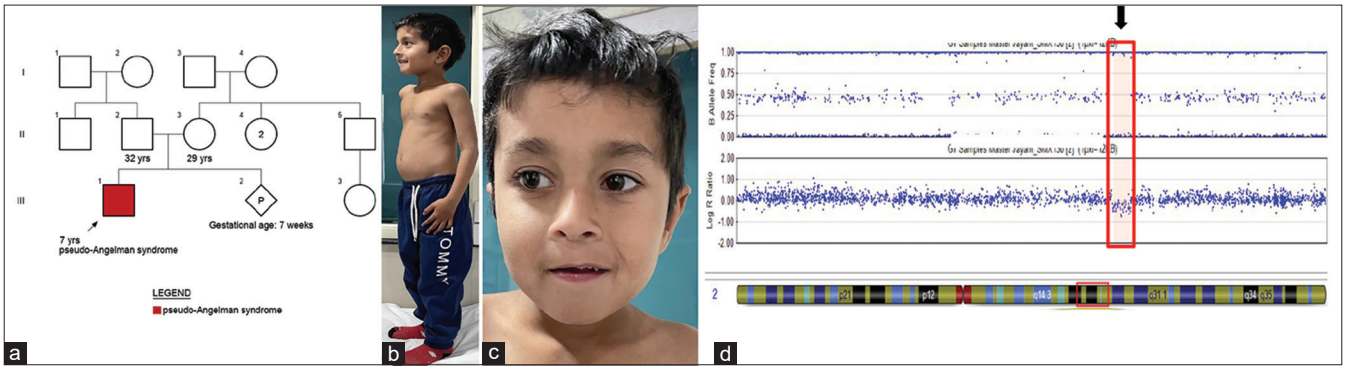

Figure 1: (a) Three-generation pedigree of the family. (b) Image showing the side profile of the proband showing depressed nasal bridge, micrognathia and prominent ears, and comparatively long limbs. (c) Image showing the frontal profile of the face of the proband at 7 years of age. Note narrow forehead, medial flaring and sparse lateral eyebrows, prominent nasal bridge, anteverted nares, long and smooth philtrum, thin vermillion border, and hypodontia. (d) The array image showing heterozygous deletion in the 2q23.1 cytoband (log R ratio – 0.5)-red box

The child was referred to a developmental pediatrician. Formal cognitive assessment revealed an intelligence quotient of 75 (borderline intelligence). It was observed that the child appeared alert and was extremely interactive with an excessively friendly nature and cheerful disposition. He made eye contact and communicated with the examiners and his parents using short sentences. He was able to follow instructions that were phrased in simple language. It was noted that he exhibited frequent bouts of spontaneous laughter without any triggers. However, there were also some autistic features. The child displayed the inability to appreciate social boundaries (that was out of proportion to the degree of cognitive impairment), hyperactivity (he kept on roaming around the clinic during the evaluation, despite being repeatedly told not to), and hand stereotypies in the form of intermittent hand clapping (without apparent cause) and writhing movements.

A syndrome search was performed by a clinical geneticist using Online Mendelian Inheritance in Man, Pictures of Standard Syndromes and Undiagnosed Malformation, and London Dysmorphology Database. The "handles" that were used were: happy demeanor and seizures. The differential diagnoses included: chromosomal disorders such as Kleefstra syndrome (9q34 deletion), 22q microduplication, and 2q microdeletion; and monogenic disorders that included Pitt–Hopkins syndrome (heterozygous pathogenic variants in TCF4 or a microdeletion involving TCF4), Mowat–Wilson syndrome (heterozygous pathogenic variants in ZEB2), and AS that is due to abnormal methylation at 15q11.2-q13 or a pathogenic variant in UBE3A. The list was then reviewed by applying the clinical, behavioral, and dysmorphism that had been identified in this child.

Out of these, the clinical phenotype of AS was considered the most likely, though typical features such as flat occiput, strabismus, wide mouth, widely spaced teeth, protruding tongue, or prognathia, were not present. However, the methylation specific-multiplex ligation probe amplification was negative for abnormal methylation at 15q11.2-q13, ruling it out completely. We proceeded with the next step in genetic testing, a chromosomal microarray, which revealed pathogenic heterozygous microdeletion of 401 kb at cytoband 2q23.1 encompassing the genes *ORC4* and *MBD5* [Figure 1d]. This was consistent with 2q23.1 microdeletion, also known as pseudo-Angelman phenotype. Biallelic variants in the *ORC4* are known to cause Meier–Gorlin syndrome, characterized by short stature, failure to thrive, distinct dysmorphic facial features, delayed bone age, and absent/hypoplastic patella. Since this child had normal stature and palpable patella, we did not evaluate the *ORC4* deletion any further.[1]

The couple underwent genetic counseling for the ongoing pregnancy. They were apprised of the following facts: most of these deletions are *de novo*; the recurrence risk in the mother's current and subsequent pregnancies was very low; but since germline mosaicism can also lead to recurrence (albeit in a few cases), prenatal diagnosis was nonetheless advisable. The couple agreed to an amniocentesis at 16-weeks' gestation, which revealed an unaffected status of the fetus, and they decided to continue with the pregnancy. The elder son continued follow-up with the developmental pediatrician for the continuation of detailed evaluation and planning of an individualized education plan that would include multidisciplinary interventions.

Discussion

Behavioral characteristics are often helpful in syndrome identification. In view of the typical handle that helped us establish the diagnosis in this case, we present a brief description of the clinical phenotype of a few genetic disorders that are associated with a "happy" disposition. This behavioral phenotype includes persistent smiling and excessive bouts of spontaneous laughter, both of which occur without any trigger.

The most common syndrome (incidentally considered in this case as well) is AS. In addition to the laughter and smiling, it is characterized by cognitive impairment, autistic features, the aforementioned dysmorphism, ataxia, hand flapping, seizures, microcephaly, and fair complexion. The combination of the ataxia, unusual gait, and happy disposition leads it to be referred to as "happy puppet" syndrome.[2] The tuning fork test is a reliable bedside test for identification; affected children respond to the sound of a struck tuning fork with a wide smile, outburst of laughter, and tendency to lean toward the vibrating tuning fork.[3]

Pseudo-AS or 2q23.1 microdeletion, which was identified in this case, is due to MBD5 haploinsufficiency. The manifestations include developmental delay, seizures, and the behavioral phenotype that encompasses hyperactivity, autism spectrum disorder, self-injury, aggression, and social withdrawal, in addition to the happy demeanor. The dysmorphic features include a broad forehead, highly arched eyebrows, short nose, depressed and wide nasal bridge, downturned corners of the mouth, everted vermilion of the lower lip, tented and thin vermilion of the upper lip. Skeletal abnormalities (small hands and feet, fifth finger clinodactyly, brachydactyly, sandal gap, etc.) and cardiovascular anomalies (atrial and ventricular septal defects) have been reported in a few cases.[4] Antiepileptic drugs are routinely utilized for seizure control in the 80% of affected children who have seizures.[4] Feeding difficulty and constipation are reported in infancy in 90% due to the associated hypotonia,[4] and may require consultation with a nutritionist. Medication may be considered for aggressive behavior on a case-to-case basis. Sleep disturbances are managed by strict sleep hygiene and drugs such as melatonin and trazodone. The clinical and behavioral phenotype in the proband was consistent with published literature and confirmed by the genotype.

Christianson syndrome due to 2q23.1 microdeletion is also referred to as X-linked AS due to its close resemblance to AS (happy disposition, ataxia, and epilepsy). However, the distinct dysmorphism (microcephaly, long, and narrow

face with prominent nose, jaw, ears, and open mouth with uncontrolled drooling), abnormal eye movements, the absence of tuning fork response, and less affected intellect are important differentiating features.[5]

The following descriptions are of a few less commonly known syndromes associated with a happy demeanor. Pitt–Hopkins syndrome (caused by heterozygous pathogenic variants in TCF4 or a microdeletion involving TCF4) can be differentiated by the presence of typical facial features, which include deep-set eyes, wide nasal root, short philtrum, and full upper and lower vermilion. In addition, they may display an unusual breathing pattern.[6] The dysmorphism seen in Mowat–Wilson syndrome (due to heterozygous pathogenic variants in ZEB2) comprises a prominent pointed chin, low-hanging columella, open mouth expression, and uplifted earlobes. Gastrointestinal disorders (Hirschsprung's disease and chronic constipation) and structural heart defects may also be seen.[7] Kleefstra syndrome[8] results from heterozygous deletion at chromosome 9q34.3 (that includes at least part of EHMT1) or a heterozygous intragenic pathogenic variant of EHMT1, affected individuals have Down syndrome such as facies and cognitive impairment (with severe speech delay) with prominent neurological involvement. Glass syndrome[9] (due to either *de novo* heterozygous mutations in the SATB2 gene or *de novo* heterozygous deletions of chromosome 2q32-q33) is characterized by pre-and postnatal growth retardation, short stature, dental anomalies, and ectodermal abnormalities (skin, hair, and nail).

In conclusion, behavioral phenotypes aid in the clinical characterization of various syndromic genetic disorders. A happy disposition in a child with intellectual disability should prompt the clinician to consult a geneticist and developmental pediatrician to delineate the cognitive and behavioral dimensions. These not only help in the planning of the intervention and behavior modification strategies but also direct the sequence of genetic testing.

Lessons learnt

- In children with significant behavioral issues, deep phenotyping should include a detailed cognitive and behavioral assessments by an expert.
- After deep phenotyping is completed, genetic testing should be planned according to whether the clinician and geneticist have a specific diagnosis, probable diagnosis, or no diagnosis in mind
- If no specific diagnosis can be appreciated, chromosomal microarray is recommended in cases with dysmorphism, cognitive impairment (global developmental delay/intellectual disability), and significant behavioral abnormalities.

Informed consent

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

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 name and initials will not be published and due efforts will be made to conceal the 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

Immunoglobulin A Vasculitis After a Not So Innocuous Wasp Bite

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Abstract

Background: Immunoglobulin A vasculitis (IgAV), previously known as Henoch–Schonlein purpura (HSP), is the most common vasculitis in children. Previous studies have identified various triggers of IgAV, with infections being the most common. We present herein a 9-year-old girl who developed IgAV with nephritis following a wasp sting. **Clinical Description:** A 9-year-old girl presented to us with a history of wasp sting 7 days ago, followed by the appearance of reddish, raised rashes over the back of her lower limbs, which later spread all over the body. She also developed edema over the face, abdomen, and lower limbs along with pain abdomen. On examination, she was afebrile, was normotensive, and had periorbital edema and bilateral pedal edema with multiple discrete palpable, nonblanching purpura predominantly over the extensor surfaces of the lower and upper extremities and the trunk. Abdominal examination revealed no tenderness. Complete blood counts, blood urea, serum creatinine, and liver function tests were normal. Urinalysis showed microscopic hematuria and nephrotic range proteinuria. Skin biopsy of the lesions showed evidence of IgA vasculitis. Renal biopsy was suggestive of HSP nephritis class 3. **Management and Outcome:** She was managed with oral corticosteroids, mycophenolate mofetil, and enalapril and had remission of proteinuria. The renal function tests and blood pressure continue to be normal. **Conclusion:** Few case reports exist of IgAV precipitated by insect bites; however, we could not find any previous reports of IgAV with nephritis following a wasp sting in children. This report adds to existing knowledge regarding precipitating factors for IgAV in children.

Keywords: Henoch–Schonlein purpura, immunoglobulin A vasculitis, nephritis, wasp sting

Immunoglobulin A vasculitis (IgAV), previously known as Henoch–Schonlein purpura, is the most common vasculitis observed in the pediatric age group. It is a small-vessel vasculitis that presents with characteristic skin lesions in the form of erythematous palpable purpura. In a subset of children, the complete triad of the disease that includes gastrointestinal, musculoskeletal, and renal manifestations is seen.[1,2] Various triggers of IgAV have been identified, with infections being the most common precipitating factor.[3] There are published case reports of IgAV occurring following insect bites (fire ant) and bee stings.[4,5]

Here, we present a girl who developed IgAV with nephritis following a wasp sting that was managed with immunosuppressive therapy. To the best of our knowledge, this is the first reported case since an exhaustive scientific literature search was unable to identify any previous case.

Clinical Description

A 9-year-old girl presented with a history of being stung by a wasp 7 days earlier. This was immediately followed by the appearance of generalized pruritic, reddish, raised rashes that subsided within 24 h after treatment with oral anti-inflammatory and antihistaminic medication. Three days afterward, reddish, raised, painless, and nonpruritic skin lesions and rashes were noted. These initially erupted over the back of her legs and later spread all over her body. The size varied, with a diameter ranging from 1 to 1.5 cm. Within the next 24–48 h, the child developed swelling over her face (mainly around her eyes) that progressed to involve her abdomen and legs. There was no history of joint swelling or pain, abdominal pain, reduced urine output, or passage of reddish or cola-colored urine.

There was no preceding history of cold, cough, or fever. There was no past history suggestive of allergies such as wheezing, redness and/or excessive watering of the eyes, recurrent bouts of sneezing or eruption of itchy, red rashes following the ingestion of any food items or other triggers. She was the fourth born of a nonconsanguineous marriage with no significant family history. She was immunized, and her diet and academic performance were appropriate for her age.

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She was conscious and alert. She was afebrile. Her pulse rate was 84/min and regular. She had a blood pressure (BP) of 98/72 mmHg (between 50th and 95th centiles for age). There was no respiratory distress. The generalized physical examination revealed periorbital and bilateral pedal edema. Multiple, discrete, palpable, nonblanching purpura were present predominantly on the extensor surfaces of the lower extremities, both arms, and trunk. There was no pallor, icterus, or significant lymphadenopathy. The joint examination was normal. There was no tenderness or organomegaly on abdominal examination, but shifting dullness was present suggestive of ascites. The examination of other systems was normal. Based on the combination of purpura predominantly involving the extensor surfaces and edema, a possibility of IgAV was considered. The edema suggested possible renal involvement, but there was no oliguria, hematuria, or hypertension. The likelihood of an adverse drug reaction following paracetamol and antihistaminic drugs that had been taken after the wasp sting was less.

Management and Outcome

First-line investigations hemogram (hemoglobin 12.1 g/dL, total leukocyte count 9300/mm^3, and platelet count 3.3 lac/mm^3), kidney function test (urea 19 mg/dl and creatinine 0.42 mg/dl), and liver function test (specifically serum albumin 2.3 g/dl) were normal. Urinalysis showed numerous red blood cells (RBCs) per high-power field (HPF) <20% of which were dysmorphic and proteinuria (2+ to 3+ on dipstick). The urine protein–creatinine ratio was 3.5 (elevated), and 24-h urine protein excretion was 4.9 g/day (increased). Serum C3 was 98 mg/dl (normal 90–110 mg/dl), and antinuclear antibodies and dsDNA were negative. Abdominal ultrasound revealed normal-sized kidneys (right 8.4 cm and left 8.6 cm) with mild attenuation of corticomedullary differentiation. The biopsy of the skin lesions confirmed small-vessel vasculitis and IgA was present 3+ in the dermal vessels, consistent with IgAV [Figure 1]. A renal biopsy was performed in view of the proteinuria being in the nephrotic range. This showed 22 glomeruli with variable degrees of mesangial expansion, mesangial hypercellularity, endocapillary proliferation, and tuft necrosis. There was no evidence of segmental sclerosis or crescents, and the blood vessels and tubulointerstitial compartment were unremarkable. This corresponded to the International Study of Kidney Disease in Children (ISKDC) grade III IgA

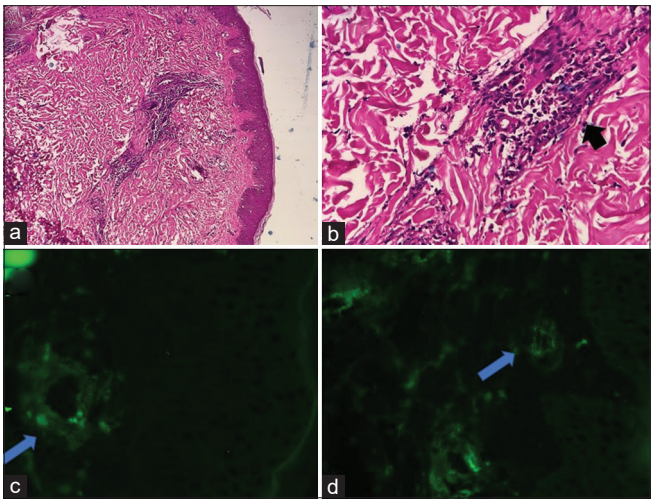

Figure 1: Photomicrographs of histopathological and DIF findings of skin biopsy. (a) Photomicrograph of skin biopsy shows epidermis and dermis (H and E, ×10), (b) High-power view shows moderate perivascular mixed inflammatory infiltrate around dermal capillaries (black arrow), evidence of vasculitis noted in the form of infiltration into the vessel wall, extravasation of RBCs, and endothelial swelling. (c) DIF for IgA showed 3+ granular positivity in the dermal capillary wall (blue arrow) (FITC, ×40). (d) DIF for IgA showed 1+ granular positivity in the dermal capillary wall (blue arrow) (FITC, ×40). DIF: Direct immunofluorescence

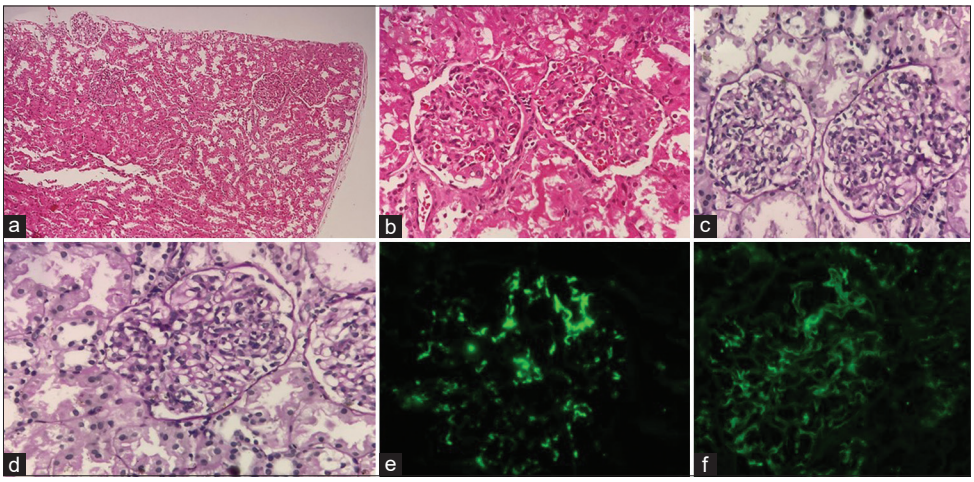

Figure 2: Photomicrographs of histopathological and DIF findings of renal biopsy. (a and b) Photomicrograph of renal biopsy with the glomeruli showing variable degrees of mesangial expansion and mesangial hypercellularity (H and E, ×10 and ×20). (c and d) PAS stain sections show highlight variable degrees of mesangial expansion and mesangial hypercellularity (PAS stain, ×20 and ×40). (e) DIF for IgA shows 3 + granular mesangial and glomerular capillary wall positivity (FITC, ×40). (f) DIF for IgG showed 1+ granular mesangial and glomerular capillary wall positivity (FITC, ×40). DIF: Direct immunofluorescence, IgG: Immunoglobulin G, PAS: Periodic acid–Schiff. FITC: Fluorescein isothiocyanate–dextran

nephropathy [Figure 2].[6] Direct immunofluorescence showed IgA 3+ with the absence of C3, C1q, immunoglobulin G (IgG), and IgM. The final diagnosis was IgAV with class III nephritis.

She was managed with oral corticosteroids (2 mg/kg/day for 4 weeks followed by tapering doses), mycophenolate mofetil (MMF) (800 mg/m^2), and enalapril (as per the European consensus guidelines).[7,8] The rash and edema resolved in 2 weeks. Monthly follow-up visits included monitoring of BP (remained normotensive), renal function tests (within normal limits), and 24-h urine protein (reduced to 800 mg/day by 2 months and 350 mg/day by 6 months' follow-up). Microscopic hematuria is persisting (8 RBCs/HPF) at the last follow-up.

Discussion

The incidence of IgAV is 3–27 cases per 100,000 children. IgAV with nephritis is seen in approximately one-third of children. Most affected children exhibit gross or microscopic hematuria with no or only mild proteinuria. Only about 2% have been reported to have proteinuria in the nephrotic range and other features of severe glomerulonephritis.[2,7] In this case, IgAV with nephritis was confirmed by nephrotic range proteinuria and ISKDC grade III IgA nephropathy on kidney biopsy. Since recent guidelines recommend early immunosuppressive therapy in cases with moderate-to-severe proteinuria,[9] we treated the child with corticosteroids and MMF, following which the skin lesions and edema resolved and proteinuria reduced considerably.

There are many similarities as well as differences between IgA vasculitis (IgAV) and IgA nephropathy (IgAN). IgAV and IgAN could represent different extremities of a continuous spectrum of the same disease, as evidenced by episodes of IgAV as well as IgAN among siblings, parents in the same patients at two periods of life, and, more recently, recurrences in kidney allograft.[10] As a result, IgAV could well be the systemic form of the IgAN. The differences between both entities could be primarily the clinical presentation, with IgA nephropathy usually affecting older children and young adults and typically involving only the kidneys, whereas IgAV affects mostly children and involves the skin and connective tissues, gastrointestinal tract, joints, as well as the kidneys.

The four-hit theory elucidates the pathogenesis of IgAV with nephritis. This includes increased production of galactose-deficient IgA1 and IgG autoantibodies that recognize galactose-deficient IgA1, form immune complexes, and get deposited in the glomeruli. The first two hits apparently occur when there is exposure to infectious agents or other antigens. Thus, these may have a role in the disease precipitation, especially due to dysregulated mucosal immunity.[8] The most common triggering microorganism is Group A *Streptococcus*, but other bacteria, viruses, and protozoa have been incriminated.[3] Our patient developed typical features of IgAV within 3 days of the wasp sting. In our literature search, we found a case report of IgAV having being precipitated by a bee sting. The essential difference between a bee sting and a wasp sting is that the former can sting only once as it loses its stinger and the amount of bee venom injected is 50 μg, whereas the wasp can sting multiple times, each time introducing 2–15 μg of wasp venom. Bee venom contains melittin, while wasp venom contains acetylcholine and serotonin. Both contain substances that trigger histamine release and hyaluronidase that helps the venom to spread within the tissues.

To conclude, genetic factors, disrupted mucosal immunity, and immune complexes with abnormal IgA or IgA antibodies are essential in the pathogenesis of IgAV. Insect bites and bee stings have been known to trigger IgAV with nephritis in children. Given the similarity between bee and wasp venom, whether the wasp sting represents an association or causation is a question that can only be answered by more reports of similar cases.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Aluminum Phosphide Toxicity: A Rare Cause of Multiorgan Dysfunction Syndrome

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Abstract

Background: Aluminum phosphides (ALPs) are still being used in developing countries as a pesticide despite the fact that ingestion and/or inhalation can cause significant morbidity and mortality. The generation of phosphine when ALP comes in contact with water leads to the blockade of electron transfer, which inhibits oxidative phosphorylation and in turn, cellular respiration in multiple organ systems. **Clinical Description:** A 3-year-old Turkish girl and her family were inadvertently exposed to overnight inhalation intoxication after a tablet of ALP was dissolved in water and used as a pesticide for Isot pepper, a local spice used in their household. The child presented with rapidly progressive respiratory distress and coma. The other members displayed mild respiratory symptoms. **Management:** At the time of admission, she was in altered sensorium, tachycardic, tachypneic, hypoxic, and in shock. She was immediately intubated and intermittent positive pressure ventilation started. Shock was managed as per the standard protocol. The child emanated garlic odor breath, had sluggishly reactive bilateral mitotic pupils. She had cardiorespiratory arrest within 30 min of intubation and could be revived. Despite supportive treatment, multiorgan dysfunction syndrome developed cardiac, pulmonary, renal, hepatic, coagulopathy, hyperglycemia, and metabolic acidosis. She succumbed to another cardiorespiratory arrest before plasmapheresis and continuous renal replacement therapy could be started in an attempt to eliminate the toxins. Consent for autopsy was not given. **Conclusions:** ALPs poisoning still occurs in developing countries and is a leading cause of mortality. The most common cause of death within the first 24 h is cardiovascular collapse.

Keywords: Aluminum phosphide, cardiac failure, inhalation, intoxication, MODS

The treatment of agricultural products with pesticides such as aluminum phosphides (ALP) is high in low- and middle-income countries (LMICs). Ingestion or inhalation of ALP may cause severe cases of acute and/or chronic poisoning. Once consumed, ALP combines with water and the hydrochloric acid present in the stomach to form phosphine gas. This gets rapidly absorbed from the gastrointestinal tract to enter the systemic circulation and results in multiple organ failure.[1] ALP toxicity has been widely reported since the 1980s. Most intoxications are due to accidental ingestion followed by suicidal ingestion.[1] Around 300,000 deaths occur per year globally, mostly from LMIC.[2] An Indian study of autopsies performed on cases of poisoning over 25 years reported of mortality causes. ALP was detected the most common cause after 1982, with an incidence of 65%.[3] Metal phosphides such as aluminum, magnesium, and calcium phosphides are popular in LMIC because of their potency, cheapness, and minimal adverse effects in crop protection the storage of cereals, animal feed, and tobacco leaves, despite the high risk of human mortality.[4] The ALP tablets are sold without restriction in Turkey and India, even though they are potentially toxic.[5] Their use in high-income countries is minimal. Even almost a decade ago (1983–2003), only 188 cases of ALP poisoning were reported from Germany (65% accidental).[6]

In this case, we report the circumstances and death of a Turkish child due to multiorgan failure within 24 h of inhalation of ALP that was being for the preservation of local Isot pepper. The aim of reporting this case is to sensitize the pediatricians to also enquire about the use of ALP as a pesticide or preservative in households when one encounters a child presenting with sudden onset, inexplicable cardiorespiratory failure.

Clinical Description

A previously healthy 3-year-old girl was brought to our pediatric emergency department with sudden onset altered

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sensorium and breathing difficulty overnight. She had been apparently well on going to bed and was noticed to have difficulty in breathing on awakening which rapidly worsened till she lapsed into altered sensorium. The labored breathing involved chest retraction.

At admission, she was noted to be cyanosed. Her temperature was 36.5°C, heart rate 172 beats per minute (min), regular, but with low volume, respiratory rate 68/min with severe respiratory distress, SpO_2 80% in room air, capillary refill time 4 s, and blood pressure 69/32 mm Hg (<3rd percentile). The weight was 15 kg (normal for age). Other anthropometric parameters were not taken. The Modified Glasgow Coma Scale was 6; E1M3V2. She was immediately intubated and started on intermittent positive pressure ventilation (IPPV) and fluid management for shock was initiated with 0.9% normal saline (NS) intravenous (IV) fluid as per the standard protocol. On the spot testing revealed hyperglycemia that was out of range. The arterial blood gas (ABG) analysis was consistent with metabolic acidosis; pH 6.67 (normal 7.35–7.45), pCO_2 29.9 mm Hg (normal 35–45 mm/Hg), HCO_3 9 mmol/L (normal 18–22 mmol/L), and lactate 16.8 mmol/L (normal 0–2 mmol/L). The patient was immediately shifted to the pediatric intensive care unit where she was started on mechanical ventilation. The random blood sugar (RBS) confirmed hyperglycemia of 450 mg/dl (normal 60–110 mg/dl), but urinary ketones were negative. Serum sodium (Na+) was 129 mEq/l (normal 35–145 mEq/l) and serum potassium (K+) 5.9 mEq/l (normal 3.5–5.5 mEq/l). Fluid management comprised of 0.9% NS (1000 cc/m^2) with insulin (0.01 IU/kg/h), IV $NaHCO_3$ (1 cc/kg), and empirical IV antibiotics (cephtriaxone). Subsequently, we initiated a detailed history and examination to ascertain the cause of sudden deterioration in a previously healthy child.

Management and Outcome

There was no preceding history of any fever, cough, coryza, change in the voice, rashes, or sore throat. The child did not have any diarrhea, vomiting, hematemesis or abdominal pain. The child did not have any seizures, fall or trauma to the head. There was no history of redness of eyes, swelling of face or lips, itchy rash, or wheezing immediately following ingestion of any food or exposure to any substance at home. History of a bout of sudden coughing and choking associated with bluish discoloration, following play with a small toy or consumption of any small food items suggestive of foreign-body inhalation was not forthcoming. There was no history of preceding injury to the chest, past allergies, or recurrent wheezing. The parents were not related and the family history was not contributory. The child was immunized and developmental milestones were age appropriate. The family belonged to a low socioeconomic strata and lived together in a single room. A significant history of isolated respiratory symptoms (without fever, cough, or coryza) in multiple family members was present, and an unknown poisoning was suspected. On further probing, her mother disclosed that ALP tablets had been used as an preservative in the local Isot pepper pot in the evening.

The child's nutritional status appeared good. The cyanosis had resolved post-IPPV. A strong "garlic" odor was present. There was no pallor, jaundice, rashes, petechiae, purpurae, or ecchymosis. Both pupils were mitotic and sluggishly reacting to light. Tone and power assessment were inconclusive due to medications given for respiratory paralysis *in lieu of* IPPV. The deep-tendon reflexes were normal and plantars downgoing. The cardiovascular, respiratory, and abdominal systems were normal. Based on circumstantial history and clinical phenotype, a provisional diagnosis of ALP poisoning was kept, and her clothes were removed. Diabetic ketoacidosis was also considered, although there was no history of increased frequency of urination, hunger, thirst, or recent weight loss, or family history of diabetes mellitus. Since there is no specific antidote, supportive therapy was started. In this situation, calcium infusion and magnesium sulfate were used for membrane stabilization.

She had a cardiorespiratory arrest within 30 min of intubation and required cardiorespiratory resuscitation, following which she was continued on the management of shock as per standard protocol; initially for fluid refractory shock, followed by adrenaline for fluid refractory-dopamine resistant shock. Table 1 gives the results of the preliminary hemogram and biochemical tests. These indicated renal and hepatic dysfunction. Fresh-frozen plasma was administered for the coagulopathy. The electrocardiogram showed sinus tachycardia of 168 beats/min, with regular RR interval, normal PR interval, QRS duration, and an isoelectric ST segment. Troponin-T levels were elevated; 36.6 pg/ml, normal 0–14 pg/ml. An echocardiogram detected a systolic ejection fraction of 32% (normal >55%). The chest X-ray showed bilateral diffuse opacities suggestive of pulmonary edema. The child continued to deteriorate progressing rapidly from catecholamine-resistant shock to persistent catecholamaine-resistant shock, despite the escalation of established medical algorithmic approach, but without any evidence of improvement.

We repeated her investigations after 12 h [Table 1] which reflected the deteriorating clinical status. The worsening ABG parameters (pH 7.07, pCO_2 23 mm Hg, HCO_3 10.2 mmol/L, and lactate 9.8 mmol/L), hyperkalemia, hyponatremia, hyperglycemia (RBS 643 mg/dl), coagulopathy, and cardiac failure (Troponin-T 36.6 pg/ml) reflected the rapidly progressive and severe cardiac, renal, central nervous system, hepatic and pulmonary involvement, signaling multiorgan dysfunction syndrome. Before we could initiate plasmapheresis and continuous renal replacement therapy, the child had another cardiorespiratory arrest and succumbed. The family did not consent to an autopsy.

Discussion

Isot pepper is a traditional hot pepper that is produced in Şanlıurfa, the south-eastern region of Turkey.[5] Turkish people

Table 1: Reports of the child with aluminum phosphides poisoning at admission and after 12 h

Investigations (units)	Admission	At 12 h	Normal values
Hemoglobin (g/dl)	11.4	9.4	10.8-15.6
Total leukocyte count (per mm^3)	14.21×10^3	316×10^3	$4.5\text{-}14\times10^3$
Serum sodium	129	127	135-145
Serum potassium	5.9	6.1	3.5-5.5
Blood urea nitrogen	74	98	11-39
Serum creatinine	1.11	2.6	0.4-0.6
Serum bilirubin (mg/dl)	1.6	3.5	0.3-1
Serum aspartate transaminase (U/L)	79	579	5-33
Serum alanine aminotransferase (U/L)	36	436	5-32
Prothrombin time (s)	21.9	34.9	10-14
Activated plasma thromboplastin time (s)	46.7	42.3	21-36
International normalized ratio	1.8	2.8	0.05-1.2

use it as a spice in their meal preparation. In Turkey, various commercial tablet preparations are available that are dissolved in water. This particular household was using a 500 mg tablet dissolved in water as a pesticide to protect their Isot pepper. Since the entire family slept in the same room, and other family members were also symptomatic and did not give a history of ingestion, it was presumed that poisoning was inhalation. When ALP comes in contact with moisture, phosphine gas is released and a dose of 1400 mg/m^3 for 30 min can be fatal.[7,8] This family was presumably exposed overnight.

The underlying pathophysiology is the blockade of electron transfer, particularly of cytochrome c oxidase, which inhibits oxidative phosphorylation and, in turn, affects cellular respiration and results in the activation of peroxide radicals. Phosphine also inhibits catalase and depletes glutathione, which may result in the cell wall and cell ion channel dysfunction as well.[7] When poisoning is due to ingestion, manifestations occur within 10 − 15 min and progress rapidly. Early symptoms may be gastrointestinal (nausea, vomiting, hematemesis, and epigastric pain) or respiratory. An odor of garlic may emanate from the patients' breath.[7] Inhalation of high amounts of phosphine lead to cardiac failure, dysrhythmias (ventricular/atrial tachycardia, ventricular/atrial fibrillation, torsades de pointes, etc.), acute respiratory distress syndrome, and hepatic/kidney failure.[7,8] Central nervous system manifestations include seizures, ataxia, paraesthesias, tremors, and coma.[7] Various dyselectrolytemias occur hypo/hypernatremia, hypo/hyperkalemia, or hypo/hypermagnesemia. Both hypo/hyperglycemia may be seen.

Symptomatic patients should be closely monitored. Medical personnel who come in close contact with victims of intoxication should wear rubber gloves and a full-face mask. It is recommended that the patient's contaminated clothes should be removed and the skin and eyes are washed. Treatment is supportive. Calcium is added for the stabilization of the cell membranes. Magnesium and N-acetylcysteine may act as antioxidants. Other modalities such as Vitamin E, melatonin, glutathione, betacarotene, steroid, and hyperbaric oxygen have been tried, but their efficacy is unclear.[7,8] Renal replacement therapies can be applied in addition to bicarbonate support in patients with persistent metabolic acidosis.[5] Treatment of acidosis and removal of high-molecular-weight cytokines by hemodiafiltration may be helpful if initiated in time.[8] We were unable to initiate plasmapheresis in this case.

Lessons learnt

- Aluminum phosphide is still used in low- and middle-income countries as a pesticide
- Mode of poisoning can be inhalational or ingestion, both of which can result in multi organ dysfunction
- Renal replacement therapies should be considered in persistent metabolic acidosis
- Most deaths are due to cardiovascular collapse in the first 12–24 h.

Declaration of patient consent

The authors certify that they had 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

Eosinophilic Myenteric Ganglionitis with Degenerative Leiomyopathy: Dual Causes of Chronic Intestinal Pseudo-Obstruction

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Abstract

Background: Chronic intestinal pseudo-obstruction (CIPO) is an umbrella term for a range of different conditions characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic evidence of dilated intestines and air-fluid levels, due to impaired propulsion in the absence of an anatomical occluding lesion. It is a diagnostic challenge and can mimic Hirschsprung's disease. **Clinical Description:** A 10-month-old boy presented with a history of recurrent episodes of constipation since the age of 6.5 months. The first two had resolved with symptomatic treatment. The third had been associated with bilious vomiting and required exploratory laparotomy. He was referred to us when there was no symptomatic improvement. The child underwent extensive workup that included a review of earlier investigations (contrast-enhanced computerized tomography abdomen, barium enema, and sigmoid biopsy) as well as upper gastrointestinal endoscopy, workup for secondary CIPO, esophageal and antroduodenal manometry, genetic studies, for primary CIPO. A laparotomy with concurrent adhesionolysis, appendectomy, gastrostomy, and ileostomy was undertaken, which included full-thickness biopsies at multiple sites. This revealed both degenerative leiomyopathy and eosinophilic myenteric ganglionitis (EMG). Known associations of CIPO, an underactive bladder, and sinus arrhythmias were also detected. **Management:** The infant was provided with supportive therapy. A trial of steroids was given for the EMG. The child had multiple bad prognostic factors and also protracted multiple nosocomial infections. He succumbed to his illness and complications after 40 days of hospitalization. **Conclusion:** The combination of EMG and degenerative leiomyopathy has not been reported in CIPO before.

Keywords: Degeneration, eosinophilic ganglionitis, Hirschsprung's disease mimicker, leiomyopathy, pseudo-obstruction

Chronic intestinal pseudo-obstruction (CIPO) is an umbrella term for a range of different conditions characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic evidence of dilated intestines and air-fluid levels, due to impaired propulsion in the absence of an anatomical occluding lesion. The motor alterations lead to the inability for normal transit of nourishment and secretions along the gastrointestinal tract. The prevalence of CIPO is largely unknown in children. A nationwide survey in Japan reported a prevalence of 3.7 in 100,000 children under 15 years of age.[1] The clinical presentation is heterogeneous depending on the predominant segment of intestinal involvement, and includes abdominal distention, vomiting, constipation, failure to thrive and abdominal pain. Diarrhea is often present due to the slow transit of ingested food within the intestines. This triggers a sequence of bacterial overgrowth, malabsorption, and malnutrition. The most severe disorders display antenatal evidence of dilation of the gastrointestinal and urinary systems. This subset represents the most common group of pediatric CIPO patients with diffuse involvement of the GI tract. In a review of 105 pediatric cases of CIPO, approximately 75% presented within the 1st year of life, with 67% presenting within the 1st month. Prenatal signs are detected in about 20% of cases.[2]

CIPO may be primary, secondary (collagen vascular disorders, paraneoplastic conditions, autoimmune or metabolic disorders) or a part of syndromes, i.e., the megacystis-microcolon-intestinal hypoperistalsis syndrome. It may also be broadly classified as myopathic or neuropathic according to the underlying

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pathophysiology. Till date, there are only few cases which have reported eosinophilic myenteric ganglionitis (EMG) as the cause. EMG is an inflammatory neuropathy, characterized by a marked eosinophilic infiltration of the myenteric plexus/myenteric ganglia, which causes intestinal obstruction.[2-4] Degenerative leiomyopathy is a myopathy characterized by a prolonged history of abdominal distention and megacolon and has been reported exclusively in young Africans.[3-5]

In this report, we present a case of an infant of Indian origin with CIPO due to a dual pathology, biopsy-proven EMG, and concomitant degenerative leiomyopathy. To the best of our knowledge, it has not been reported earlier in literature.

Clinical Description

A 10-month-old boy was referred to us with complaints of abdominal distension, bilious vomiting, and constipation for 2 weeks. At 9.5 months, he had bilious vomiting, constipation, and abdominal distension, for which he was admitted to a local hospital. According to parental history and whatever medical records were available, he had undergone a barium enema (that had shown a transition zone in mid sigmoid) and contrast-enhanced computerized tomography (CECT) of the abdomen. Based on these, Hirschsprung's disease had been suspected and he underwent exploratory laparotomy with a sigmoid colostomy. Peroperative colonic biopsy (frozen section) was suggestive of absent ganglionic cells. The child did not show any improvement postoperatively and underwent a colostomy revision to descending colostomy on the 3rd postoperative day. When he was started on a liquid diet subsequently, the child developed abdominal distension and bilious aspirates again. That was the reason for the referral for further evaluation and management to our tertiary center.

We reviewed all aspects of history. It emerged that the child had been experiencing recurrent episodes of constipation: for a few days at 6.5 months of age which was relieved with over-the-counter laxatives; at 7.5 months, for which he was started on laxatives and some household remedies for 2 weeks and showed symptomatic improvement; and the last episode at 9.9 months, when he was operated on. A history of intermittent dribbling of urine was also elicited. There was no history of his receiving treatment for urinary tract infections. The infant had been started on complementary feeds at 6 months, and the diet and water intake were adequate.

The boy was the second issue of unrelated parents with a history of a previous abortion. The mother had hypothyroidism, for which she had been prescribed Thyronorm (100 μg) and was compliant. She also had cholestasis of pregnancy that was managed conservatively. An antenatal ultrasound showed mild right pelvicalyceal separation and hydronephrosis. The baby was born by at term gestation by normal vaginal delivery. His birth weight was 3.5 kg, and he cried immediately after birth. The perinatal period had been uneventful, he had passed meconium within 24 h of life, the routine newborn screening evaluation was normal, and he was discharged as per hospital protocol. According to his parents, the infant achieved all milestones normally till he fell ill and was completely immunized for age. There was no significant family history. His 7-year-old brother was healthy.

At admission, the child was hemodynamically stable. His temperature was normal, pulse rate 94/min, respiratory rate 24/min, SpO_2 98% in room air, and blood pressure 90/70 mm Hg in the right arm supine position. Anthropometric parameters revealed a weight of 8 kg (between 3 and 50th centile of the Indian Academy of Pediatrics [IAP] growth chart), and a length of 80 cm (97th centile on the IAP chart). The *in situ* nasogastric tube contained bilious aspirates. There was no pallor, icterus, edema, or dysmorphic features. Abdominal examination revealed generalized abdominal distension, a tympanitic note in the upper abdomen, bladder dullness, and sluggish bowel sounds in all four quadrants. There was no guarding, rigidity, tenderness, or organomegaly. The rest of the systemic examination was normal.

A clinical possibility of pseudo-obstruction due to dysmotility was kept. The points in favor were feeding intolerance, continuous bilious aspirates, abdominal distension, and sequential X-rays showing extensive small bowel dilatation in the absence of any significant anatomical obstruction on the CT scan. A history of intermittent dribbling of urine was also in favor of the above diagnosis. The points against were the biopsy report of absent ganglionic cells. An alternative diagnosis that was also considered was postoperative complications secondary to adhesions that may have developed and resulted in subacute intestinal obstruction. The third, albeit remote, possibility of total colonic aganglionosis or hypoganglionosis was also kept. However, the late presentation and absence of microcolon were points against this differential.

Management and Outcome

The infant was kept on intravenous fluids, nil per orally, with continuous Ryle's tube aspiration. His abdominal roentgenogram revealed significantly dilated small bowel loops. The CECT abdomen and the barium enema study were reviewed. Since there was predominant small bowel dilatation without significant dilation of the large bowel loops, the possibility of a transition zone in the distal ileum was considered. However, in view of the nondilated distal colon and the absence of an obvious transition in the rectosigmoid area, Hirschsprung's disease appeared to be less likely. We also reviewed the frozen sections of the previously conducted sigmoid biopsy. Presence of ganglion cells in all the three specimens with positivity for calretinin on immunohistochemistry (IHC), effectively ruled out Hirschsprung's disease. An upper gastrointestinal (GI) endoscopy was performed that showed a dilated stomach with a wide and open pylorus. The following secondary causes were ruled out by lack of specific findings on the endoscopy as well as negative test results: hypothyroidism (thyroid-stimulating hormone– 1.51 pg/ml and Free T4 0.86 ng/dl), hypoparathyroidism (PTH 30.2 pg/ml), celiac disease (tTg Ig A <3 U/ml), cytomegalovirus and Epstein–Barr

virus infection by negative polymerase chain reaction, systemic lupus erythematosus (negative anti-nuclear antibody), muscular dystrophy (creatine phosphokinase <20 U/L), eosinophilic gastroenteritis (no evidence on endoscopic biopsies), and food allergy (immunoglobulin E panel not contributory).

Esophageal and antroduodenal manometry was attempted to investigate whether the cause of the pseudo-obstruction was myopathic or neuropathic, but only a partial study was possible as child was not very cooperative when asked to swallow during the study of an hour (since the child needs to comply with instructions this invasive procedure cannot be done under the influence of anesthesia or sedatives). This revealed doubtful peristalsis in the esophagus with absent contractile activity in the stomach. We were unable to perform colonic manometry due to the colostomy and nonavailability of the appropriate catheter size. Clinical exome sequencing for primary/idiopathic CIPO was also non-contributory.

In view of the report of possible renal anomalies in the antenatal ultrasonogram (but had not been investigated further), history of intermittent urinary dribbling, and the finding of an overstretched bladder on the CECT abdomen, we planned a vesico-cystourethrogram. This reported a large bladder (with 270% extended bladder capacity). The urine study also revealed large bladder capacity and delayed bladder sensation (with more than 200% filling) indicative of an underactive bladder. This was managed by enabling the parents to perform clean intermittent bladder catheterization and neuromodulation physiotherapy. A cardiac evaluation was undertaken due to known cardiac associations with CIPO. The electrocardiogram displayed sinus arrhythmia, and the echocardiography was normal.

The child was started on a minimal number of nasogastric feeds (7.5 ml peptide formula given every 2 hours), but were withheld due to recurrence of feed intolerance. The same thing happened when the modality was changed to nasojejunal feeding; the child continued to have large aspirates with significant bowel distension (predominantly the small bowel), so they were also stopped. Therefore, the child's nutritional requirements were provided by the parenteral route (kabiven peri twice a week and aminoven thrice a week).

On the 15th day of admission, the child developed a fever and was investigated, suspecting a nosocomial infection. This was confirmed by a positive C-reactive protein and Klebsiella growth in the blood culture. Urine routine microscopy detected fungal hyphae and the fungal culture grew candida albicans. They were managed with antibiotics (meropenem and tigecycline as per drug sensitivity) and antifungals (fluconazole) as per hospital protocol.

The child stopped passing stools through colostomy on the 20th day of admission and developed increased bilious aspirates. A Gastrografin study revealed dilated proximal intestinal loops with reflux of contrast into the stomach, raising the suspicion of an obstruction at the level of the ileum. A CECT was repeated, which revealed small bowel intestinal obstruction with a possible transition zone in the right iliac fossa. The possibility of adhesions at the level of mid ileal loops was considered and we decided to perform a laparotomy with concurrent adhesionolysis, appendectomy, gastrostomy, and ileostomy.

Full-thickness biopsies were taken from the stomach, duodenum, jejunum, and colon. Histopathology revealed a significant infiltrate of eosinophils, with eosinophilic cryptitis in the mucosa. These infiltrated both the layers of muscularis propria, and the ganglions in the inter-myenteric plexus. Eosinophil degranulation was also present [Figure 1]. The smooth muscle layers of the stomach, colon, and inner circular layer of the small bowel wall showed features of degenerative myopathy, with smooth muscle actin and desmin stain displaying loss of the muscle fibrils [Figure 2]. There was no evidence of fibrosis, vasculitis, vacuolation of the muscle fibers, or abnormal thickening of muscle layers. The muscularis mucosae were unremarkable. There was no evidence of aganglionosis,

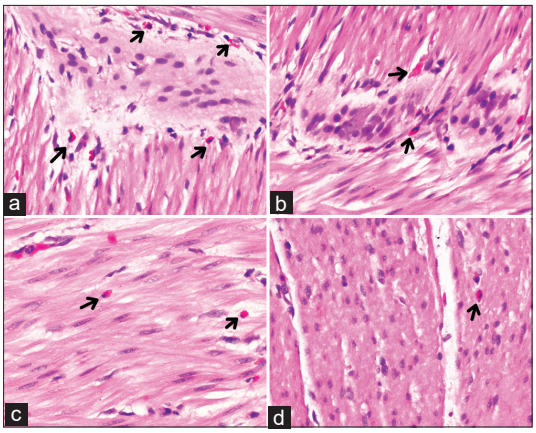

Figure 1: Histological images show prominent infiltrate of eosinophils (arrows) in the ganglia of myenteric plexus (a and b: H and E, ×200) and within the layers of muscularis propria (c: arrows, H and E, ×200). The muscle layers, in addition to the eosinophilic cell infiltrate (arrow), did not reveal vacuolation of inclusion (d: H and E, ×200)

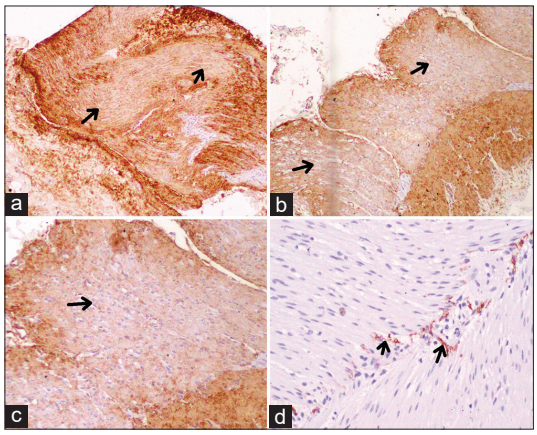

Figure 2: Immunohistochemical staining for SMA in gastric (a: ×100), and small bowel biopsies show marked degeneration and loss of SMA-positive smooth muscle bundles from the inner circular muscle layer (b: ×100, c: ×200). Calretinin stain for the interstitial cell of Cajal showed normal cell network around the myenteric ganglion (d: ×200). SMA: Smooth muscle actin

hypoganglionosis, or intestinal neuronal dysplasia. Stains for Interstitial cells of Cajal were present in most areas but partially lost in the stomach (possibly secondary to the degenerative changes). Significant lymphoid cell infiltration was not detected around the neuronal ganglion on CD8 IHC staining. Based on the above features, a diagnosis of degenerative leiomyopathy in the presence of eosinophilic enteritis, myositis, and myenteric ganglionitis of the intestinal wall was kept. A trial of steroids was given under the cover of antibiotics after discussion with parents. However, the clinical condition worsened and the child succumbed to culture-proven pseudomonas and Klebsiella septicemia on the 40th day of hospitalization.

Discussion

The clinical presentation of CIPO may be acute**,** subacute, or recurrent episodes of gastric, intestinal, and/or colonic obstruction. The symptoms depend on the extent and the site of gastrointestinal tract involvement. Some cases are characterized by initial normalcy of variable duration in infancy, followed by progressive intestinal failure, with bowel and often urinary tract dilatation (as in our patient). The remainder may become symptomatic throughout the first two decades of life.[6]

The concomitant pancreato-biliary system, cardiac, and urinary bladder dysfunction (with or without megacystis and megaureter) have been reported in up to one-third of cases and need to be investigated accordingly.[6] Our case had sinus arrhythmia and megacystis with a hypocontractile detrusor (bladder adynamia). There is an increased risk of volvulus, gut dilatation, adhesions, or concurrent malrotation that requires urgent surgical interventions.

Depending on the predominant involvement of enteric neurons, smooth muscles, or interstitial cells of Cajal, CIPO is histopathologically classified as neuropathy, myopathy, or mesenchymopathy. The most common form of neuropathic myenteric ganglionitis is lymphocytic ganglionitis, where the myenteric plexus is infiltrated by CD4 and CD8 positive lymphocytes. In EMG, the functional gastrointestinal obstruction is associated with eosinophilic inflammation of the myenteric plexus. Myopathies are broadly classified as inflammatory or degenerative. Degenerative myopathy may be hereditary, sporadic, or typically reported in young African children who present as megacolon without aganglionosis (pseudo Hirschsprung's disease). Histopathology in these cases reveals vacuolization and fibrosis of smooth muscle fibers. These findings were absent in this case.[7] The absence of family history and a negative clinical exome raises the possibility that the degenerative leiomyopathy was sporadic in this case degenerative myopathy.

The treatment is challenging and requires multidisciplinary effort. EMG patients have been managed with dietary modification (amino acid-based formula), immunosuppression, anti-inflammatory medications, surgery, or an eclectic combination of all.[4] Immunosuppression may be beneficial when immune-mediated insult has not completely damaged the regulatory cells. The reason why our patient did not respond to dietary modification and immunosuppressive therapy may be due to the double pathology.

The prognosis of CIPO in children remains guarded, with 30% dying in childhood and the remaining being dependent on parenteral nutrition, with frequent hospitalization. Poor prognostic factors include neonatal-onset, myopathic type, urinary involvement, and requirement of surgery.[7] The patient had concomitant myopathic involvement, an underactive bladder, sinus arrhythmias, and three surgeries, all contributing to the poor outcome.

Lessons learnt

- Chronic intestinal pseudo-obstruction (CIPO) should be considered in children with symptoms of intestinal obstruction, but no clinical or investigative evidence of an anatomical occluding lesion
- CIPO may have associated bladder and/or cardiac involvement and should be investigated accordingly
- Full-thickness biopsies with microscopy immunohistochemical study should be undertaken to aid in early diagnosis.

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 understand that the name and initials will not be published, and due efforts have been made to conceal the same, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Unexplained Anasarca in Type 1 Diabetes Mellitus: Breaking the Hypoalbuminemia – Persistent Diarrhea Cycle

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Abstract

Background: Undiagnosed Type 1 diabetes mellitus (T1DM) often presents as diabetic ketoacidosis (DKA). We report a child with newly diagnosed T1DM who developed anasarca and persistent diarrhea following resolution of DKA and was referred to us for the same. **Clinical Description:** We reviewed the clinical history, examination, and investigations that had been undertaken. Our clinical evaluation was in concurrence with the referring hospital-anasarca with probable partially treated spontaneous bacterial peritonitis (SBP). However, the cause of the subacute anasarca and persistent diarrhea was unclear. The child was empirically started on broad-spectrum antibiotics for the SBP, a high-protein diet to build up the protein, and continued the same subcutaneous insulin, on which he was euglycemic. After ruling out usual causes, i.e., renal, hepatic, and cardiac, we reviewed the possibility of celiac disease, tuberculosis, insulin edema, and hypothyroidism. **Management:** When he did not improve despite a good appetite, adherence to management, and all tests were inconclusive, we reviewed the etiopathogenesis. Untreated T1DM had led to chronic negative catabolism that had precipitated severe hypoproteinemia. A vicious cycle had set in which hypoalbuminemia was leading to bowel wall edema, resulting in protein malabsorption, perpetuation of diarrhea, and further hypoproteinemia. Our assumption proved to be correct when a single dose of parenteral albumin broke the cycle, and the child improved drastically with the resolution of diarrhea within 24 h and the edema in a few days. **Conclusions:** This case highlights the implications of severe catabolism in a patient with untreated diabetes and how this may be a self-perpetuating condition.

Keywords: Anasarca, diarrhea, hypoproteinemia, malabsorption, type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a chronic disorder characterized by hyperglycemia that occurs due to autoimmune destruction of the beta islet cells of the pancreas. The characteristic symptoms are polyuria, polydipsia, polyphagia, and lethargy. In many cases of new-onset diabetes mellitus, these symptoms may not be noticed by the child, or the parents, and the child may present with diabetic ketoacidosis (DKA) at the time of diagnosis. Studies have described that the prevalence of DKA at first diagnosis of diabetes mellitus is as high as 59%.[1] Children with diabetes can have diarrhea due to infective causes or due to noninfective comorbidities such as celiac disease.

We hereby report this case of an adolescent boy who was referred to us in view of anasarca and persistent diarrhea following the resolution of DKA. We systematically investigated him for all the common causes of anasarca as well as diarrhea but could not find any cause. Finally, we reviewed the pathophysiology of anasarca and hypoproteinemia and speculated that a simple change in management might break a vicious cycle, that was otherwise not ending spontaneously. We report this case as we were unable to find similar cases on a literature search. We believe it may be under-reported due to nonrecognition of this phenomenon. Sharing our experience may help others in managing similar patients.

Clinical Description

A 15-year-old boy with newly diagnosed T1DM with DKA at presentation was referred to us with a history of generalized swelling of the body, diarrhea, and pain abdomen that had started insidiously, a few days after resolution of DKA. The child was apparently well 2 months back when the parents noticed that he was becoming very tired by the end of the day, even by routine activities that he was normally accustomed

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to doing. There had not been increase in strenuous activities, or extra academic work that was causing him to sleep less. There was no history of fever, chronic cough, breathing difficulties, progressive pallor, diarrhea, or decreased oral intake due to illness or dieting. The child did not report any stress or depressed mood. The mother had not been worried initially, as his appetite had become voracious (he was always hungry, despite eating 5–6 meals a day with larger servings). However, the parents grew concerned when he started losing weight over a month, manifesting as looseness of clothes. He was taken to a local practitioner who made a diagnosis of enteric fever and started him on azithromycin and ofloxacin empirically for 2 weeks, despite no clinical evidence and inadequate workup. The child continued to lose weight. It was noticed that he would awaken multiple times at night to urinate, but there was no fever, pain, or burning sensation while passing urine, or urgency. Following 1 and half months of this illness, he developed difficulty in breathing that progressively worsened over 3 days and for which he was hospitalized. Although the lethargy increased, there was no history of loss of consciousness or seizures. At admission, the child was diagnosed with DKA based on clinical manifestations, tachypnea, and the presence of severe metabolic acidosis, hyperglycemia, and ketonuria. Antibiotics (details unavailable) were initiated in view of suspected sepsis. The DKA resolved within 3 days, and he was started on subcutaneous insulin, as his blood sugar levels started optimizing.

The child started developing generalized swelling within a week of hospitalization. Periorbital puffiness appeared first, followed by abdominal distension and subsequently swelling of the lower limbs over 3 days. There was no history of fever, breathlessness, awakening at night due to cough or respiratory discomfort, jaundice, decreased urine output, or frothy urine. There was no history of the appearance of reddish rashes associated with excessive itchiness. The child was not receiving any intravenous (IV) fluids during this period. The abdominal distension was accompanied by the development of loose stools within a day. These were watery without blood or mucous, and occurred 8–10 times a day. There was no history of vomiting. The child also started to experience diffuse abdominal pain, mild in intensity, and not localizing to any particular site. There was no identifiable aggravating (food intake or on moving around) or relieving (vomiting, intake of food or antacids) factor. Since the child had been consuming food from the hospital kitchen and there were no other similar cases in the ward, the possibility of food poisoning due to consumption of contaminated food or drink, and osmotic diarrhea were excluded. The treating team considered the possibility of spontaneous bacterial peritonitis and ordered a paracentesis. He was initially started on ceftriaxone at admission, which was changed to ofloxacin and metronidazole. We reviewed the documents from the referring hospital and noted normal reports, except leukocytosis with a total leucocyte count (TLC) of 35,000/mm^3, and neutrophilia (77% neutrophils [N] and 10% lymphocytes [L]). Only the cytology reports of an ascitic fluid analysis were available, which revealed 640 cells/mm^3 with 20% N, 80% L. The child was referred to us to determine the cause of anasarca that had developed following the resolution of DKA when there was no overt clinical indicator or test report to suggest an underlying renal, cardiac, or hepatic cause.

At the presentation to our hospital, the child appeared sick and had obvious anasarca. His heart rate was 90 beats/minute (min), respiratory rate was 20 breaths per min, blood pressure 110/60 mmHg (all the vitals were normal for his age), and he was afebrile. His weight was 27.1 kg (Z score − 3.26), height 150 cm (Z score − 1.89), and body mass index 12 kg/m^2 (Z score − 3.15). There was no pallor, icterus, cyanosis, clubbing, or stigmata of chronic liver disease. On per abdominal examination, the abdomen was distended, and the overlying skin was normal. There was mild generalized tenderness and shifting dullness but no palpable organomegaly. There was no renal angle tenderness. On chest auscultation, air entry was decreased with dullness on percussion – suggestive of bilateral pleural effusion. The cardiovascular and neurologic examinations were within the normal limits. There was thus no clinical evidence of a hepatic, cardiac, or renal cause of edema.

Management and Outcome

Our clinical evaluation was in concurrence with the referring hospital. The clinical phenotype suggested anasarca with probable partially treated acute bacterial peritonitis, but the cause of anasarca was not clear. We decided to continue empirical treatment with broad-spectrum antibiotics while continuing the diagnostic work. There was no anemia (hemoglobin 14.7 g/dL). Although leukocytosis and neutrophilia persisted (TLC 20,100/mm^3 with 74% N), the C-reactive protein was 5.31 mg/L (normal <6 mg/L), and the blood culture was sterile. Kidney function tests were normal; blood urea nitrogen 37 mg/dl and serum creatinine 0.47 mg/dl. The liver function tests showed normal bilirubin levels (0.36 mg/dl) and enzymes (serum glutamic-oxaloacetic transaminase 47 U/L, and serum glutamate pyruvate transaminase 10 U/L), but there was hypoproteinemia (total serum protein 2.99 g/dL), hypoalbuminemia (1.49 g/dl), and globulin levels of 1.5 g/dl. Proteinuria was absent on urine dipstick evaluation. Ascitic fluid cytology showed 150 cells with 95% L, biochemistry was normal (ascitic fluid sugar 133 mg/dL and protein 1.66 g/dL), there were neither acid-fast bacilli on Ziehl–Nelson staining nor bacteria on gram staining, and the culture was sterile. Although unlikely, workup for dengue fever was negative. An abdominal ultrasound revealed normal liver, spleen, and kidneys but mild-free fluid in the abdomen and pelvis. Long segment, circumferential wall thickening involving the ascending, transverse, and descending colon was seen. There was no abnormal luminal dilatation. These findings were suggestive of colitis, the most likely etiology being infective or inflammatory. However, the stool routine examination was normal. Hence, preliminary investigations remained inconclusive.

Since the child was allowed per orally, a high-protein diet was started. His blood sugar levels remained within the normal limits on the subcutaneous split-mix insulin regime. Although his abdominal pain resolved, the anasarca and diarrhea did not improve. Repeat serum albumin values did not increase despite the high-protein intake (2 g/kg/day), and no source of protein loss except for diarrhea, which continued for the next 10 days in the hospital, despite the adequate antibiotic cover. Since, by definition, the child had persistent diarrhea, we decided to look for evidence of malabsorption and common causes of malabsorption by revisiting history, examination, and planning relevant investigations.

The stool was neither explosive nor associated with gaseous distention, nor was it greasy. Stool pH was normal and reducing substance negative. As celiac disease is known to occur with Type 1 DM, serum anti-tissue transglutaminase antibodies were checked for and found to be negative. Total serum immunoglobulin A was also normal. There was the absence of evidence of abdominal tuberculosis (TB) on the computerized tomography (CT) scan. However, the CT abdomen showed gross ascites, moderate bilateral pleural effusion, and edematous colonic loops with thickening of jejunal folds. Nonetheless, a pleural tap was performed to rule out TB. Microscopy showed 200 cells/mm^3 with 95% L; the pleural fluid sugar was 129 mg/dl and protein 1.74 g/dl; Ziehl–Neelsen staining and gram staining were negative; and culture was sterile. The thyroid function test was also normal, excluding hypothyroidism, though the edema was pitting. We also kept the possibility of insulin, edema a rare complication of insulin therapy.[2] Insulin edema can also occur within the 1st week of initiating insulin therapy. However, it has a female preponderance and may be associated with pulmonary edema. In our patient, the edema was not self-limiting, and there was no pulmonary edema. Moreover, our patient had persistent diarrhea and bowel edema, which are not described with insulin edema.

Finally, the possibility of a vicious cycle of hypoproteinemia, leading to bowel wall edema, and causing further protein malabsorption that was resulting in persistent diarrhea and refractory hypoproteinemia was considered. The only way to confirm this theory was to break the cycle by administration of parenteral albumin. The child was transfused IV 20 g of albumin. This led to a dramatic resolution of diarrhea and a decrease in anasarca within 24 h, and complete resolution over the next 2 days. He did not require any more doses of albumin. Oral protein ingestion was restarted, and the child has been under follow-up for his T1DM for the last 3 years. Though the blood sugar control is variable due to waxing and waning of compliance, a similar phenomenon has not recurred.

Discussion

The main action of insulin on protein metabolism in T1DM is to decrease the breakdown of protein.[3] Untreated T1DM is associated with severe catabolism with loss of both protein and energy due to the complete lack of insulin. Insulin deprivation in untreated diabetes leads to a net increase in protein breakdown, mostly in the skeletal muscles. The initial hypoalbuminemia resulting from the unrecognized T1DM led to anasarca and bowel wall edema, which perpetuated protein malabsorption, manifested as diarrhea, and resulted in a vicious cycle despite insulin and though a high amount of protein was being ingested [Figure 1]. The boy had a complete and speedy recovery once parenteral albumin was administered. Since albumin is a biological product with its own inherent safety concerns, there was no concrete indication in giving it for anasarca, especially since the child's appetite was good.

The effect of insulin on protein metabolism varies depending on the tissue or the type of protein. Fractional synthesis rates of albumin are decreased in T1DM due to insulin deficiency, while the fractional synthesis rates of fibrinogen are increased. In adults, the level of serum albumin is inversely associated with the risk of ketosis in hospitalized individuals with T2DM.[4] Hypoalbuminemia is associated with increased complications and reduced short-term and long-term survival in critically ill patients.[5] We could not find any similar data in children on a literature search.

In the context of DM, albumin synthesis is dependent on adequate insulin reserve. Studies have demonstrated an inverse relationship between serum albumin and hemoglobin A1c levels, the pathophysiology being insulin deficiency causing both hyperglycemia and decreased albumin due to different mechanisms.[6,7] In patients who have been recently started on insulin, insulin edema is also an important and under-reported cause of edema.[2] It is associated with transaminitis and occurs due to increased sodium and fluid retention after starting insulin. It is a self-limiting condition and has to be managed symptomatically, primarily by salt and fluid restriction.

To conclude, the management of this case reiterated that it is always worthwhile to go back to the basics. Once we understood the etiopathogenesis of the manifestations beyond

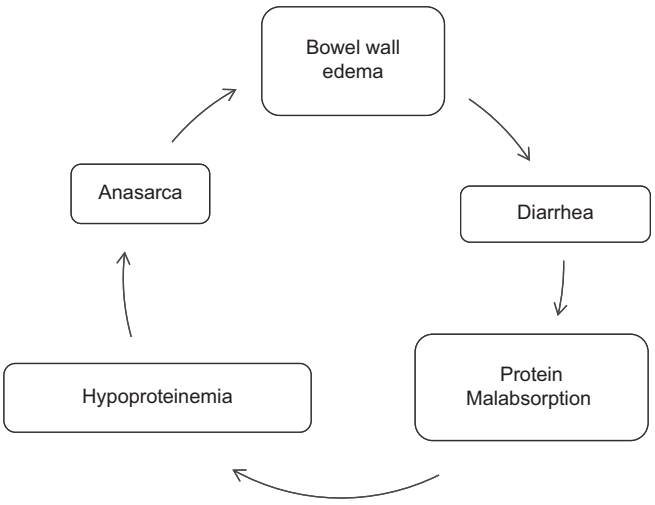

Figure 1: Vicious cycle of hypoproteinemia, diarrhea, and edema in the patient

the common pathophysiological causes, we were able to arrive at the appropriate reason for the anasarca and diarrhea and find an effective solution.

Lessons learnt

- Untreated T1DM is a state of severe catabolism
- Hypoalbuminemia leading to anasarca may occur following the resolution of DKA
- Hypoalbuminemia can lead to bowel wall edema, which will lead to diarrhea and further hypoalbuminemia. This can continue as a difficult to treat self-perpetuating cycle. A single dose of parenteral albumin can produce a dramatic improvement in the patient.

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

Congenital Dyserythropoietic Anemia Type IV with Kruppel-Like Factor 1 E325K Mutation in a Preterm Neonate: Case and Literature Review

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Abstract

Background: Clinical, pathologic, and genetic heterogeneity is a challenge in identifying and classifying congenital dyserythropoietic anemia (CDA). CDA type IV, the rarest CDA with only 11 reported cases, results from KLF1 gene mutation. **Clinical Description:** A male preterm neonate presented with jaundice, anemia, pulmonary hypertension and hepatosplenomegaly in the immediate postnatal period, requiring multiple red blood cell transfusions. **Management and Outcome:** The workup for non-immune haemolytic anemia including red blood cell structural and enzymatic studies and were normal, with peripheral blood smear showing multiple polychromatic cells and numerous nucleated red blood cells including binucleate ones and fetal haemoglobin of 91.2%. Genetic testing revealed KLF1 E325K mutation suggestive of CDA type IV, though parental testing was normal, suggesting de novo mutation. The infant has been receiving packed RBC transfusion every three to four weeks initially and then every two months. The baby is now of twelve months of age, and receives oral vitamin B12 and folic acid supplementation for ineffective erythropoiesis. Though his weight is in the 3rd centile for age and height, he has been developmentally normal. **Conclusions:** Our report, the first description of a CDA type IV diagnosis in the neonatal period, adds to the limited knowledge of this disorder, which we also comprehensively review. The report highlights the phenotype of the disorder and the importance of neonatal genetic testing in a case of transfusion dependent anemia, having ruled out other causes.

Keywords: Congenital dyserythropoietic anemia, congenital dyserythropoietic anemia type IV, Kruppel-like factor 1 mutation; neonate

Congenital dyserythropoietic anemia (CDA) is a heterogeneous group of anemia's characterized by the impaired differentiation and proliferation of the erythroid cell lineage, leading to monolinear cytopenia.[1] The hallmarks of ineffective erythropoiesis include morphologically abnormal erythroblasts (in the bone marrow) and circulating erythrocytes and evidence of hemolysis. However, this particular hematological profile can be seen in several other blood disorders such as hereditary hemolytic anemia, hereditary stomatocytosis, Diamond–Blackfan anemia, Fanconi anemia, other inherited bone marrow failure syndromes, hereditary spherocytosis, thalassemia, and even iron-deficiency anemia. Therefore, arriving at a diagnosis can be quite challenging and requires a rational approach.

CDA is classified into several categories based on clinical, pathologic, and genetic features: Types Ia, Ib, II, III, IV, V, VI, and other variants involving multiple genes such as CDAN1, c15orf41, SEC23B, KIF23, Kruppel-like factor 1 (KLF1), and GATA-1. Genetic confirmation is essential due to the many non-CDA hematological differentials listed earlier and the fact that considerable heterogeneity exists in the various types of CDA.

Type IV CDA is an autosomal disorder that results from mutations in the KLF1 gene, located on chromosome 19p13.2 which encodes for KLF1. This factor is a master regulator of terminal erythroid differentiation, affecting key cellular pathways and structures, such as division, iron metabolism, heme and globin synthesis, plasma membrane, and cytoskeleton. KLF1 directly activates beta-globin gene expression by binding to the gene's promoter, and indirectly silences gamma-globin gene expression by activating *BCL11A* that encodes a gamma-globin gene repressor, thus

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bringing about the switch from fetal to adult hemoglobin (Hb) expression.[2] As of December 2019, about 66 variants of the KLF1 gene had been reported and linked with a variety of phenotypes besides CDA Type IV, including embryonic lethality, hereditary persistence of fetal Hb, borderline HbA2, and inhibitor of the Lutheran blood group. An exhaustive literature search found only 11 patients reported in the PubMed database, out of which 9 had genetic confirmation.

We report a preterm neonate presenting with transfusion-dependent anemia who was diagnosed with this disorder. Not only does this add to our limited knowledge of CDA IV, but none have been diagnosed during the neonatal period till date. In addition, we provide a comprehensive review of the nine genetically confirmed cases.

Clinical Description

A baby boy was born at 35-week gestation by emergency cesarean section (indication being meconium-stained liquor, with fetal distress. The pregnancy of the 31-year-old primiparous mother had been uneventful until she had developed preeclampsia in the third trimester of pregnancy. There were no risk factors for sepsis before the birth**.** The baby weighed 2.8 kg, was nonvigorous at birth and required positive-pressure ventilation for 30 s. The Apgar score was 7 and 9 at 1, and 5 min, respectively. Following this, he developed respiratory distress and was shifted to the neonatal intensive care unit. He was supported with noninvasive ventilation (continuous positive pressure airway) and was hemodynamically stable. In view of the clinical setting, the diagnosis kept was meconium aspiration syndrome. Other supportive measures such as empirical antibiotics, intravenous fluids, and trophic feeds were started, and investigations were planned. The chest X-ray was nonspecific, and the sepsis markers were not suggestive of sepsis.

The baby was noted to have icterus at 7 h of life, with serum bilirubin of 12.2 mg/dL, and managed with intensive phototherapy. Relevant clinical history was probed into, examination performed, and investigations planned to determine the cause of the pathological jaundice. There was no history of consanguinity, unexplained abortions or infantile deaths, significant family history of jaundice within 24 h of birth, requiring double volume exchange transfusion, or severe anemia requiring multiple blood transfusions. Apart from the respiratory parameters, the vitals were stable, and there was no evidence of congestive heart failure. There was no pallor, ecchymosis, cephalhematoma, bulging fontanelle, or edema. There were no major or minor congenital anomalies. However, hepatosplenomegaly (liver and spleen 4 cm and 1 cm below the costal margin, respectively) and a hyperdynamic precordium were noted. The remaining systemic examination was normal.

There was no blood group incompatibility as both mother and baby were A positive. The total serum bilirubin was 12.2 mg/dL with 0.5 mg/dl direct component and without any liver enzyme elevation. The preliminary hemogram showed a Hb of 12.5 g/dL and 15% reticulocytes with normal total leukocyte and platelet counts. Investigations were planned to rule out hemolytic anemia**.** Abdominal ultrasonography confirmed hepatosplenomegaly with coarse hepatic echotexture. Functional echocardiography revealed pulmonary hypertension, with a pulmonary arterial pressure of 40 mmHg. The baby was on full enteral feeds by day 3 days of life. Till then, he had not displayed any features of hypoxic-ischemic encephalopathy; hence based on the clinical profile and available investigations, a clinical diagnosis of meconium aspiration syndrome with secondary pulmonary hypertension was kept. The cause of pathological jaundice, mild anemia, and hepatosplenomegaly was still uncertain, pending awaited reports.

Management and outcome

Osmotic fragility testing demonstrated poor osmotic resistance in the red blood cells (RBCs) in buffered normal saline. RBC enzyme studies (glucose-6-phosphate dehydrogenase and pyruvate kinase) were normal. Direct agglutination test (direct Coombs test) and indirect coombs test were negative. The report of the high-performance liquid chromatography (HPLC) that had been sent on the 2nd day of life showed 91.2% Hb F, 4.3% HbA_0, and undetectable HbA_2 [Figure 1c], which was considered normal for a newborn. A minor fraction of Hb was eluted in the S window, suggesting Hb variant mimicking sickle Hb, and eluting in the HbS window. The significance of this finding was uncertain. Thus, the peripheral smear picture, and normal RBC fragility, RBC enzyme, RBC membrane tests, and the hemoglobin HPLC ruled out immune hemolytic anemias, thalassemia, hereditary spherocytosis, stomatocytosis, and iron-deficiency anemia. Diamond–Blackfan and Fanconi anemia were excluded clinically based on the absence of typical dysmorphisms and absence of other typical features. Secondary dyserythropoiesis due to the perinatal hypoxia and its respiratory sequelae resulting from the meconium aspiration syndrome, though hypothetically plausible, did not explain the persistent anemia and falling Hb levels (that could not be attributed to blood sampling either).

Packed RBCs were transfused at 15 ml/kg on day 5 of life for increasing anemia (Hb having fallen to10.6 g/dL and other cell lines maintained) in the presence of requirement of respiratory support and 40% FiO_2 oxygen. The baby's respiratory distress gradually improved. Respiratory support was weaned off by day 9 of life and feeding transitioned to exclusive breastfeeding. Phototherapy continued as per the bilirubin levels [Figure 1a] and was stopped on day 10 of life. The baby was discharged on day 15 of life with a provisional diagnosis of nonimmune hemolytic anemia, under evaluation. On day 19 of life, the baby came for his first follow-up visit, though asymptomatic appeared pale, was found to have Hb of 7.3 g/dL (indicating ongoing hemolysis) and was given a blood transfusion.

In view of the nonimmune hemolytic picture without any identifiable RBC enzyme or membrane defect, genetic

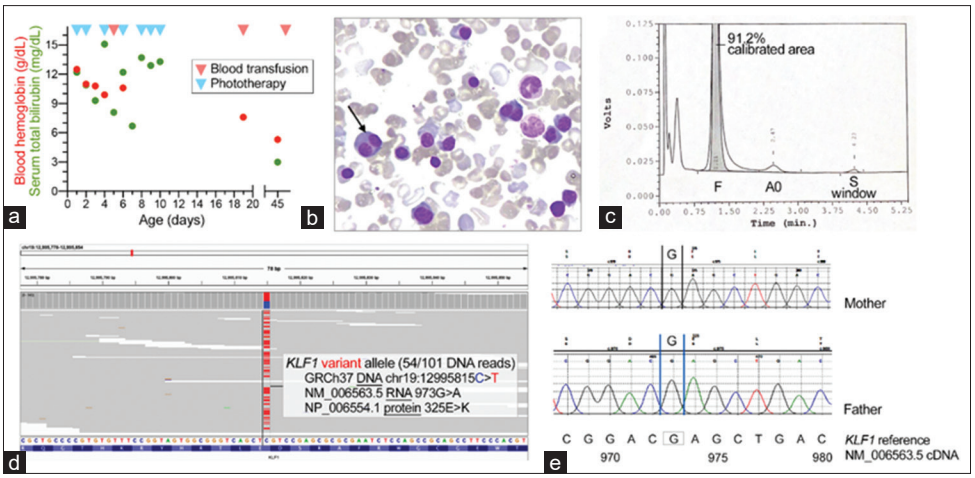

Figure 1: *Congenital dyserythropoietic anemia type IV in a preterm neonate.* (a) Blood Hb and total bilirubin measurements were obtained during the first 1.5 months of life. Days on which blood transfusion and phototherapy were received are indicated. (b) Microscopy of Leishman-stained peripheral blood smear showing multiple polychromatic cells and numerous nucleated red blood cells including binucleate ones (*arrow*). (c) Blood hemoglobin profile in high-performance liquid chromatography suggesting an HbF concentration of 92.1%. (d) Aligned blood genomic DNA sequencing reads at the chromosome 19 position where the *KLF1* E325K allele variant (C > T sequence change in the minus chromosome strand, in *red*) is detected in 53% of the reads. Shown is a screenshot of aligned read data in the Integrative Genomics Viewer software. Gray indicates no sequence change compared to the reference GRCh37 genome. Identifiers of GenBank reference RNA and protein sequences are noted. (e) Screenshots of Sanger DNA sequencing chromatograms of a *KLF1* amplicon in blood of the case's parents indicating absence of the E325K allele. Hb: Hemoglobin, *KLF1:* Kruppel-like factor 1

testing was planned. Targeted exon DNA sequencing of a 298-gene-panel (Orion Focus, Neuberg Diagnostics, Chennai, India) on Illumina platform and sequencing data analysis were performed as a commercial service by Neuberg Diagnostics. Of 64 million reads that were obtained, 95% aligned with the GRCh37/UCSC hg19 reference genome with high mapping quality. Sequencing coverage was 100% for 291 genes, including KLF1, and 90%–100% for 7 genes. Variant calling and filtering were as per the company's proprietary ORIONSeek algorithm that incorporates criteria defined by the American College of Medical Genetics. The sequencing revealed a single likely-pathogenic sequence variant. This G > A variant in the coding strand of KLF1 gene at chr19:12995815 (hg19 reference), had an allele frequency of 0.53 at a sequencing depth of 101 [Figure 1b and d], and is predicted to result in the substitution of glutamic acid with lysine at amino acid 325 (GenBank sequence NM_006563.4: C.973G>A; p. E325K). Sanger DNA sequencing of the parents' peripheral blood did not show this variant [Figure 1e], which suggested that the baby's heterozygous *KLF1* mutation was *de novo*. No sequence variation was seen in exons of the *HBA1*, *HBB*, or *HBD* Hb genes (that were also covered by the sequencing panel).

The infant has been on regular follow-up and receiving packed RBC transfusion and oral Vitamin B12 and folic acid supplementation as supportive management for ineffective erythropoiesis. The frequency of transfusion has reduced from the initial 4 weeks' interval to 2 months now. He is now 12 months old, with weight for age and length for age below the 3rd centile, age-appropriate acquisition of developmental milestones and mild splenomegaly. At present, the baby is not on iron chelators. It will be started after the tenth blood transfusion. Hematopoietic stem-cell transplant is being planned.

Discussion

Ineffective erythropoiesis is reduction in the production of mature erythrocytes originating from a pool of immature erythroblasts, whereas dyserythropoeisis refers to abnormal morphology and/or maturation of erythrocytes that is associated with ineffective erythropoiesis**.** The preliminary diagnosis of CDA is based on both: morphological indicators of ineffective erythropoiesis (nucleated erythroblasts in PBS) and dyserythropoiesis (the presence of multinucleated erythroblasts, atypical cytoplasmic inclusions, and intercellular bridges in bone marrow smear).[2] The PBS in our case showed multiple polychromatic cells and numerous nucleated RBCs with binucleate forms. We did not consider bone marrow aspiration (BMA) as the monocytopenia, early transfusion dependency, and clinical exclusion of differentials that may have warranted a BMA, which prompted us to consider CDA and plan the specific genetic testing early on.

Nine genetically proven CDA Type IV cases have been described in the literature.[1,3-10] The clinical details of these and the present case are in Table 1. We have not included two cases that were reported as CDA Type IV on the basis of bone marrow study without genetic confirmation.[11,12] The timing of clinical presentation is variable ranging from *in utero* (manifesting as hydrops in three cases), the neonatal period, and early childhood. The various manifestations and number of children in which they were seen include organomegaly,[6] anemia on 1st day of life,[5] jaundice,[3] pulmonary hypertension,[2] urogenital anomalies,[2] short stature,[2] and cardiomyopathy.[1]

Table 1: Profiles of reported cases of *KLF1* mutation-associated congenital dyserythropoietic anemia Type IV[b]

Year (*sex*)	Perinatal period	Clinical manifestations	Hematological profile	HbF (%)	KLF1 mutation[b]	Management
1991 (girl)[3]	Hydrops Term jaundice, anemia	Anemia, splenomegaly	PBS: NCNC anemia BM: Normoblastic erythroid hyperplasia, basophilic stippling in erythroblasts and RBCs	50	Het. c.973G>A/p.E325K	Regular BT in 1st year of life
2010 (boy)[4]	Hydrops fetalis, in utero BT PT 28 weeks	Jaundice, HSM Dysmorphic: Large AF, HCM micropenis, hypospadias, hypertelorism, short stature Diagnosed 8 years	PBS: Circulating erythroblasts, poikilocytosis, anisocytosis, orthochromatic erythroblasts BM: Marked hyperplasia of erythroid lineage	37.5	De novo het. c.973G>A/p.E325K	Transfusion dependent till 4 years then had splenectomy
2013 (boy)[5]	Jaundice anemia	HSM, hemolytic facies, short stature. Diagnosed at 8 years	PBS: Binucleate erythroid forms, anisocytosis poikilocytosis, schistocytes, polychromasia, nucleated RBCs BM: Erythroid hyperplasia, dyserythropoiesis	42	Het. c.973G>A/p.E325K	Transfusion-dependent, iron chelation therapy
2017 (girl)[6]	Normal	13 years anemia, HSM, polyarthralgia, weight loss. Diagnosed at 44 years	PBS: Poikilocytosis, anisocytosis, basophilic stippling, polychromia, macrocytosis erythroblasts BM: Binuclearity in orthochromatic erythroblasts, multinuclearity, <5% sideroblasts	12	Het. c.973G>A/p.E325K	Transfusion-dependent only when ill with infections Splenectomy at 36 years
2018 (boy)[7]	NR	Diagnosed at 7 years	PBS: NR BM: NR	NR	Het. c.973G>A/p.E325K	NR
2018 (girl)[8]	Hydrops fetalis, in-utero BT, PT 33 weeks	SM, dysmorphic: High receding forehead, mid-face dysplasia. Diagnosed at 10 years	PBS: Spherocytes, spiculated RBCs, nucleated RBCs, with some clover leaf nuclei BM: Orthochromatic with 3% binucleate forms, 3% cells with clover leaf nuclei	31	De novo het. c.973G>A/p.E325K	Transfusion-dependent Splenectomy at 4 years
2018 (girl)[9]	Anemia at birth, PPHT Term	Thalassemic facies, diagnosed at 6 years	PBS: Nucleated RBCs BM: Hypercellular with marked erythroid hyperplasia	40	Het. c.973G>A/p.E325K	Transfusion-dependent 4 years
2020 (boy)[1]	Anemia at birth	Hepatomegaly, anemia, jaundice. Diagnosed at 7 months	PBS: Hypochromia, polychromasia, macrocytes, ovalocytes, tear drop cells, stomatocytes, target cells, echinocytes, pencil cells, schistocytes BM: Erythroid hyperplasia, normoblasts with double nuclei, intercytoplasmic bridging between normoblasts	66.5	*Het. c.883delinsTT/p.H295Lfs* × 58 and *c.902G>T/p.R301L*	Tranfusion dependent
2020 (boy)[10]	IUGR anemia at birth, RD, cholestasis, sepsis	HSM, anemia, diagnosed at 7 months	PBS: Nucleated RBCs reticulocytosis BM: NR	16.8	De novo het. c.973G>A/p.E325K	Transfusion dependent
2022 our case (boy)	Anemia and jaundice at birth, PPHT, PT 35 weeks	Anemia and jaundice, HSM	PBS: Binucleated RBCs, anisocytosis poikilocytosis BM: NR	91.2	De novo het. c.973G>A/p.E325K	Transfusion dependent

[b]GenBank sequence NM_006563 as reference. AF: Anterior fontanelle, BM: Bone marrow, BT: Blood transfusion, GA: Gestational age, HbF: Fetal hemoglobin, HCM: hypertrophic cardiomyopathy, *het*.: Heterozygous, HSM: Hepatosplenomegaly, IUGR: Intrauterine growth retardation, NCNC: Normocytic normochromic, NR: Not reported, PBS: Peripheral blood smear, PPHT: Primary pulmonary hypertension, PT: Preterm, RBCs: Red blood cells, RD: Respiratory distress, SM: Splenomegaly

Complications of CDA IV are aplastic crisis, iron overload, hyperbilirubinemia, gallstones, and splenomegaly. This warrants frequent clinical and diagnostic monitoring.

Since transfusion dependency is apparent early in life, the management of CDA Type IV is mainly frequent blood transfusions and iron chelation therapy.[2] Two children and one adult underwent splenectomy at 4, 4, and 36 years of age, respectively. Although hematopoietic stem-cell transplantation, interferon-alpha, activin receptor ligand trap, and gene therapy have been tried in other CDAs with variable success, their

utility in Type IV remains unevaluated due to the condition's rarity.

Like in our case, all except one of the cases had the heterozygous NM006563: c.973G>A/p. E325K KLF1 mutation; the other two had heterozygous (c. 883delinsTT/p. H295 Lfs*58 and c. 902G>T/p. R301 L) mutations. The E325K variant is believed to arise *de novo,* and its inheritance has not been reported in any case, including ours [Table 1]. The E325 position is in the second zinc finger domain of KLF1 and is critical for its site-specific DNA binding. It is noteworthy that in the genetic code, only the c.973G>A type of single-nucleotide change can generate the E325K amino acid change and a change of the E325 acidic amino acid to another basic amino acid besides lysine (histidine and asparagine) is impossible with a single-nucleotide change.

Thus, genetic testing to identify such gene mutations is important to arrive at a diagnosis in transfusion-dependent anemia, once CDA is suspected. In our case, prompt genetic testing not only facilitated quick and accurate diagnosis but also let us avoid the highly invasive bone marrow biopsy procedure in a vulnerable neonate.

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

Myelin Oligodendrocyte Glycoprotein Encephalomyelitis: An unusual cause of blindness

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Abstract

Background: Myelin oligodendrocyte glycoprotein encephalomyelitis (MOG-EM) includes patients with (i) monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, or encephalitis; (ii) magnetic resonance imaging (MRI) or electrophysiological evidence of central nervous system (CNS) demyelination; and (iii) MOG-immunoglobulin G (IgG) seropositivity. **Clinical Description:** A 4-year-old girl presented with fever and excruciating headache for 10 days. Her vitals were stable and systemic examination was normal. Cerebrospinal fluid (CSF) analysis revealed 10 lymphocytes and normal biochemistry. After 5 days, she developed a fever and a seizure. Repeat CSF showed increased cells (60% lymphocytes), normal protein, and sugar. MRI brain was normal. She was managed symptomatically. CSF meningoencephalitis panel was negative. The child improved and was discharged. After 2 weeks, the headache recurred with associated blurring of vision. Bilateral papillitis, MRI brain abnormalities suggestive of acute disseminated encephalomyelitis (EM), and bilateral prolonged latency on visual evoked potential (VEP) were found. Anti-MOG antibodies were positive. The final diagnosis was MOG-EM. **Management:** The child was started on methylprednisolone therapy as per standard protocol. The vision improved and headache disappeared. She is on regular follow-up and is asymptomatic. **Conclusion:** MOG-IgG testing should be done in patients with (i) monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, or encephalitis; (ii) radiological or VEP findings compatible with CNS demyelination; and (iii) at least 1 of 25 delineated findings on MRI, fundoscopy, CSF, histopathology, clinical phenotype, or treatment response.

Keywords: Acute disseminated encephalomyelitis, myelin oligodendrocyte glycoprotein antibody disease, optic neuritis, seizures

Acute encephalitis syndrome (AES) is characterized by fever, with mental confusion, disorientation, delirium, or coma. Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating condition that predominantly affects the white matter of the brain and the spinal cord.[1,2] ADEM is a rare heterogenous autoimmune disease often triggered by a viral infection or rarely by vaccines. Due to variable manifestations, the diagnosis is often missed.

In this report, we describe a young child with AES who presented initially with features of meningeal involvement but later developed optic neuritis. Neuroimaging suggested ADEM. The presence of myelin oligodendrocyte glycoprotein (MOG) antibodies clinched the diagnosis of MOG encephalomyelitis (MOG-EM). Prompt detection is associated with better outcomes.

Case Report

A 4-year-old girl presented with fever and headache for 10 days. The fever was moderate grade, intermittent, resolving with medication. The headache was frontal, persisted throughout the day, and resulted in excessive crying. There was no history of lethargy, loss of consciousness, seizures, or behavioral manifestations. There was no history of cough, cold, sore throat, breathing difficulty, rashes, ear infection, watering of the eyes, vomiting, loose stools, or urinary complaints. The child did not receive any antibiotics. There was no significant past medical or family history. She was immunized and developing typically.

On admission, she was febrile, hemodynamically stable, and normotensive. The weight (18 kg), height (100 cm) and body mass index (17) were normal for age. There was no pallor, lymphadenopathy, or rashes. The throat and joints were normal. She was conscious (modified Glasgow Coma Scale score: 15/15), oriented to time, place, and person, but irritable. Higher mental functions (attention, memory and speech) were age appropriate. Both pupils were equal in size and reactive. The

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fundus was normal. There were no cranial or focal neurological deficits. The motor and sensory examinations were normal. There were no signs of meningeal involvement, increased intracranial pressure, or ataxia. Hepatosplenomegaly was absent. The remaining systemic examination was normal. The differential diagnoses considered in view of the subacute fever, severe headache, irritability, and absence of localizing features were an acute central nervous system (CNS) infection, viral fever, or viral hemorrhagic fever. Malaria and enteric fever were considered less likely due to the absence of organomegaly.

Management and Outcome

Initial investigations revealed hemoglobin of 8.4 gm/dl; normal total leukocyte count of 8040 cells/mm^3, with a differential count of 51% neutrophils, 43% lymphocytes, 2% eosinophils, and 4% monocytes; and platelet count of 3.2 lakhs/mm^3. The C-reactive protein was normal (0.1 mg/dl). Cerebrospinal fluid (CSF) analysis showed 12 cells with 100% lymphocytes and normal protein and sugar levels. Samples were sent for CSF viral studies, and the child was started on antibiotics, acyclovir, and symptomatic management.

There was slight improvement between the 2nd and 4th days of admission, with decrease in fever and reduction in headache. The CSF meningoencephalitis panel was negative. On the 5th day of admission, she developed fever with chills, increasing drowsiness, and right focal seizures. The GCS was 12/15 (E3V4M5). There was no other change in the examination. She was euglycemic, normocalcemic, and had no dyselectrolytemia. She was started on antiepileptic drugs. Cerebral malaria was suspected and antimalarials started. However, the tests for malaria were negative. Magnetic resonance imaging (MRI) of the brain was normal. A repeat CSF examination showed an increase in cells (63 total, 60% lymphocytes and 40% neutrophils), normal sugar (40 mg/dl), but mildly increased proteins (52 mg/dl). The electroencephalogram was normal. The child improved clinically. Fever abated by day 3 and there was no recurrence of seizures. She was discharged after 7 days without any neurological sequelae and a clinical diagnosis of viral meningoencephalitis.

After 3 weeks, the child returned with complaints of blurring of vision and headache. There was no pain upon eye movement, or nystagmus. There was no history of fever, seizures, or altered sensorium. A repeat MRI (brain) revealed widespread diffuse asymmetrical diffuse hyperintensities in the T2 images involving the brainstem, basal ganglia, and peduncles, suggestive of ADEM [Figure 1]. Salient ophthalmological findings were normal visual acuity and fundus, bilateral papillitis, and bilateral prolonged latency on visual evoked potential (VEP), as depicted in Figure 2. Since ADEM is one of the most common presentations of MOG antibody disease (MOGAD), accounting for almost 50% of pediatric MOGAD patients, CSF and serum samples were sent for anti-neuromyelitis optica (NMO) and anti-MOG antibodies, and a trial of steroids started. The child was given pulse methylprednisolone (25 mg/kg/day) for 5 days, continued for 4 weeks, tapered, and stopped. The report that anti-MOG antibodies were positive became available midcourse. By this time, the child's headache had disappeared (end of the 1st week) and vision had improved (by the 2nd week). Currently, after 3 months, the child is stable and asymptomatic. The final diagnosis is MOG-EM (as per latest nomenclature).[3]

Discussion

ADEM is usually a diagnostic challenge for a clinician due to its multifocal presentation that includes multiple neurological deficits and encephalopathy. The manifestations include fever (67%), lethargy (60%), vomiting (57%), weakness (50%), ataxia (50%), and headache (17%).[1,2] Kotlus *et al*.,[4] reported 6 of 10 pediatric ADEM patients with optic neuritis. Half of them had bilateral involvement. Other ocular manifestations described were decreased visual acuity, pain upon eye movement, nystagmus, and peripapillary hemorrhages.[5] Other neurologic features were ataxia, hemiparesis, hypoesthesia, and dysarthria. ADEM presenting as isolated optic neuritis is uncommon.

MOG is a glycoprotein of the myelin sheath that plays an important role in the adhesion of myelin fibers and the regulation of oligodendrocyte stability. Their epitopes are highly immunogenic, and modulate the immune system. Anti-MOG antibodies have been reported in 40%–68% of children with ADEM.[6] The current gold standard for the identification of immunoglobulin G (IgG) antibodies to MOG is cell-based assay utilizing fluorescence-activated cell sorting or indirect fluorescence test. Full-length human MOG should be used as target antigen and Fc-specific or IgG1-specific secondary antibodies to avoid cross-reactivity with IgM and IgA antibodies.[3]

MOGAD was the term that was previously used for the autoimmune inflammatory demyelinating disorder that presented with optic neuritis, myelitis, and encephalitis.[7] According to recent recommendations, the term MOG-EM

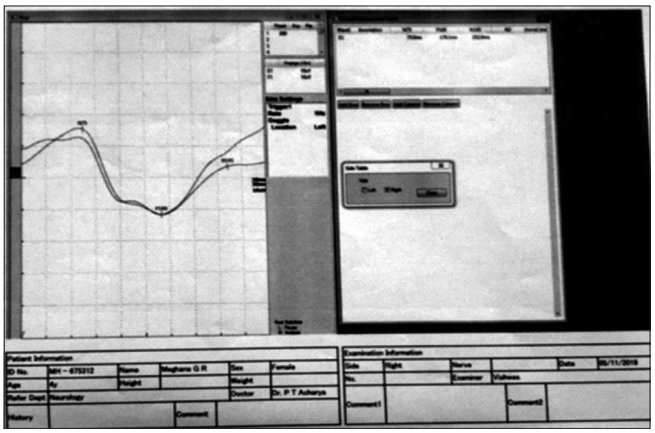

Figure 1: VEP report with bilateral prolonged latencies. VEP: Visual evoked potential

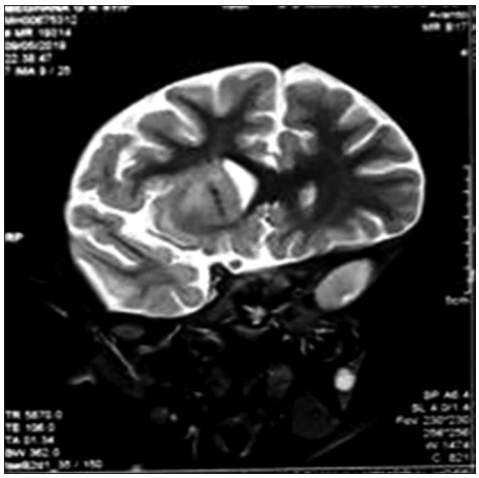

Figure 2: MRI (brain) T2 image showing widespread diffuse asymmetrical hyperintensities in the brainstem, basal ganglia, and peduncles suggestive of ADEM. ADEM: Acute disseminated encephalomyelitis, MRI: Magnetic resonance imaging

should be used in patients who meet all of the following criteria:[3] (i) monophasic or relapsing acute Optic Neuritis (ON), myelitis, brainstem encephalitis, or encephalitis, or any combination of these syndromes; (ii) MRI or electrophysiological (VEP in patients with isolated ON) findings compatible with CNS demyelination; and (iii) seropositivity for MOG-IgG as detected by means of a cell-based assay employing full-length human MOG as target antigen

The indications for MOG-IgG testing in adult and adolescent patients[3] presenting with an acute CNS demyelination disorder of autoimmune etiology are as follows: (i) monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, encephalitis, or any combination thereof; (ii) radiological or, only in patients with a history of optic neuritis, electrophysiological (VEP) findings compatible with CNS demyelination; and (iii) at least one of the 25 delineated findings on MRI, fundoscopy, CSF, histopathology, clinical phenotype, and treatment response. In young children with acquired demyelinating disease, the indications for MOG-IgG testing are not as rigorous, since MOG-EM is significantly more frequent in this age group.

Once a diagnosis of MOG-EM is suspected, early treatment with steroids should be started. Intravenous immunoglobulin (IVIG) can be used if steroid-unresponsive, at a total dose of 2 g/kg for 2–5 days.[8] Upcoming trials show that early initiation of IVIG might be beneficial.[9]

ADEM with persistent MOG antibody is at risk of developing any of the three demyelinating conditions: multiphasic ADEM, NMO spectrum disorder with longitudinally extensive transverse myelitis, or recurrent optic neuritis. Therefore, regular follow-up is essential to monitor these children.

Lessons Learnt

- ADEM should be considered a cause of acute encephalitis syndrome when polyfocal neurological deficits and encephalopathy are present
- Anti-MOG antibodies have been reported in 40%–68% of children with ADEM
- MOG-EM includes patients with (i) monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, or encephalitis; (ii) MRI or electrophysiological evidence of CNS demyelination; and (iii) MOG-IgG seropositivity.

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 images and other clinical information to be reported in the journal. The parents understand that name and initials of the patient will not be published and due efforts will be made to conceal the patient's 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

Partial DiGeorge Syndrome with Hypertrophied Arytenoids in a Neonate: Expanding the Clinical Phenotype

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Abstract

Background: DiGeorge Syndrome (DGS) is caused by the 22q11 deletion. There is wide variation in the phenotypic presentation due to incomplete penetrance. Since dysmorphism is subtle in neonates, a high index of suspicion should be kept. **Clinical Description:** A 2.8 kg term baby girl born of a cesarean section developed stridor and respiratory distress and was referred to our hospital at 14 days for the persistence of symptoms. The manifestations were severe, requiring respiratory support, and not explainable by clinical findings, radiological atelectasis, and normal echocardiography. The baby had hypocalcemia (that had been noted and treated earlier), hypoparathyroidism and Vitamin D deficiency, for which standard therapy was started. Airway endoscopy revealed hypertrophied arytenoids which have not been reported in DGS before. **Management:** The presence of abnormal laryngeal with hypocalcemia prompted us to consider DGS. The likelihood became stronger when a chest ultrasonogram detected athymia. The identification of 22q microdeletion by fluorescence *in situ* hybridization confirmed the diagnosis. It was decided to perform supraglottoplasty to avoid the postoperative complications associated with direct vocal cord repair. The postoperative period was uneventful. The immunological profile was normal, besides a low count of normal CD4+ naïve cells. The final diagnosis was partial DGS. **Conclusion:** Genetic testing for 22q11 deletion should be done in the presence of laryngeal pathology and any of the following: congenital cardiopathy, velopharyngeal insufficiency, thymic hypoplasia, and neonatal hypocalcemia.

Keywords: Di George syndrome, hypocalcemia, hypoparathyroidism, stridor, supraglottoplasty

DiGeorge Syndrome (DGS) due to 22q11 deletion is the most common microdeletion syndrome with a global incidence of 1/4000–6000 live births, and affecting 0.1% fetuses.[1] The classical features of DGS popularized by the mnemonic CATCH 22, (cardiac abnormalities, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia), also include renal anomalies, parathyroid hypoplasia, velopharyngeal insufficiency, learning difficulties, behavioral abnormalities, and schizophrenia. In most cases, the underlying defect is a heterogeneous deletion of a 3 million base pair on the long arm at the 11.2 locus[2] that affects 30–50 genes. While an autosomal dominant inheritance is known in DGS, this is seen in only 10%. The majority of cases (90%) occur due to *de novo* mutations as the structure of the 22q11 region is prone to rearrangements.[3] Craniofacial and laryngeal malformations, in addition to anomalies of the heart, thymus, and parathyroid glands, are the result of dysregulation of the migration of neural crest cells, and differentiation of the branchial arches.[4] There is marked variability in clinical manifestations due to incomplete penetrance. The term complete DGS is used to describe those patients who are athymic and have no circulating T-cells (<1%), and partial DGS for those with thymic hypoplasia and the presence of circulating T-cells.[5] Milder variants are often missed since the facial dysmorphism is subtle in neonates and infants. Affected individuals are often only identified in the pediatric age group when they are evaluated for language delay or behavioral issues; and rarely later due to adult-onset diseases.

An early diagnosis of DGS, therefore, requires a high index of suspicion by the clinician. We report a baby referred to us for persistent stridor and the need for ventilatory support since birth, in whom a diagnosis of DGS was finally established. While multiple types of laryngeal abnormalities have been reported in literature, to our knowledge, this is the first case of DGS with hypertrophied arytenoids that required surgery.

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Clinical Description

A baby girl was born to a 26-year-old primigravida at term gestation. The antenatal course had been unremarkable, except for a maternal COVID infection in the 2nd trimester, which resolved without hospitalization. The baby was born via cesarean section in view of a transverse lie. The birth weight was 2.8 kg. Although the baby cried immediately at birth and did not require any resuscitation, she was noted to have a weak cry with stridor. In view of persistent stridor, recurrent apnea, and cyanosis during crying, the baby was referred to another center on day 2 of life. Her medical documents revealed that she was treated for hypocalcemia (level unknown), right-sided pneumonia (based on chest radiograph), and probable sepsis (details not available). During 12 days of hospitalization, she received antibiotics (nature unknown), calcium supplementation, oxygen administration by nasal prongs, and nasogastric feeds (as described by parents). The parents left against medical advice, and brought the baby to us on day 14 of life.

At admission, the baby had cold stress, a heart rate of 155/min (min), respiratory rate 58/min, respiratory distress with suprasternal and intercostal retractions (Downe score 3/10), and saturation of 90% on room air. The baby had still not regained her birth weight (11% weight loss on day 14 of life). There was no pallor, cyanosis, gross congenital deformity, or obvious facial dysmorphism. Chest auscultation revealed reduced air entry on left side with normal cardiovascular exam. The rest of the systemic examination was normal.

The baby was placed under a radiant warmer. Bedside investigations revealed euglycemia and compensated respiratory acidosis on arterial blood gas analysis (pH 7.37, PO2 34 mm Hg, PCO2 65 mm Hg, and HCO3 37 mmol/L). Respiratory support was provided by heated humidified high-flow nasal cannula with a flow of 5 l/min, and 35% FiO_2. A provisional diagnosis of persistent pneumonia and laryngomalacia was kept.

Management and Outcome

The chest radiograph, showed right-sided segmental atelectasis in the left lobe [Figure 2]. The thymic shadow was appreciated. Though the initial hemogram showed leukocytosis and neutrophilia (total leukocyte count 22,700/mm^3 with 68% neutrophils and 30% lymphocytes, and platelet count 4.35 lakh/mm^3), the sepsis workup (C-reactive protein <5 g/dL), and blood culture (sterile) excluded active infection. The nasopharyngeal swab for the respiratory syncytial virus was negative. Salient abnormalities included hypocalcemia (ionized Ca^{2+} 0.89 mmol/L, total 8.3 mg/dl), hyperphosphatemia (9.2 mg/dl), parathyroid hormone (PTH) levels of 25 pg/ml – that though within the normal range, was relatively low considering the level of hyperphosphatemia), and Vitamin D insufficiency (13 ng/ml). We suspected transient hypoparathyroidism and started the baby on calcitriol, a phosphate binder oral calcium acetate, and oral calcium supplementation after administering intravenous calcium gluconate (presuming the stridor to be symptomatic hypocalcemia).

In view of persisting respiratory distress and stridor, two-dimensional echocardiography and airway endoscopy were planned. The former revealed a structurally normal heart. The airway endoscopy showed large bulky arytenoids, very short aryepiglottic (AE) folds, bulky ventricular folds, and mobile vocal cords [Figure 1]. There was inspiratory collapse of supraglottic structures, with redundant tissue around the AE folds. A clinical suspicion of DGS was kept in view of the recurrent hypocalcemia, hypoparathyroidism, and unusual laryngeal findings. Since the thymus had been reported on the radiograph, a chest ultrasonogram was done to confirm its presence. As it was not visualized, it was deemed as absent. Confirmatory genetic evaluation of DGS was done by Fluorescence *in situ* hybridization testing, which revealed a 22q microdeletion. Immunological workup comprising B- and T-cell markers (memory and naïve T-cells) revealed no abnormality, aside from a low count of normal CD4+ naïve cells. A final diagnosis of partial DGS was made, and the parents underwent genetic counseling. No other anomalies or organ dysfunction associated with DGS were found.

The ear, nose and throat (ENT) surgical team performed a supraglottoplasty, in which the AE fold was released, and coblator ablation of the redundant tissues was performed. The respiratory distress resolved, and she became oxygen independent by the 14th and 17th postoperative days, respectively. The baby was discharged on the 21st postoperative day, on prophylactic antibiotics and management of hypoparathyroidism, as per standard protocol. Currently, the infant is being followed up by a multidisciplinary team (pediatrics, endocrinology, ENT, genetics and hematology departments). Further immunological workup is planned at 3 months, to decide whether injectable human recombinant PTH will be required or not.

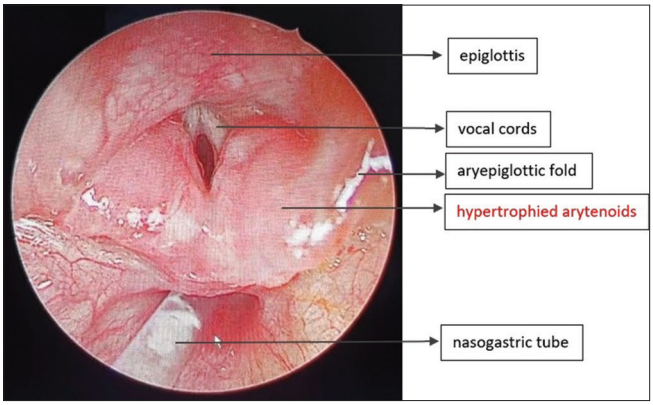

Figure 1: Airway endoscopy revealing large hypertrophied arytenoids, very short aryepiglottic folds and bulky ventricular folds

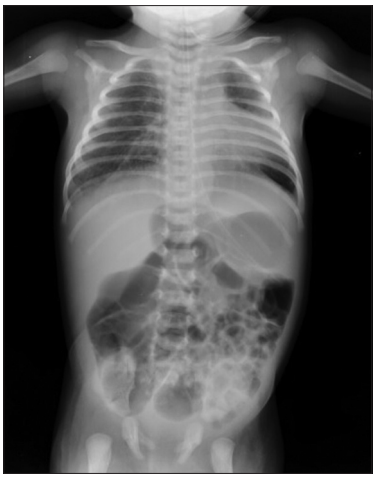

Figure 2: X-ray chest of the neonate at admission showing atelectasis of the left mid zone

Discussion

DGS is usually suspected in a newborn with cardiac defects, refractory hypocalcemic convulsions associated with low levels of PTH, or rarely due to clinical manifestations of severe immunodeficiency.[2] Laryngeal abnormalities are observed in 14% to 18%.[6,7] The spectrum includes subglottic stenosis, glottic webs, vocal cord paralysis, laryngomalacia, vocal nodules, and bronchial malposition. This neonate had laryngomalacia with bulky arytenoids. Hypertrophied arytenoids have been documented in Richieri-Costa Pereira Syndrome.[8] To the best of our knowledge, this is the only case of DGS in which the hypertrophied arytenoids compromised the laryngeal inlet to such an extent that surgical intervention was required. The surgical team decided to take the cautious approach of supraglottoplasty, rather than direct arytenoid intervention. Iatrogenic laryngeal complications such as paralysis of the left vocal fold, posterior vocal fold erosion, and dislocated arytenoid, although rare (<5%), have been observed after multiple surgeries and airway evaluations. A recent study observed swallowing difficulties and nasal regurgitation in nearly 50%, even in the absence of palatal defects.[9] While partial DGS may not have absent T-cells (as in our case), patients are still predisposed to infections, with over 60% of them experiencing recurrent infections such as sinusitis and otitis media.[10]

It has been recommended to test for the 22q11 deletion in children with any laryngeal pathology associated with at least one of the following anomalies: congenital cardiopathy, velopharyngeal insufficiency, thymic hypoplasia, and neonatal hypocalcemia.[6] Our observation of hypertrophied arytenoids, a new laryngeal pathology not previously described, further reaffirms the above recommendation.

Lessons learnt

- DGS is one of several syndromes clubbed under the 22q microdeletion syndrome
- The diagnosis of DGS requires high index of suspicion in the neonatal period
- A neonate with any laryngeal pathology should be worked up for 22q microdeletion in the presence of at least one of the following anomalies: congenital cardiopathy, velopharyngeal insufficiency, thymic hypoplasia, and neonatal hypocalcemia.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Factor XIII Deficiency in a Mother-Baby Dyad

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Abstract

Background: Factor XIII deficiency is a rare autosomal recessive coagulation disorder with varied presentations including prolonged bleeding from the umbilical cord stump, defective wound healing, recurrent miscarriages, or life-threatening intracranial hemorrhage. **Clinical Description:** A male baby was born at term gestation to a fourth gravida mother with a history of two abortions in the past. He was born out of a third-degree consanguineous marriage, with smooth perinatal transition, but developed multiple episodes of seizures associated with poor feeding and lethargy after 24 h of life. **Management:** On evaluation, septic screen, metabolic screen (serum electrolytes, calcium, and blood sugar), and coagulation assays were normal. Ultrasonogram revealed a hyperechoic lesion restricted to the left cerebral hemisphere, suggestive of an intraparenchymal hemorrhage. Magnetic resonance imaging brain showed left intraparenchymal hemorrhage with significant mass effect and midline shift. In view of intracranial bleed with normal coagulation assay and other causes being ruled out, factor XIII clot solubility assay was sent and found to have undetectable levels. Factor XIII levels of the mother were also found low (5.5%) though the levels in the father were normal. The baby was managed conservatively with supportive measures in the form of anticonvulsant and anti-edema measures. He recovered successfully and is under close follow-up. **Conclusion:** A high index of suspicion of factor XIII deficiency should be kept in any neonate presenting with intraparenchymal hemorrhage and recurrent abortions in the mother. This case is being reported to highlight factor XIII deficiency in recurrent pregnancy loss and neonatal intracranial bleeding. Prenatal screening for factor XIII deficiency in these circumstances will help in effective management of future pregnancies.

Keywords: Factor XIII deficiency, intracranial bleeding, neonate, recurrent pregnancy loss

Bleeding in a newborn can be caused by many heterogeneous causes and requires a systematic approach to arrive at a diagnosis. Plenty of clues can be discerned from the history and examination which gives direction to the investigative plan. For example, if the bleeding baby is sick, the common differentials include sepsis, necrotizing enterocolitis, disseminated intravascular coagulation, or liver disease, whereas in a well neonate with bleeding, diagnoses such as immune-mediated thrombocytopenia, Vitamin K deficiency, qualitative platelet defects, or deficiencies of various clotting factor should be considered. Similarly, neonates presenting with petechiae or small mucosal bleeds are usually due to platelet disorders, while the more voluminous spontaneous umbilical stump, intracranial, or gastrointestinal hemorrhage is more commonly associated with disorders of coagulation. The common coagulation disorders in a neonate include Hemophilia A and B and von Willebrand disease and rarely severe deficiencies of fibrinogen and factors VII, X, and XIII.

Factor XIII deficiency is a coagulopathy that has an autosomal recessive inheritance and thus more commonly observed in populations with a high rate of consanguineous marriages.[1] The prevalence is estimated to be one in 2–5 million live births. Factor XIII deficiency often gets missed in a bleeding neonate until a detailed history and complete clinical evaluation is done.

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The clinical presentation is varied, and besides manifestations that range from prolonged bleeding from the umbilical cord stump to life-threatening intracranial hemorrhage, it can also cause defective wound healing and recurrent miscarriages. The prevalence of intracranial bleed is around 30%, which is much higher than that reported in other coagulation disorders.[2]

We report a mother–baby dyad with factor XIII deficiency who presented with recurrent miscarriages in the undiagnosed mother and intracranial hemorrhage in the 2-day-old baby.

Clinical Description

A baby boy was brought to the emergency department on day 2 of life with seizures, refusal to feed, and poor activity that had started after 24 h of life. The baby had passed urine and

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stools after birth. The first manifestation was a multifocal tonic-clonic seizure lasting for 2 min that occurred within 24 h of life. Subsequently, the baby had three more seizures over the next 4 h, before we received him in our emergency. There was no history of progressive pallor, jaundice, bleeding from any site, appearance of bluish patches, or rashes.

He was born of a third-degree consanguineous marriage to a fourth gravida mother with an uneventful antenatal period. Quickening had been perceived at 20 weeks of gestation. There was no history of any maternal drug intake during pregnancy, apart from the routine iron and calcium supplementation. The baby was delivered via spontaneous vaginal delivery at term gestation. There was no history of any febrile illness, leaking per vaginum, or repeated vaginal examinations before delivery. The birth weight was 2.6 kg, and the APGAR scores were normal. The baby had received intramuscular Vitamin K (1 mg) after birth. He was discharged after 18 h of life, once breastfeeding had been established. There was no family history of recurrent bleeding or poor wound healing in the mother, the elder 12-year-old sibling, or any other family member. The second and third pregnancies had ended as abortions at 12 and 6 weeks of gestation, respectively.

At admission, the baby was lethargic, normothermic, with a heart rate of 160 beats per minute, respiratory rate of 56 breaths per minute, no retractions, SpO_2 of 90% in room air that increased to 97% with oxygen, and normal capillary filling time. His weight was 2.4 kg, length 47 cm, and head circumference 32.5 cm, all of which were between 0 and − 2 standard deviation for age. General physical examination revealed a normal-sized, nonbulging anterior fontanelle. The sutures and posterior fontanelle were normal. The spine was normal, and there were no gross congenital anomalies. There was no cyanosis, pallor, jaundice, bruises, petechiae, or purpura. The cry was weak, and the spontaneous limb movements were decreased but symmetrical. The tone in all four limbs was reduced. Both pupils were equal in size but sluggishly reacting to light. There was no cranial nerve involvement. The examination of the cardiovascular and respiratory systems was normal, and no organomegaly was appreciated. Based on the clinical phenotype of a sick baby with seizures and nonrespiratory hypoxemia, the differential diagnoses considered included hypoglycemia, dyselectrolytemia, neonatal sepsis with meningitis, congenital anomalies involving the central nervous system (CNS) with compromised respiratory drive, and inborn errors of metabolism (IEM) with CNS and possibly cardiac involvement. Investigations were planned accordingly.

Management and Outcome

The baby was immediately started on maintenance intravenous (IV) fluids and oxygen by prongs (at 2 l/min). The blood sugar at admission was 112 mg/dl. He was shifted to the neonatal intensive care unit (NICU) where he was started on anticonvulsant drugs (phenobarbitone) and IV antibiotics (cefotaxime 150 mg/kg/day and amikacin 15 mg/kg/day). The results of the hemogram, electrolytes, sepsis screen, and coagulation profile were within normal limits [Table 1]. The neurosonogram detected a hyperechoic lesion restricted to the left cerebral hemisphere, suggestive of considerable intraparenchymal hemorrhage. Therefore, we deferred getting a metabolic screen for IEM and instead planned a magnetic resonance imaging (MRI) brain. This revealed left intraparenchymal hemorrhage with significant mass effect and midline shift in the left temporal lobe and subfalcine, tentorial, and uncal herniation [Figure 1]. The baby was started on anti-edema measures (3% saline). A neurosurgery opinion was sought, and we were advised to continue conservative management. Since the baby had intraparenchymal bleed in the setting of normal coagulation profile and normal platelets, the possibility of factor XIII deficiency was considered and the specific semiquantitative clot solubility assay was performed.

There were no further episodes of seizures, the baby did not require oxygen to maintain saturation, and the sensorium had

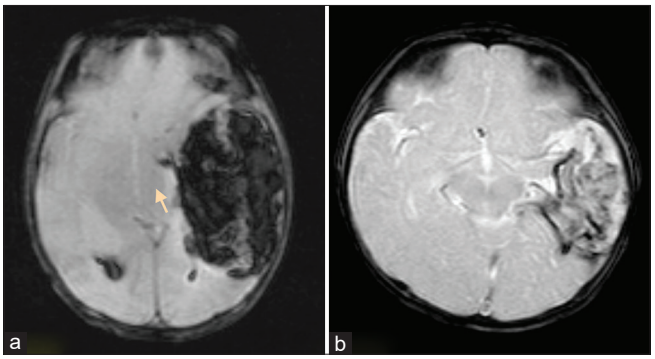

Figure 1: Magnetic resonance imaging of the brain (a) on day 2 of life: Heterogeneous area in the left temporal region (white arrow) suggestive of an intraparenchymal hemorrhage, causing significant mass effect, obliteration of adjacent left lateral ventricle, and midline shift toward right. (b) At 5 months of age: Complete resolution of the previously noted hemorrhages. Significant gliotic changes and encephalomalacia are seen in the left temporal lobe and part of the left parietal lobe leading to significant volume loss

Table 1: Performed laboratory parameters along with their results

Parameter	Result
Hemoglobin	15.8 g/dL
Total leukocyte count	11,600 cells/cu.mm
Differential leukocyte count	48% neutrophils and 43% lymphocytes
Packed cell volume	47.2%
Platelet count	262,000/cu.mm
Peripheral smear	Normal, with no evidence of hemolysis or sepsis
C-reactive protein	Negative
Blood culture	Sterile
Random blood glucose	89 mg/dL
Serum calcium	8.3 mg/dL
Serum sodium	146 mEq/L
Prothrombin time (test/control)	15.1/13.5 s
Activated partial thromboplastin test (test/control)	34.6/32 s
International normalized ratio	1.12

started to improve 3 days after admission. Nasogastric feeding was initiated and slowly increased, until the baby was able to exclusively breastfeed by the 8th day of life. The umbilical stump fell off by the end of the first week, and there was no prolonged bleeding from the site. The baby was discharged on oral phenobarbitone from NICU on day 13 of life with a diagnosis of left intracranial hemorrhage with probable factor XIII deficiency. At discharge, the child was breastfeeding and cry, activity, and tone had improved. The anterior fontanelle and head circumference (33 cm) were normal. Danger signs were explained to the parents, and he was advised regular follow-up in our high-risk newborn clinic.

The report of the factor XIII assay became available by his first follow-up visit and was found to be undetectable, confirming the diagnosis. Taking into consideration the autosomal recessive inheritance of factor XIII deficiency, parental consanguinity, and significant history of recurrent abortions, factor XIII levels were sent for both parents as well. The mother's reports revealed very low levels of factor XIII (<5.5%), whereas the father's levels were normal. Molecular testing was advised but deferred for later due to financial constraints. Thus, the final diagnosis was factor XIII deficiency with left intracranial hemorrhage. The parents were counseled about the nature of the disease, precautions to be taken prior to any possible piercing, surgical intervention, or dental extraction, the need for regular follow-up, the screening of the elder sibling, and the option of prenatal diagnosis if the planned another pregnancy.

The last visit was when the infant was 5 months old. He was asymptomatic with no recurrence of seizures on anticonvulsant drugs, no history of bruising or bleeding from any site, and absence of any focal neurological deficits. His developmental milestones were appropriate for age, and the head circumference growth curve plotted was following the normal trajectory. A follow-up MRI brain was done, which showed near-complete resolution of the hemorrhages. However, there was significant encephalomalacia involving the left temporal lobe and part of the left parietal lobe.

Discussion

Factor XIII is a tetramer belonging to the transglutaminase family. It is made up of two catalytic A subunits and two regulatory B subunits. Once activated, the A subunit cross-links alpha- and gamma-fibrin chains, thus increasing clot strength and fibrinolytic resistance and also playing a crucial role in the coagulation cascade. Since factor XIII helps in the cross-linking of fibrin with fibronectin, it has an important role in helping in the attachment of the placenta to the uterus. That is the reason why factor XIII deficient women have spontaneous detachment of the placenta leading to recurrent miscarriages. It is well known that pregnancy is a hypercoagulable state per se. An analysis of antenatal women with normal course of pregnancy showed that factor XIII levels decrease during the second and third trimesters and in the immediate postnatal period for a normal woman. Thus, in factor XIII deficient women, this expected decrease reaches much lower nadir, increasing the predisposition to miscarriages and preterm delivery.[3] Factor XIII concentrate has to be administered every 7–10 days, beginning from 5 weeks of gestation once for deficient women to maintain the necessary factor levels for the maintenance of pregnancy. Recently, treatment options with recombinant factor XIII substitutes have shown promising results with successful pregnancy and neonatal outcomes as well.[4]

The diagnosis of factor XIII deficiency is often missed due to normal coagulation test results. Once suspected, a variety of specialized laboratory tests are required to confirm the diagnosis. These include *in vitro* tests such as clot solubility assay, factor XIII activity assay, factor XIII antigen assay, factor XIII inhibitor assay, and molecular diagnosis by identifying the genetic mutations of A or B subunit.[5] Once the parents are screened and the molecular mutation is identified, the prenatal diagnosis for the targeted mutation can be performed. This can be done by polymerase chain reaction with restriction fragment length polymorphism using noninvasive methods like obtaining cell-free fetal DNA from the mother or by extraction of DNA by chorionic villous sampling.[6] Genetic analysis in a large cohort has revealed a high heterogeneity in the nature of mutations and showed that the mutations were mainly due to subunit A of factor XIII. Hence, screening of the affected family members helps in the prenatal diagnosis of the subsequent pregnancies.[7] Treatment of factor XIII deficiency includes fresh frozen plasma, cryoprecipitate, or replacement with recombinant factor XIII. Indications for replacement therapy include those neonates who develop bleeding in congenital factor XIII deficiency, as prophylaxis for children with severe deficiency, and throughout the pregnancy of affected women to prevent miscarriages. The dose for routine prophylaxis is 35 IU/kg of recombinant factor XIII A monthly. In a child with intracranial bleed initial dose of 30 IU/kg for 4 days followed by 10 IU/kg for 10 days should be given. This should be followed by routine prophylaxis.[8]

This report emphasizes that subclinical factor XIII deficiency should be considered among women with history of recurrent pregnancy loss and in a newborn with intracranial bleeding and normal coagulation assay. This can prevent further pregnancy losses, aid in prenatal diagnosis, and prevent life-threatening hemorrhages in the newborn.[9]

Lessons learnt

- Since routine hemostatic evaluation in a newborn with intraparenchymal hemorrhage will miss factor XIII deficiency, a high index of suspicion should be kept if there is no other apparent cause
- Factor XIII analysis should be included in the work-up of women with menorrhagia and recurrent abortions, once common causes have been ruled out
- Screening for factor XIII deficiency in mothers with recurrent pregnancy loss aids in effective management of current pregnancy and early screening in the newborn can prevent morbidity and mortality.

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

Suspecting Neonatal Severe Primary Hyperparathyroidism in Late Onset Neonatal Sepsis

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Abstract

Background: Neonatal severe primary hyperparathyroidism (NSPHPT) is disorder characterized by severe hypercalcemia and severe hyperparathyroidism resulting from a loss of function of the calcium-sensing receptor (CaSR), encoded by a gene located on the long arm of chromosome 3 (3q-13.3-21). It can be fatal if timely management is not initiated. **Clinical Description**: A 10-day-old exclusively breastfed girl presented with poor feeding, constipation, and lethargy for 2–3 days before admission. She was born of third-degree consanguinity to a primiparous woman with normal gestation. Born at term, with a birth weight of 3.1 kg, she was discharged uneventfully on day 3 of life. At admission, she was hemodynamically stable and normothermic but exhibited tachypnea, dehydrated with 15% weight loss as compared to birth weight, lethargy, and hypotonia. Salient investigations showed euglycemia, no dyselectrolytemia, and negative sepsis screen, but severe hypercalcemia and hyperparathyroidism. A final diagnosis of NSPHPT was made. Clinical exome sequencing showed homozygous CaSR gene frameshift mutation on chromosome 3. **Management**: Hypercalcemia was managed initially by standard protocol, including furosemide, hyperhydration, bisphosphonates, and cinacalcet. Subsequently, parathyroidectomy was performed at 2 months of age. Postoperatively, the infant is 5 months old and thriving well. **Conclusion**: NSPHPT should be considered in the presence of features of clinical sepsis, failure to timely regain birth weight, and a profile suggesting atypical calcium homeostasis.

Keywords: Calcium-sensing receptor mutation, hypercalcemia, hyperparathyroidism, parathyroidectomy

Neonatal severe primary hyperparathyroidism (NSPHPT) is a rare autosomal recessive disorder of calcium homeostasis that manifests with severe hypercalcemia and metabolic bone disease in early neonatal life. The prevalence of this condition is reportedly two to five cases per 100,000 individuals.[1] The common manifestations include hypotonia, lethargy, polyuria, dehydration, gastrointestinal dysmotility, poor feeding, respiratory distress, and failure to thrive. NSPHPT can be fatal if left untreated.[2,3]

This disorder results from a loss of function of the calcium-sensing receptor (CaSR), encoded by a gene located at 3q-13.3–21.[4] This G-protein-coupled receptor is found in many tissues in the body but predominantly in the parathyroid gland and kidneys, where its actions are more marked.[5] There are about 300 different CaSR inactivating mutations that have been discovered till date. The type of mutation affects the clinical severity and response to treatment. Homozygous inactivating CaSR mutations usually present with the aforementioned manifestations of severe hyperparathyroidism during the neonatal period. In contrast, heterozygous inactivating CaSR mutations are usually mild and asymptomatic, leading to familial hypocalciuric hypercalcemia (FHH).[6]

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The cause of hypercalcemia in NSPHPT is multifactorial.[7] These include decreased sensitivity of receptors in the parathyroid glands to calcium levels, increased osteoclastic activity, and increased bone resorption leading to hypercalcemia. The goal of NSPHPT is to initially control the severe hypercalcemia by medical management (intravenous hyperhydration, diuretics, bisphosphonates, and calcimimetics), followed by definitive management (total or subtotal parathyroidectomy of the hyperplastic parathyroids).[8-10] We report a newborn admitted to our neonatal intensive care unit with a provisional diagnosis of late-onset sepsis with dehydration, who was subsequently diagnosed with NSHPT. The main aim is sharing the challenges that we faced in the management.

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Clinical Description

A10 days old baby girl presented with parental complaints of poor feeding, lethargy, constipation for 3 days, and decreased urine output for a day. The baby was born to a 27-year-old primiparous woman by cesarean section in a private hospital. The antenatal period was uneventful, with normal quickening, perception of fetal movements, and absence of any medical or obstetric illnesses. The mother was immunized and did not receive any medication during pregnancy except for routine iron, calcium, and folic acid supplementation. There was no history of maternal illness or any high-risk factors for neonatal sepsis preceding the birth. The baby cried immediately after birth, weighed 3.1 kg, and had no immediate postnatal complications. She was started on breastfeeding soon after delivery and discharged on day 3 of life. She was not given any prelacteals. The baby became symptomatic on day 7 of life with the aforementioned complaints. There was no history of fever, vomiting, cough, coryza, difficulty in breathing, excessive crying, seizures, abdominal distention, jaundice, or receiving any drugs or "ghutti." She was first in birth order and the product of a third-degree consanguineous marriage. There was no significant family history of unexplained neonatal or infantile hospitalizations or death.

On examination, the baby was lethargic, moderately dehydrated, had a heart rate of 150/min, respiratory rate of 64/min (with no retractions), oxygen saturation of 95% on room air, blood pressure 66/42 mmHg, the temperature of 36.5°C, and capillary refilling time of 3 s. The weight at admission was 2.5 kg (indicating a weight loss of 600 g since birth), length was 51 cm (between 1 and 2 standard deviations [SD]), and head circumference was 35.5 cm (between 1 and 2 SD). The general physical examination revealed the absence of pallor, icterus, or gross congenital anomalies. The anterior fontanelle was normal in size and neither depressed nor bulging. Although she was hypotonic, she was moving all her limbs spontaneously and equally. There was no cranial nerve or focal neurological deficit. The abdominal examination did not detect any hepatosplenomegaly. The rest of the systemic examination was unremarkable. Based on this evaluation, we kept a possibility of late-onset sepsis and dehydration.

The blood sugar level was 96 mg/dl. The baby was immediately started on intravenous fluids (a bolus followed by maintenance fluids), first-line antibiotics (ampicillin and gentamicin), and oxygen support. Initial investigations sent included sepsis screen, blood sugar, liver function tests, kidney function tests (KFTs), C-reactive protein (CRP), and a blood culture. The sepsis screen was negative (CRP 3 mg/dl, normal total leukocyte count, and absolute neutrophil count). Hence, a lumbar puncture was not done. The blood culture was also later reported to be sterile. The liver function and KFTs were normal (serum sodium 138 mEq/ml, serum potassium 3.9 mEq/ml, serum creatinine 0.58 mg/dl, and serum urea 25 mg/dl). The ultrasound of the abdomen and cranium was also normal. These results excluded our first impression of late-onset sepsis.

Salient biochemical abnormalities noted were increased serum calcium 35.5 (normal 8.5–10.5 mg/dl), low phosphorus 2.1 (normal 3.5–7.5 mg/dl), and high alkaline phosphatase 860 IU/L (normal 100–800). This profile prompted us to plan parathyroid hormone (PTH) and Vitamin D levels. PTH was markedly raised to 660 pg/ml (normal 6.5–36.5 pg/ml). The results of the investigations are given in Table 1. Thus, the differentials were narrowed down to disorders of the parathyroid gland, especially since the common causes of hypercalcemia (iatrogenic, acute renal failure, maternal Vitamin D intoxication, and hypoparathyroidism) were ruled out. Other differentials that were considered and disregarded are given in Table 2. Normal serum and urinary calcium and PTH levels in both parents ruled out FHH. The presence of severe persistent hypercalcemia and hyperparathyroidism, in a setting of a third-degree consanguineous marriage led us to suspect genetic causes of hypercalcemia. Therefore, we planned a clinical exome sequencing, which identified a

Table 1: Salient investigations related to calcium homeostasis at admission

Investigations	Results	Reference value
Serum calcium (mg/dl)	35.3	8.5-10.5
Ionized calcium (mg/dl)	16.4	4.5-5.0
Serum phosphorus (mg/dl)	2.1	3.5-7.5
Serum magnesium (mg/dl)	2.1	1.8-2.4
Alkaline phosphatase (IU/L)	860.0	100.0-800.0
Serum parathyroid (pg/ml)	660.0	6.5-36.5
Serum 25-hydroxyvitamin D3 (pg/ml)	22.0	30.0-10.0
Urinary calcium: creatinine ratio	2.38	

Table 2: Differential diagnosis of neonatal severe primary hyperparathyroidism

Causes of hypercalcemia	Points in favor/against
Acute renal failure	KFT normal
Maternal Vitamin D intoxication, hypoparathyroidism	History not suggestive
Excessive intake of calcium, Vitamin D, and Vitamin A in neonate	History not suggestive
Parathyroid adenoma, carcinoma	Histopathology report not suggestive
Phosphate depletion	Phosphate level normal
Subcutaneous fat necrosis	Physical examination not suggestive
Distal RTA	Electrolytes and bicarbonate levels normal
Syndromes such as Williams–Beuren, IMAGe syndrome, and antenatal barter Type 1, 2	Physical and facial features normal
CaSR mutation; heterozygous (FHH), homozygous (NSPHPT)	Exome sequencing suggestive of homozygous NSPHPT
Neoplasia such as bone tumors, pheochromocytoma, leukemias, and lymphomas	White blood cell counts and blood pressure normal

KFT: Kidney function test, RTA: Renal tubular acidosis, CaSR: Calcium-sensing receptor, FHH: Familial hypocalciuric hypercalcemia, NSPHPT: Neonatal severe primary hyperparathyroidism

homozygous CaSR gene frameshift mutation on chromosome 3, at 122003135delC;p.Tyr789fs location suggestive of NSPHPT. The final diagnosis was NSPHPT. Genetic counseling regarding the same was done.

Management and Outcome

After initially giving three boluses of 10 ml/kg/h for the dehydration, the baby was continued on intravenous fluid infusion along with injection of furosemide (1 mg/kg/dose). Despite this, hypercalcemia persisted. Hence, injection pamidronate was administered as a daily infusion (0.5 mg/kg over 4 h) for 3 days. Since this also did not decrease the calcium levels either, it was discontinued; injection of cinacalcet (0.5 mg/kg/day) was started on the 4th day of admission. Following this, the calcium level decreased to 12.5 mg/dl within 48 h. Over the next 2 days, it had further decreased to 11.1 mg/dl. The baby was switched to oral cinacalcet from day 6th onward. Intravenous furosemide was continued till 1 day before discharge. At discharge, 18th day of life and 9th day of admission, the baby was on exclusive breastfeeds, hemodynamically stable, displayed adequate weight gain, and was clinically active and normocalcemic on oral cinacalcet (30 mg/day). However, on her first follow-up visit (27th day of life), we detected hypercalcemia (despite good compliance with the medication) with a level of 15 mg/dl, although the ultrasound abdomen did not find calcium deposits. A pediatric surgery consultation was taken following, and the parents were counseled about the need and urgency of total parathyroidectomy. There was an inadvertent delay due to the ongoing COVID-19 pandemic. During the period of first admission to surgery the baby had two episodes of hypercalcemia. For the same reason she was admitted at 30th and 45th days of life respectively. The baby was operated at 2 months of age, and the postoperative period was uneventful. The histopathological biopsy report showed parathyroid hyperplasia with no features of malignancy. The baby is currently on regular follow-up, receiving daily replacement therapy of calcium 500 mg, Vitamin D 1000 IU, and calcitriol 0.25 μg. At 5 months of age, she is thriving well, with a weight of 6.4 kg and a length of 68 cm.

Discussion

NSPHT is a rare condition and is not often included in the differential diagnoses of a sick and dehydrated neonate and thus often gets missed. This condition should be considered in the neonatal period if manifestations such as lethargy, polyuria, failure to thrive, dehydration, gastrointestinal dysmotility, or poor feeding are present; or if hypercalcemia is identified. This is what happened in this case. After sepsis was excluded, laboratory reports related to calcium homeostasis became available; treatment for severe hypercalcemia was initiated as per the standard protocol. The biochemical phenotype of severe hypercalcemia and hyperparathyroidism leads us to suspect two differentials; an underlying genetic disorder (which was eventually established) and neoplasia such as adenomas of the parathyroid gland (which was excluded by histopathology).

Bisphosphonates such as zoledronic acid are being increasingly used in neonates and children with hypercalcemia to inhibit the osteoclastic bone resorption that gets triggered by the uncontrolled hyperparathyroidism in NSPHPT.[11] Another drug that is frequently used is cinacalcet. This is a type II calcimimetic that behaves as a positive allosteric activator of the CaSR.[2] It interacts with the transmembrane domain and makes the receptor more sensitive to Ca^{2+}. These events suppress PTH, thereby increasing renal calcium excretion and effectively decreasing the serum calcium levels. Ideally, total parathyroidectomy should be done as soon as the condition has been detected, and the acute crisis managed, as outlined earlier. Total parathyroidectomy with or without autotransplantation of a part of the parathyroid gland is the definitive therapy. The child will need lifelong calcium and supplementation due to the iatrogenic state of surgical hypoparathyroidism and subsequent hypocalcemia.

As NSPHPT is an extremely rare condition, missing the diagnosis can be life-threatening for a neonate. Early diagnosis and prompt and appropriate medical management are very important in the initial phase for stabilization and prevention of complications. Given that there is a wide repertoire of manifestations due to mutations in CaSR, clinicians must keep a high index of suspicion in a newborn with hypercalcemia, irrespective of symptoms, and investigate accordingly once concurrent hyperparathyroidism is identified.

Lessons learnt

- Neonatal severe primary hyperparathyroidism (NSPHPT) should be suspected in neonates with clinical manifestations of sepsis and a negative septic screen
- A calcium-sensing receptor (CaSR) mutation should be suspected in severe neonatal hypercalcemia
- In NSPHPT, the medical management of hypercalcemia should be followed by total parathyroidectomy (with or without auto transplantation of a part of the parathyroid gland) and lifelong supplementation of calcium.

Authors contributions

NYM and SANA were involved in patient management and drafted the case report; MA conceived the concept and critically analyzed the manuscript, and UAQ was overall supervising the case management.

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Conflicts of interest

There are no conflicts of interest.

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A Sick Neonate with Red Eyes: Opthalmia Neonatorum

A 4-day old boy presented to us with fever and excessive crying for 2 days, rapidly progressive swelling of both eyes for a day, and refusal to feed for a few hours. He was born at home, at 32 weeks gestation, to an immunized, unbooked, second gravida mother. Pregnancy had been uneventful till the onset of labor. The delivery was conducted by an untrained birth attendant. No eyedrops were instilled. The baby cried immediately at birth, weighed 1.7 kg and was started on breastfeeds and bottle feeds. At admission, the neonate was euthermic but sick and lethargic. The heart rate was 160/min, respiratory rate 50/min, capillary refill time normal, and saturation 95% on room air. Hypoglycemia was detected. There was pronounced bilateral periorbital swelling with conjunctival redness and thick mucopurulent, hemorrhagic discharge [Figure 1]. A clinical diagnosis of late-onset sepsis with ophthalmia neonatorum was kept. Blood samples and conjunctival culture swabs were taken. Intravenous fluids and broad-spectrum antibiotics were started. Salient reports included leukocytosis of 29,000/uL, absolute neutrophil count 5510/uL, thrombocytopenia (platelets 43,000/uL), elevated C reactive protein (88 mg/L), and direct hyperbilirubinemia (total bilirubin 14.4 mg/dL and direct 3.27 mg/dL). Renal function tests were unremarkable. The patient developed septic shock, required inotropes and ventilatory support and succumbed within 48 h. The blood culture was sterile, but conjunctival culture grew *Pseudomonas aeruginosa*.

Ophthalmia neonatorum is acute, mucopurulent conjunctivitis that presents in the first 4 weeks of life. The incidence is 1%–2% in India.[1] Chemical conjunctivitis was common when 2% silver nitrate was used for prophylaxis against gonococcal conjunctivitis. Infections are caused by Chlamydia, bacteria and viruses. The clinical presentation includes conjunctival erythema, chemosis, and edema of the eyelids, with thick, purulent eye discharge. The onset of symptoms may help in diagnosis. Chemical conjunctivitis presents within 24 h. Conjunctivitis due to Neisseria presents in the first 48 h, Chlamydia by the 5th–14th day, whereas Pseudomonas and viruses by the 2nd or 3rd week. Pseudomonas comprises 1.2%–5.9% of all neonatal conjunctivitis.[2] Preterm and low birth weight babies are at high risk for Pseudomonas infections.

Etiological diagnosis is established by gram stain (bacteria) and Giemsa stain (Chlamydia) of conjunctival scrapings, cultures, and polymerase chain reaction studies. World Health Organisation guidelines recommend immediate antibiotic administration directed toward Neisseria and Chlamydia single-dose third-generation cephalosporins for Neisseria, and erythromycin or azithromycin for Chlamydia.[3] Delay in treatment can result in corneal perforation, blindness, or death.

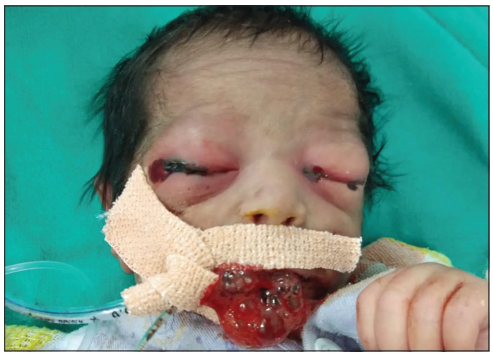

Figure 1: Bilateral periorbital swelling with hemorrhagic discharge

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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Siblings with Depressed Nasal Bridge due to Fetal Warfarin Syndrome

A 24-year-old mother who underwent a mitral valve replacement surgery for rheumatic heart disease, conceived and gave birth to two successive babies while she was on oral warfarin (5 mg/day). In both pregnancies, she remained unaware of having conceived till the end of the first trimester. The first issue was a girl born at 29 weeks gestation by cesarean section due to premature rupture of membranes. Her birth weight was 1370 g, and she was discharged at 34 post menstrual age. The second issue (born after 2 years) was a boy born at term by cesarean delivery and weighing 3050 g. Both babies had a depressed nasal bridge [Figure 1]. Other features of warfarin embryopathy (craniofacial deformities, microcephaly, optic atrophy, dorsal or ventral midline dysplasia, limb defects, digital hypoplasia, and skeletal stippling) were not found. Since other syndromes with depressed nasal bridge (Down syndrome, achondroplasia, cleidocranial dysostosis, congenital syphilis, Stickler and Williams syndrome) were excluded by the absence of associated anomalies, the final diagnosis was FetalWarfarin Syndrome (FWS).

Warfarin sodium inhibits the synthesis of Vitamin K-dependent clotting factors, and is therefore useful in patients at risk of developing thromboembolic events. Its low-molecular weight allows easy placental passage, manifesting as FWS (also known as de Sala Syndrome). *In utero*, warfarin blocks the recirculation of Vitamin K that may lead to hemorrhage within several organs. It also interferes with Vitamin K reductase activity, disrupting the synthesis of proteins such as osteocalcin and Gla matrix, which are essential for nasal bone and cartilage growth. Inhibition of arylsulfatase results in features mimicking chondrodysplasia punctata.[1] The classical clinical phenotype includes a variable combination of nasal hypoplasia, depressed nasal bridge, short limbs and digits, and stippled bone epiphysis.[1,2] There are reports of isolated neurological manifestations like hydrocephalus, or isolated cleft lip and palate. The incidence of FWS ranges from 0% to almost 30% of exposed pregnancies, with an average risk of 6%.

Children with FWS require multidisciplinary management according to the anomalies present. Women with prosthetic valves should be on lifelong anticoagulation, and warfarin is the preferred anticoagulant. Due to the high risk of FWS (15%–25% when dose >5 mg/day and 1.5%–2.5% when ≤5 mg/day), professional bodies have recommended the replacement of warfarin by heparin in the first trimester (between 6 and 12 weeks) during organogenesis.[1,2,3] However, since warfarin has a long half-life, substitution even at the 6th week may still be too late to prevent embryopathy. In addition, substitution may cause an increase in thromboembolic events in the mother, so a one-on-one discussion with the expecting couple needs to be undertaken explaining the maternal risks of switching vis-à-vis the fetal risks involved. Prenatal diagnosis of warfarin embryopathy is difficult, and even high detail ultrasonography may not detect the anomalies. Warfarin should be discontinued again after the 34–36th weeks of gestation.

Figure 1: Siblings with FWS: (a) first born preterm girl on 20th day of life; and (b) second born term boy on 1st day of life. FWS: Fetal warfarin syndrome

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Paroxysmal Tonic Upgaze in an Infant: A Clinician's Dilemma

A 12-month-old boy presented with multiple episodes of looking upward for 3 days, more during the early morning. The duration varied from few seconds to minutes, and there was no loss of consciousness [Figure 1]. The antenatal period was normal. The child was born at term by cesarean section (indication previous cesarean). The birth weight was 3.5 kg. The baby was kept under observation for 48 hours for transient perinatal depression at birth but was discharged uneventfully. There was no significant past or family history. The development was proceeding normally according to acquisition of milestones. Vital parameters, anthropometry, general physical, ophthalmological, neuro-developmental, and systemic examinations were normal. The parents brought a recording of the event [Video 1 (video available from: *https://www.ipcares.org/articles/2022/2/2/images/IndianPediatrCaseRep_2022_2_2_123_346249_sm2.mp4*)]. Blood sugar, serum electrolytes, brain magnetic resonance imaging, and video electroencephalography (EEG) were normal. A diagnosis of paroxysmal tonic upgaze (PTU) was made. The parents were advised whole exome sequencing and counseled about the disorder. The child is under follow-up. No medications have been started.

PTU is a rare nonepileptic paroxysmal dystonia occurring during infancy and early childhood. It is characterized by the recurrent episodes of sustained bilateral upward ocular deviation with downbeating nystagmus in attempted down gaze, normal horizontal eye movements, occasional ataxia, and without altered sensorium. They are frequently misdiagnosed with focal or absence seizures, salient differentiating features being semiology and normal video EEG.[1,2] The exact pathogenesis is still unknown, although mutations have been found in the CACNA1A, GRID2, and SEPSECS genes, also associated with ataxia.[3,4] The prognosis is good with a benign course and symptomatic resolution within months. There is no role of anti-convulsant drugs.

Figure 1: Infant displaying paroxysmal tonic upgaze

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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Visible Intestinal Peristalsis in a Child

A 4-year-old boy presented with recurrent episodes of vomiting for 4 weeks, each nonbilious and projectile in nature. He also had decreased intake of food but no diarrhea, abdominal pain, or distention. There was a significant history of pica. Examination revealed moderate acute malnutrition and pallor. Abdominal inspection revealed visible intestinal peristalsis in the right hypochondriac and epigastric region [Video 1 (video available from: *https://www.ipcares.org/articles/2022/2/2/images/IndianPediatrCaseRep_2022_2_2_124_346265_sm2.MP4*)]. Ultrasonography showed a dirty shadow in the stomach. Barium follow-through showed inhomogeneous filling defects at 3, 6, and 9 h suggestive of a bezoar [Figure 1]. The family was advised surgery but left against medical advice.

Visible peristalsis are waves of movement across the abdomen that often originate from the left upper quadrant and move to the right lower quadrant direction. They are typically a sign of gastric outlet or intestinal obstruction.[1] Intestinal obstruction may not always present with typical manifestations. Visible intestinal peristalsis may be overlooked by the parents and clinician. In young infants, a common cause is hypertrophic pyloric stenosis. Beyond this, the usual underlying pathology are mechanical causes of obstruction resulting from hernia, diverticular disease, tumors, adhesions, strictures, intussusception, volvulus, or foreign body (swallowed material, bezoar, and parasite). Nonmechanical causes of obstruction such as paralytic ileus or Ogilvie's syndrome (acute colonic pseudo-obstruction) will not manifest with this sign, as gut motility is reduced, and there is no anatomical obstruction. Untreated bezoars may lead to gastric perforation.[2] They are common among children with pica.[3]

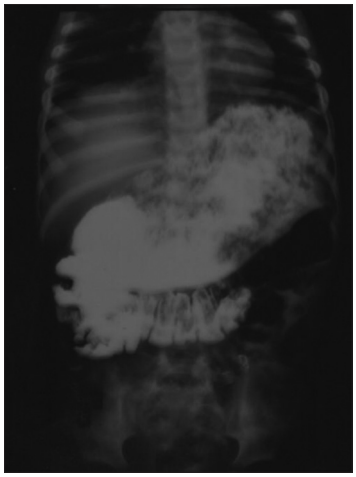

Figure 1: Barium follow-through at 9 h showing inhomogeneous filling defects, indicative of bezoars

Declaration of patient consent

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Managing a Child with Acute Rheumatic Fever in a Remote and Rural Clinic: Role of Decentralized Primary Healthcare

Acute rheumatic fever (ARF) is an autoimmune inflammatory process that develops as sequelae of Group A streptococcal (GAS) infection. Most cases of ARF occur in children aged 5–15 years. Apart from the fever, ARF has extremely variable manifestations, with heart and joints being commonly involved. In a small proportion of children, especially in girls, the basal ganglia may be affected. This manifests as chorea or hemichorea. Although no specific diagnostic or confirmatory test exists, a combination of symptoms, signs, and supportive tests (Modified Jones criteria) is applied to help establish diagnosis. Persons affected with ARF are predisposed to recurrences following subsequent GAS infection, resulting in the dreaded cardiovascular sequelae rheumatic heart disease (RHD).

In this article, we share a case report of a 13-year-old girl who presented to one of our rural primary health-care clinics with abnormal, purposeless movements of one-half of the body. Based on her presenting signs and symptoms, we diagnosed her as having ARF, and managed her accordingly. Using this case report, as an illustration, we discuss the challenges of diagnosing and managing ARF in rural primary health-care settings, and various solutions that theoretically exist for the prevention of RHD but need to be practiced in ground reality on a much wider scale.

Case Report

Sarita (name changed), a 13-year-old girl presented to the AMRIT Clinic at Rawach, a remote village, among the last villages of the hilly region of Mewar. She was brought to the clinic by her parents. Sarita's complaints were primarily the insidious onset of abnormal movements of her left upper limb for around 1.5 months. Due to the movements, she was having difficulty in walking and carrying out activities of daily living. She had stopped going to school since the movements had started. On probing further, we elicited a significant history of having painful swelling of knee joints initially, followed by similar involvement of ankle joints a few days later. The swelling was not associated with restriction of movements. We also learnt that Sarita has been having mild grade fever since the onset of illness. Her parents had consulted various traditional practitioners and received some medications. Her fever and joint swellings had resolved a week or two before the limb movements had started. There was no history of preceding sore throat or skin lesions.

She had not experienced similar complaints in the past, and neither had any other family member. Her parents are farmers who own a small piece of land that they maintain for their livelihood. Neither of the parents ever went to school. Sarita is the third child in birth order. She has two sisters and an elder brother; who works as a migrant worker, providing financial support to the family. They live in a single room *kutcha* house with poor ventilation.

On arrival, the child was conscious and oriented, but irritable. She was having continuous, purposeless movements of the left upper limb and to a lesser extent of the left lower limb, indicative of chorea [Video 1]. There were no other neurological abnormalities or deficits.

Sarita had a temperature of 99.9°C with elevated pulse rate of 100/min, that was regular, with normal volume and character. The respiratory rate was 20/min, and the blood pressure was normal. The jugular venous pressure was not elevated. The child had mild pallor and no cyanosis. There was no edema or other signs of congestive heart failure. The skin did not show any nodules or rash. Her joints were normal, without any swelling, erythema, or tenderness, and displayed normal range of movements. The salient examination findings on systemic examination were the absence of cardiomegaly and a grade 2 soft diastolic murmur in the mitral area on cardiac auscultation. The liver and spleen were not palpable, and the remaining systemic examination was normal.

Based on the presence of three major Jones Criteria – chorea, carditis and migratory polyarthritis- we made a probable diagnosis of ARF.[1] However, we faced major challenges, when it came to satisfying the essential criteria. We could not test for antistreptolysin O (ASO) and erythrocyte sedimentation rate, because the child was extremely uncooperative (*see later*), and would not allow us to draw blood for a sample. For the same reason, we could not take an electrocardiogram. In addition, the parents were unable to take the child to a city hospital for an echocardiography (ECHO), since it is situated about 100 km away.

Sarita displayed extreme fear of all medical procedures. When we tried to give her injectable Benzathine Penicillin (BP), she ran away from the clinic. And, when staff members and her parents attempted to bring her back, she began to throw stones at them to ward them off. However, with some patience and counseling, she agreed to return on the condition that she is given oral medication, instead. She was started on oral amoxicillin (50 mg/kg for 10 days) for controlling the active infection, and sodium valproate (20 mg/kg) for managing the chorea. We also added prednisolone (1 mg/kg) for managing the presumed activity.

On follow-up, after a week, her irritability had reduced and chorea lessened significantly. Vitals were stable, but tachycardia was still persisting. A well-audible diastolic murmur in the

Figure 1: Sarita with Senior Health Worker of AMRIT Clinic 3 weeks after initiating treatment

mitral area had become apparent, with no opening snap. The symptomatic improvement and establishment of rapport with staff members resulted in our managing to convince Sarita to submit to at least one shot of intramuscular 12 lacks units of BP after a drug sensitivity test. Once she had experienced it, she overcame her morbid fear and agreed to continue with injectable BP prophylaxis, in addition to the steroids and valproate. By the 3rd week of initiation of therapy, the chorea had disappeared, her pulse rate had decreased to 84/min and the murmur had disappeared [Figure 1].

The family was satisfied with her recovery. A month afterward, Sarita did not come for her scheduled follow-up visit. This prompted our health workers to make a home visit. It was found that the child had resumed going to school. The family was counseled regarding the need for regular prophylaxis and the consequences of missing even a single dose. She was brought to the clinic on the next day and she was administered the missed dose. Tapering off steroids was started as per standard protocol. Additional counseling was done regarding maintaining dental hygiene. The child has been under our follow-up for 3 months and is doing well.

Discussion

The occurrence of ARF in developed countries has declined dramatically over the past decades, largely on account of improvement in living conditions and socioeconomic status; and early diagnosis and management of streptococcal sore throat infections.

In India, we do not have data on the incidence of ARF, but the prevalence of its sequelae, RHD, is available. Forty percent of the global burden of RHD is estimated to be from India, alone. In a review of school-based surveys conducted between 2008 and 2014, based on echocardiography results, RHD prevalence was 5 to 51 per 1000 children in the age group of 5–15 years, across different states.[2] As expected, the states with more developed primary health-care systems such as Kerala, had a much lower prevalence (5.84/1000 children in Trivandrum) than those with less developed health systems such as Rajasthan (51/1000 children in Bikaner district).[2]

RHD significantly affects the quality of life, and managing RHD is a complex and expensive process; often becoming unavailable and inaccessible for poorer populations. For example, the price of a valve replacement in India ranges from Rs 300,000 to Rs 500,000. While in the long run, improvement in living conditions (and reduction in overcrowding) would lead to a decline in the incidence of ARF and RHD, there are two specific interventions that can reduce the morbidity and the burden associated with the initial illness and its aftermath.

First, timely identification and adequate treatment of an upper respiratory infection (URI) caused by Group-A streptococcus is critical. A Cochrane review of the accuracy of rapid antigen detection tests (RADts) in the diagnosis of streptococcal pharyngitis revealed fairly high sensitivity (86%) and specificity (95%).[3] However, the cost and challenges in availability of the RADts in most primary health-care settings, restricts its use. Thus, primary health-care providers have to rely on clinical guidelines such as the Integrated Management of Neonatal and Childhood Illnesses, according to which antibiotics are not recommended for the treatment of URI. Alternately, health-care providers may use antibiotics ad hoc for inadequate duration, which do not eliminate the streptococci. In both scenarios, the risk of ARF and subsequent RHD is not diminished, underscoring the need for such a test.

Second, it is equally important to identify and manage ARF on time (as we did in this case, despite the numerous challenges), so as to prevent the progression of carditis. With suitable training, use of standardized protocols, and availability of teleconsultation (in places where medical professionals are unavailable), it is not difficult to identify and manage ARF even in a remote and rural setting, as this case study demonstrates. Non-availability of ECHO in the primary care settings, or even at district levels, makes it more difficult to timely identify, and manage ARF and RHD. Wider availability of tele-echocardiography can offset this constraint at the primary care level.[4]

Finally, the prevention of recurrence requires that the affected individual returns every 3–4 weeks to the health facility for BP prophylaxis for a minimum of 10 years.[5] Children belonging to marginalized populations or living in the periphery can avail these injections regularly, only if the health-care facility is close by and well stocked and equipped. We need to ensure that this essential drug is available at all Primary Health Centers and Health and Wellness Centers with requisite protocols for administration in place.

We hope that Sarita will be able to continue with the required prophylaxis. In her circumstances, there are several social barriers that may preclude this eventuality: limited mobility of a girl, dependence on male members to bring her for her

follow-up visit, and though she is only 13-year-old, the very real possibility of early marriage.

People in rural areas face many barriers to accessing quality healthcare for preventing, promoting, and treating illnesses such as ARF. Only a responsive primary health-care service with empathetic and skilled providers, can offset these challenges, and ensure requisite care. When supported with simple and appropriate diagnostics, protocols, and teleconsultation, the healthcare of populations living in rural areas, can be transformed to be available at a cost that these communities will be able to afford. It is imperative for pediatricians to support the development of such decentralized health-care systems.

Declaration of patient consent

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An Adolescent Girl with Lytic Erosion of the Rib: What is the Diagnosis?

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We describe the clinical course of an adolescent girl, who presented with unilateral chest pain, and progressively worsening shortness of breath. The clinical examination confirmed the presence of pleural effusion. On radiological evaluation, the lungs were normal, but there was a lytic lesion in the anterior end of a single rib, with periosteal thickening of multiple ribs on the same side. There was associated pleural thickening as well. The learning objectives of this case are to demonstrate a clinicoradiological approach toward the diagnosis and the use of appropriate investigations to confirm the diagnosis.

Clinical Description

A 12-year-old girl presented with left-sided chest pain and shortness of breath for 8 months. At the onset of her illness, she had sustained a trivial trauma to the left side of the chest. As she walked past a stationary motorcycle, its handle grazed her left chest. Within a few hours, she perceived a dull ache at the site of contact and a pea-sized swelling that was soft but slightly tender to touch. There was no history of any bleeding or bruising of the overlying skin. She was able to breathe normally. A local private practitioner opined that it could be a fracture of a rib, requiring only conservative treatment. However, it was not confirmed with a radiograph. The swelling gradually subsided over the next few days, but the dull pain persisted. Over the next few weeks, the discomfort became more diffuse, extending to the entire left side of her chest. The child reported aggravation on exertion and deep breathing, but it was not severe enough to limit her daily activities. A month later, she developed shortness of breath which was insidious in onset. Initially, it occurred with exertion (like climbing the stairs), but over 3 months, it gradually progressed to being present while walking, although not at rest.

Throughout this period, there was no history of fever, cough, loss of appetite, night sweats, bony aches and pain, increasing pallor, bleeding from any site, recurrent ulcers in the mouth, rash, photosensitivity, and pain or swelling of any joints. The child's weight remained static for about a year. The past history was not significant. There was no history of contact with tuberculosis (TB). She had been living with her grandmother since the age of 8 years. Thus, her details before that were not available. She was an average student at school.

On examination, she was afebrile, with a pulse rate of 88/min (min), respiratory rate of 24/min, SpO_2 99% in room air, and blood pressure of 100/62 mmHg. Her weight was 29.5 kg (−1.87 Z score), height 147.5 cm (−0.64 Z score), and body mass index 13.56 kg/m^2 (−2.04 Z score) as per the Indian Academy of Pediatrics growth chart reference values. General physical examination did not reveal pallor, icterus, cyanosis, clubbing, lymphadenopathy, rash, or edema. The BCG scar was present. Bone and joint examination was normal. The respiratory system examination revealed a symmetric chest with equal expansion, mild tracheal deviation to the right side, apex beat located 1 cm internal to the midclavicular line in the left fifth intercostal space, stony dullness in the left lower intercostal spaces, and diminished breath sounds in the same locations. There were no audible crackles or wheeze. These clinical findings suggested a left-sided pleural effusion. The examination of the other systems was unremarkable. A chest radiograph was ordered [Figure 1].

What are the salient findings in her chest X-ray?

The radiograph was a well-centered, well-exposed film. The striking finding was a homogeneous opacity in the left lower zone, obliterating the left costophrenic angle, and silhouetting the left heart border and diaphragm. There was no obvious tracheal deviation. These radiological findings confirmed the presence of a left-sided pleural effusion with possible collapse or consolidation (or both) of the underlying lung. Closer examination revealed broadening of the anterior end

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of the left eighth rib with the suspicion of a lytic lesion within it. The other ribs and soft tissues appeared unremarkable. A left-sided paratracheal lymph node was suspected but could not be confirmed.

What are the clinical possibilities based on the clinical history and radiograph?

We considered the following differential diagnoses based on the clinical phenotype of a suspected rib fracture following trivial trauma, a lytic bony lesion, and slowly progressing ipsilateral pleural effusion: rib bone TB, a malignant bone tumor such as Ewing's sarcoma, a benign bone tumor such as osteochondroma or eosinophilic granuloma. However, the absence of fever went against TB, the progression over months was unusual for Ewing's sarcoma, and the absence of a palpable tumor made the possibility of benign growths less likely.

What should be the next line of investigations?

Further investigations were planned as per the differential diagnoses considered. An ultrasonographic examination of the chest showed a loculated left pleural effusion of 5.2 cm × 2.6 cm. Ultrasonographic-guided pleural tap yielded yellowish fluid with rich cellularity; total leukocyte count was 14,080/mm^3 with 99.3% lymphocytes, and no malignant cells. Gram staining, Ziehl − Neelsen (ZN) staining, bacterial culture, GeneXpert, liquid medium mycobacterial culture, and fungal culture were negative. The tuberculin skin test was reactive (25 mm × 26 mm). Three samples of gastric lavage (as per institutional protocol) underwent ZN staining, GeneXpert, and liquid medium mycobacterial culture but were negative. Fiber-optic bronchoscopy was performed and the bronchoalveolar lavage revealed predominant lymphocytes without any malignant cells. ZN stain, GeneXpert, and liquid medium mycobacterial culture did not indicate TB.

What should be the next step in the clinical approach?

As the child had a history of suspected rib fracture following trivial trauma, and the pleural fluid analysis was inconclusive, we planned a contrast-enhanced computed tomography of the thorax [Figure 2].

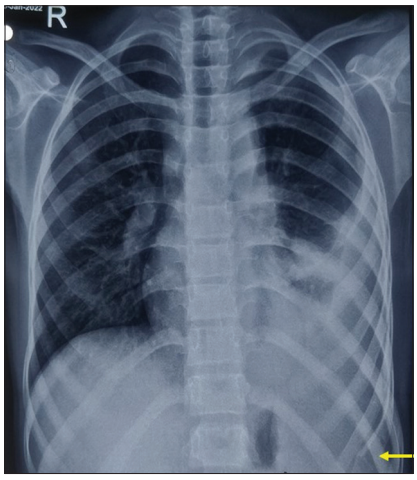

Figure 1: Chest X-ray showing left pleural effusion with collapse consolidation of the underlying lung, with broadening of the anterior end of the eighth ribs on the left side (yellow arrow)

What are the salient findings in the contrast-enhanced computed tomography thorax images?

The mediastinal window sections showed multiple, enlarged, discrete, and conglomerating lymph nodes in the prevascular, pretracheal, right paratracheal, precarinal, and bilateral hilar regions. There was sheet-like soft-tissue thickening (1.5 cm) along the costal, diaphragmatic, and mediastinal pleura on the left side with nodularity. Solid periosteal thickening involving multiple ribs on the left side and a focal lytic erosion in the anterolateral aspect of the eighth rib were noted. There was moderate pleural effusion with underlying collapse consolidation of the left lung. The radiological diagnosis based on these findings was an underlying lymphoreticular malignancy like leukemia or lymphoma.

How to proceed further?

A pleural fluid flow cytometry analysis was performed which suggested reactive pleural effusion without any evidence of malignant cells. Therefore, an ultrasonography-guided fine-needle aspiration (FNA) of the mediastinal lymph node was done. This showed multi-nucleated giant cells with epithelioid granuloma and the presence of acid-fast bacilli (AFB) on ZN staining**.** However, GeneXpert and liquid medium mycobacterial culture from the FNA sample were negative. There were no abnormal cells suggestive of lymphoreticular malignancy. Thus, based on these findings, mediastinal lymph node TB was confirmed, and the other sites of involvement (ribs and pleura) were also presumed to be due to the same etiology. In consultation with the orthopedic team, it was decided that a rib bone biopsy would be performed only in the event of nonresponse to anti-TB treatment (ATT).

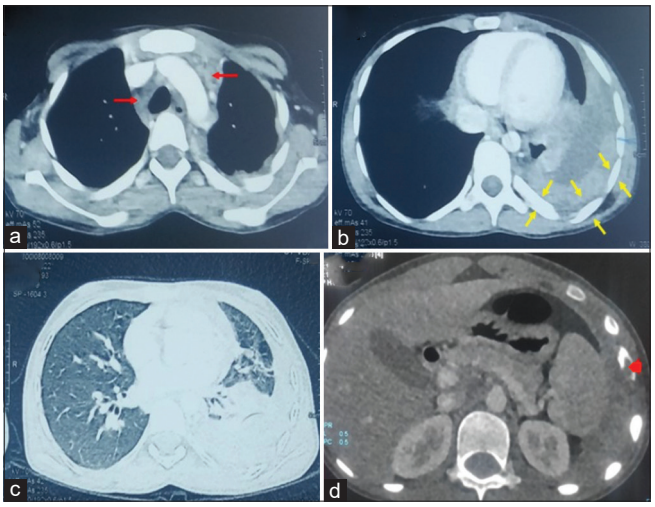

Figure 2: Contrast-enhanced computed tomography sections showing: (a) Right paratracheal and para-aortic lymph nodes (red arrows) in the medistinal window; (b) broadening of the ribs on the left side (compared to the right side), suggesting periosteal reaction (yellow arrows); (c) Left-side pleural effusion with underlying collapse consolidaton and (d) Lytic erosion of the rib on the left side (red arrowhead)

Management and Outcome

Standard four-drug ATT was started along with pyridoxine, and the child was discharged. She was closely monitored every 2 weeks to observe clinical improvement. By the end of the intensive phase of ATT, the child was symptomatically well; the chest pain and breathlessness had resolved. During this period, weight gain of 1 kg was recorded. Ultrasonography of the chest showed a reduction in pleural effusion to 4.2 cm × 1.6 cm (around 30 cc volume). Therefore, it was decided to shift to the maintenance phase of ATT with continuation of monthly follow-up.

Discussion

Osteoarticular TB accounts for only 10%–20% of extrapulmonary TB in children.[1] There are two broad pathophysiologic mechanisms of rib involvement; the first is by lymphatic or hematogenous spread. The second is by the direct extension from contiguous sites such as the lung or pleura.[2] In the index case, either mechanism could be possible, although the presence of mediastinal TB lymphadenopathy suggests a higher likelihood of lymphatic spread from that site. After the initial infection of the bone, there is marked local hyperemia that results in osteoporosis.[3] In the early stages, a radiograph may appear normal, but more advanced cases may show changes ranging from mild osteopenia to lesions suggestive of osteomyelitis. Computed tomography scan can help in identifying the extent of lesions. The radiographic features of bone TB may mimic eosinophilic granuloma, malignancy, or fungal infections.[4] Hence, it is difficult to establish the diagnosis of osteoarticular TB solely on the basis of radiological findings. In addition, <50% patients have concomitant pulmonary involvement.[5] Therefore, tissue diagnosis from the affected bone and/or other sites is ideal to confirm the diagnosis.

There is controversy regarding whether a bone biopsy or surgical removal of the rib lesion is mandatory for establishing the diagnosis of tuberculous osteomyelitis. There are several published case series and case reports, in which the diagnosis of TB could only be established on histopathology after surgical resection of the rib.[5-7] However, in TB endemic areas, due to the invasive nature of the aforementioned approach, ATT is often initiated on presumption and the response to treatment is considered an indirect confirmation of the diagnosis. In this case, the orthopedicians were of the opinion that the removal of the rib would lead to instability of the thoracic cage. They suggested that taking this risk was unjustified, since histopathology of the mediastinal lymph node had already demonstrated the presence of epithelioid cell granulomas, with giant cells and AFB. Hence, the diagnosis remained presumptive. Confirmation by molecular diagnostic methods or culture should always be attempted in all cases since these findings can also occur with infection by nontubercular mycobacteria and nocardia.

There are two views regarding the management of rib TB. Some experts emphasize the need for surgical resection or debridement along with ATT,[5,6] whereas others suggest that medical therapy alone for 12 months may suffice, reserving surgical debridement for only the 10%–15% cases that fail to improve with ATT.[8]

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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Five Feet Apart

Consider the following plot: Boy and girl meet and fall in love. The relationship is challenged by insurmountable difficulties. Both fight the odds, succeed, and live happily ever after. Add a supportive friend, and a menacing villain; and such predictable three-line plots can be stretched to 300-page novels or 2-h cinematic experiences.

Against this backdrop, "Five Feet Apart" (directed by Justin Baldoni, and released in 2019) literally stands apart. For one, the heroine (Stella) and hero (Will) have cystic fibrosis (CF) with terminal lung damage and meet in a hospital. Despite being poles apart in their attitudes toward their condition (and life in general), they fall in love. Second, the villain in this scenario is *Burkholderia cepacia* (a Gram-negative bacillus-colonizing CF lungs that is associated with progressive lung damage, hence often considered a death knell). Developed health-care systems make great efforts to reduce cross-infection by ensuring that individuals harboring *B. cepacia* avoid contact with other patients; by using masks, ensuring strict hand hygiene, and maintaining the now-famous six-feet distancing.

Stella and Will are typical white teenagers with CF. While Stella follows the prescribed protocols assiduously, Will portrays a teenage rebel, callous with CF treatment protocols. Stella, therefore, is an ideal candidate for lung transplantation, whereas Will is not. Here, candidacy for lung transplantation is based not only on the severity of the lung condition but also on the physical, mental, and psychological state of the patient, likelihood of compliance, and potential prognosis.

As they draw closer, Will learns to regard his treatment more seriously, while Stella learns to loosen up. However, the six-feet distancing rule and the strict enforcement by hospital personnel, challenge their relationship. Live-in-the-moment Will is prepared to throw caution to the winds to further the budding romance, whereas play-by-the rules Stella, is not. She finally agrees for an in-hospital date, deciding to stay five-feet apart from Will (instead of six). Ergo, the title!

The film meanders through melodramatic situations, raising obvious questions: Will the romance survive? How will a "five-feet apart" relationship work? How will it end? I shall not answer these, but dwell on other dimensions, instead.

From a cinematic perspective, the film is not exceptional. There are several hackneyed clichés and near-absurd situations. Hence, why should pediatrcians watch it? Being familiar with the intricacies of CF management, I can appreciate how well certain complex issues are depicted by the cast, and challenges faced by service providers, highlighted in the film.

In developed countries, a lot of emphasis is placed on making hospitalization as atraumatic as possible. In India and other developing nations, the experience is usually unpleasant for the child (and family). I believe the difference is partly due to the elaborate support systems. Besides medical professionals, the care team comprises of highly trained nurses, respiratory therapists, psychologists, social workers, and others, working with compassion and sensitivity, within the traditional "business-oriented" boundaries of busy hospitals. "Life goes on" for these families, in contrast, to the developing world, where "life" comes to a screeching halt.

Last but not the least, "Five Feet Apart" displays the "dependent, yet independent" behavior of Caucasian teenagers with chronic diseases, who actively participate in their own healthcare. They are encouraged to understand their disease, discuss treatment options, the consequences of nonadherence, and take responsibility for their own well-being. Thus, they exhibit greater maturity and independence than adolescents in our society. However, considering the societal transformation in India in recent times, it may not be long before we witness similar situations.

In summary, watching this film can be educational, especially for clinicians working with patients with chronic health conditions. For those who don't mind sugar-coated romantic portrayals, the storyline may be an added bonus. Oh, and for those who aver that the printed word is superior to a 1000 moving images, the book is also available!

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The Experiences of a Physician Working during the Covid 19 Pandemic

This is a description of the experiences I encountered in May and June 2021, when the entire country was in the grip of the second wave of the COVID pandemic. I was working in the COVID Intensive Care Unit (ICU) of the hospital run by the Defense Research Development Organization at Varanasi. After completing an ICU shift duty, I felt that I must pen down my the feelings and thoughts regarding the patients currently admitted under our care.

I will never forget the faces of my patients and their families in these difficult times: the son who is waiting to meet his father; the 40-year-old woman who wants to meet her daughter; the old gentleman who is only worried whether he will survive or not, because he feels there is no one else who will take care of his children (incidentally, all adults); and many others. These people have taught me the true meaning of grief and loss. I was astounded by the beauty and grace of their acceptance of their illness and possible impending mortality. It made me wonder, again and again, that when I reach the end of the journey of my life, will I be able to embrace the end so courageously. We, the doctors, are called "COVID warriors," but our patients who passed away without their loved ones around them, with only the name of their Lord on their lips, were no less truly heroic than anyone of us.

The last 3 weeks has also made me realize the importance and value of the little things in life that we simply take for granted: a conversation with family members at teatime, spending quality time with friends and colleagues, coming to work and doing our jobs, and many more. These regular, mundane daily acts acquired a much deeper spiritual significance than before, as the days rolled by, and I was surrounded by the perpetual bleeping of ventilators and monitors, the sound of my own suffocating breathing through the personal protective equipment (PPE) gear, and suffering through the forced solitude of quarantine after completing my posting. Amid all these hardships and trying circumstances, these memories are some of the little things that keep our hopes alive and make us glad to be alive. There will be anxieties, failures, and sadness, but these are valleys into which you transiently descend, only to stand up and climb out bravely to be the real hero!

I have always been a firm believer that I must invest myself completely in whatever I do, and at the same time, I stay emotionally detached from the results or consequences. Living through these times has just made my convictions stronger. We just need to believe in ourselves and keep doing the best that we can in the prevailing circumstances. Even when things start to get really hard, we should try to persevere through adversity. Many people give up on following their dreams because the work appears to become too difficult, tedious, or tiresome; however, often, you are much closer to the finish line than you may think. Moreover, if you push just a little bit harder, you will surely succeed. Every obstacle we face offers an opportunity to improve. If we are able to get by these challenging moments, we may end up much better off than when we started. We have to let go of our limiting beliefs to make the breakthroughs that are required to ultimately succeed. Do not let other people tell you that you cannot do something and do not hold onto an assumption that you cannot grow and learn from past failures. Moreover, last but not least, my prayers go out to all those who have lost their near and dear ones during this pandemic.

I am proud to be a part of the medical fraternity.

Jai Hind

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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