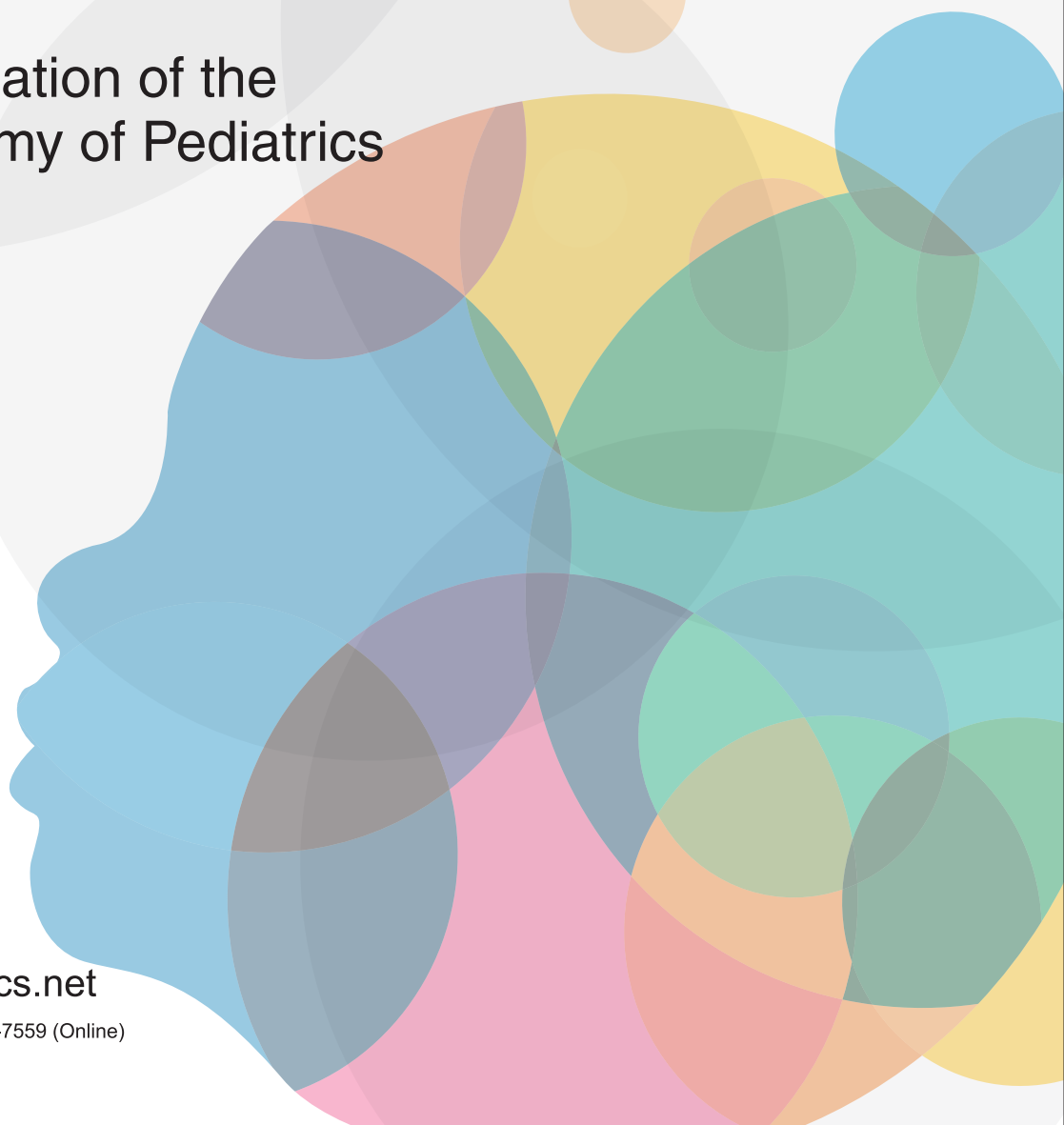
E-copy

Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

VOLUME 58
NUMBER 01
JANUARY 2021



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ISSN0019-6061 (Print) | ISSN0974-7559 (Online)

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Indian Pediatrics

January 2021 Volume 58 Number 1

Contents

Indian Pediatrics Wishes its Readers

Happy New Year 2021

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with mon1078 circulation of print/e-copies to over 31,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net.* There are no charges for publishing in the journal.

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PRESIDENT'S PAGE

Light at the End of the Tunnel

Piyush Gupta
National President, Indian Academy of Pediatrics 2021
president@iapindia.org

Each generation of modern medical professionals has been confronted with a certain set of challenges that defined their time, and each generation has overcome them with perseverance and ingenuity. It may be Fleming's discovery of penicillin in the 1920s overcoming the menace of bacterial infections, tissue cultures going mainstream in the 40s and 50s, the discovery of hitherto unknown antipsychotics and the double-helix DNA in the 50s to unveil the genetic mysteries, the oral rehydration therapy of the 60s and 70s as the most life-saving advance of 20th century, and more recently, the fight against challenge posed by AIDS. Our challenges have become increasingly complex, but each generation of scientists and doctors has been better equipped than their predecessors. We have the tools, the means, and the intent to tackle the ever-growing challenges facing us as a species. If history has taught us anything, it's that no matter the problems thrown at it, mankind prevails.

During 2020, the generation-defining fight has been the ongoing COVID-19 Pandemic. It has disrupted lives on a global scale [1], and people, more than ever, are looking at their doctors for guidance and aid. Our job, our responsibility, and our privilege as pediatricians, is to handhold our patients and their parents through this time. The wellbeing of the next generation of mankind is quite literally in our hands.

Children in India have been through something that none of us have, and it will require empathy and patience to understand what they need, to go through the transition back to things as they were. They've missed a big chunk of school, because of which they have rarely met friends or socialized. The natural build-up of immunity is at its lowest, and the related stress factor at its highest. Hospital visits are down, which means there may be a tremendous backlog of diagnosis and management of chronic illnesses, which would've been caught if not for the pandemic. Routine immunization has also suffered [2]. The economic impact has been hard, which will travel through parents' pockets to the nutritional health of children, especially in the disadvantaged sections of our society. We, as a community of doctors, must be aware of these problems if we are to come up with policy and protocols to address them. It is by no means an easy task.

Yet, good news is around the corner. Vaccinations against COVID-19 have already begun in certain parts of the world [3], and India will soon follow. Mankind will pick itself back up, as it has done countless of times. It may take a while, since we don't know how long it'll take for herd immunity to kick in, or how fast the virus may adapt to the vaccines.

The Indian Academy of Pediatrics (IAP), in turn, must adapt. We must recognize that we aren't out of the woods yet, even though we're firmly on the right path. Precautions must be taken, and as doctors, we have to lead by example.

A starting point will be the annual Central Pedicon 2021. Since a large physical congregation of members is not possible because of the prevailing situation, we have planned to have a mix of limited physical gathering coupled with a large virtual participation to create a unique hybrid event, the Central IAP Pedicon 2021. The physical leg of this hybrid conference will be held at Mumbai from 4-7 February, 2021 and will include the annual IAP events such as the Shantilal C Sheth Oration, UG and PG quiz, award papers and also hold meetings of Office Bearers, Executive Board, and the General body. We look forward to host all our IAP members on a virtual platform in this conference. In keeping with the focus of IAP next year on early childhood development [4], the theme of this conference will be "Nurturing Care for Early Childhood Development", to reflect the commitment of IAP to empower all parents and pediatricians to achieve an optimal and holistic development for children of India.

I am delighted to apprise the members of a partnership and collaboration forged between the IAP, World Health Organization (WHO), and the Unicef to

work together for the cause of early childhood development in the year 2021. The beginning of the year will be marked by IAP-WHO-Unicef Collaborative plenary sessions and a consultative meet during this hybrid conference. IAP-WHO-Unicef collaboration will also bring out a supplement of *Indian Pediatrics* devoted to ECD during 2021.

Digital education has been on the forefront of IAP activities in 2020. We hope to carry forward this momentum by establishing a digital center of excellence (DCOE) under the umbrella of Indian College of Pediatrics (ICP). This long cherished academic wing of IAP will finally start functioning in its earnest this year and will strive to achieve quality in all academic courses and fellowship being awarded by IAP and its subspecialty chapters.

In January, 2020, we conceived developing a set of Guidelines for parental education on various facets of children's day-to-day life both in health and disease. This was a long felt need of the parents in India. American Academy of Pediatrics has a devoted website on parental guidelines [5], but it was a felt demand to have India-centric parental guidelines. I am delighted to inform you that the final set of 101 Parental Guidelines prepared by more than 500 experts from all over India and abroad are almost ready to be launched. Starting first week of January, look out for release of these guidelines to all IAPians. The first set is prepared in English. Later, the plan is to translate all the guidelines in 15 Indian languages and disseminate across the length and breadth of the country to all parents who wish to read them.

There's strength in numbers. And there's strength in hope. If the 30,000 plus strong body of the IAP is set upon a hopeful future, I have belief that the challenges of the present can be dealt with effectively. Father of the Nation Mohandas Karamchand Gandhi put it in the simplest terms, '*The future depends on what we do in the present.*' That's as true now as it was when he said it.

Children are the future. And the future depends on our actions today. I quote from Jeffrey Fry "*Sometimes life seems a dark tunnel with no light at the end, but if you just keep moving forward, you will end up in a better place*." Looking forward to work together and moving in the right direction.

Funding: None; *Competing interests*: None stated.

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EDITORIAL COMMENTARY

(If) Tribal Children's Lives Matter, Measure Them!

Abhay Bang

Director, Society for Education, Action and Research in Community Health (SEARCH)
Shodhgram, Chatgaon, Dhanora, Gadchiroli, Maharashtra 442605, India. search.gad@gmail.com

Nothing exists, until it is measured!

Niels Bohr

Many of us will be surprised to know that as many as 104 million tribal people live in India, more than the national populations of 90 percent of the countries. How do tribal children in India live, and more importantly die? How many? Why? What can be done? These questions bother every pediatrician's conscience – sometime or other.

When the Government of India's Expert Committee on Tribal Health requisitioned for an estimate of the Infant Mortality Rate (IMR) for the tribal population in India, the office of the Census and Sample Registration System was unable to provide the same. The nation had not cared to measure death rates in tribal children. The committee, for its Report (2018) [1], had to depend on indirectly estimated rates based on the Census 2011 and the National Family Health Surveys (NFHS) 1 to 4.

But the generic term 'tribal people' incorporates within it 705 different tribes, each having unique culture, lifestyle, and hence, with a different child mortality rate. The great anthropologist Verrier Elwin had long ago documented the life and culture of various major tribes in India [1]. Who would provide us their IMRs? In the present issue of *Indian Pediatrics*, Verma, Sharma and Saha, three researchers from the National Institute of Research in Tribal Health, provide us exactly that [2].

From the Census of India (2011) data they have estimated the IMR, Under-5 Mortality Rate (U5MR) and Life Expectancy at Birth (LEB) for scheduled tribes (ST) from seven states – Rajasthan, Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, Jharkhand and Odisha [2]. They selected the tribes with population size large enough, indentifying 123 tribes which account for 94-97% of the total ST population in the respective states. Using the demographic methods of indirect estimation pioneered by Prof. Brass of the London School of Tropical Medicine and Hygiene, they estimated, for the first time, the IMR, U5MR and LEB for these 123 tribes [2]. They deserve kudos for this contribution.

These estimates reveal three diversities – between the total population and the ST population of India, between the seven states, and within each state, between the tribes. Since what the authors have estimated, the IMR, U5MR and LEB, are literally the estimates of life and death, they matter! What these different statistical numbers reveal are huge inequalities for the opportunity to survive – the most fundamental human right.

These researchers estimate that whereas the IMR for the total population of India, in 2006-07, was 65 per 1000 live births, it was 76 for the total ST population (705 tribes) in the country. But hidden within this number, 76,were huge diversities. The IMR for these 123 tribes varied from the lowest 48 for the Gamit tribe in Maharashtra to the highest 124 for the Birhore and Bharia tribes residing in Chhattisgarh, Jharkhand and Madhya Pradesh. Seventy six additional infants died in these later two tribes per 1000 live births.

Similarly, the U5MR among these 123 tribes ranged from the lowest of 57 in one tribe to the highest of 203 in another. It was lowest for the total ST population in Maharashtra (76) and highest (123) in Madhya Pradesh. The estimated LEB for these 123 tribes ranged from the lowest 51 years (Birhore) to the highest 72 years (Gamit).

Two major limitations of these first-ever estimates are, one, they are not actual measurements over a period of time but have been indirectly estimated from a cross-sectional data, the Census of India. Second, they pertain to the year 2006-07, in a way, already outdated. But they make a beginning of making estimates for the individual tribes. Hopefully, the estimates based on the next national Census will arrive sooner.

The two landmark reports, of the Lancet-Lowitja Global Collaboration (2016) on the Health of the Indigenous and Tribal Populations [3] and 'Tribal Health in India - the report of the Expert Committee on Tribal Health' of the Government of India (2018) [4], have

pointed out that globally as well as nationally, the indigenous and tribal people suffer worse health status and chances of survival compared to the general population in the countries. Regrettably, India had the second highest IMR for the tribal people in the world, next only to Pakistan. Now Verma, Sharma and Saha show that even within the tribes, there are large disparities between the states and within the states.

So, what do we make of this?

One, the policymakers need to appreciate the importance of segregated measurement for the tribal people as a whole and for each individual tribe. The expert committee on tribal health has underscored this need; and some movement in the academia can be seen after that. Will the Ministry of Health and Family Welfare, and the Ministry of Tribal Affairs show more action?

Second, the tribal development plans – the tribal sub-plans – and the health plans of the states should now move further and develop the tribe specific plans. Birhore tribe, whether in Chhattisgarh, Jharkhand or Madhya Pradesh, has the highest child mortality. Each tribe has different challenges, hence needs separate attention and solutions.

Third, the pediatricians and policymakers need to assert that the tribal mothers and children receive near complete coverage with the proven health care inter-ventions such as the ANC, institutional delivery, home-based neonatal care, immunization, breastfeeding and nutrition, and finally, treatment for pneumonia, diarrhea and malaria. But the coverage will improve only if measured and monitored separately for tribal children. Niels Bohr was absolutely right – (If) tribal children lives matter, measure them!

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EDITORIAL COMMENTARY

Suction First vs Drying First

SOURABH DUTTA

Neonatology Unit, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh, India.
sourabhdutta1@gmail.com

Kumar, et al. [1] have published an open-label, randomized controlled trial in this issue of *Indian Pediatrics*. Among newborn infants depressed at birth, who required the initial steps of resuscitation, they compared the effect of performing suction first or drying first on the composite outcome of hypothermia at admission or respiratory distress at 6 hours of age.

Their rationale for conducting this clinical trial was that the neonatal resuscitation program (NRP) of the American Academy of Pediatrics recommends suction followed by drying, whereas the Indian version of neonatal resuscitation program (1st edition) recommends the sequence of drying followed by suctioning [2,3]. To add to the confusion, the newborn resuscitation module of Facility Based Newborn Care follows the AAP recommendation [4]. Neither of the two sequences is evidence-based. The modification in the Indian NRP results from a concern about the increased risk for hypo-thermia in low- and middle-income countries.

For the better part of the history of neonatology, the steps of neonatal resuscitation were based on expert opinion rather than evidence. It is only for the last few decades that various steps of neonatal resuscitation have been subjected to well conducted randomized cont-rolled trials and systematic reviews [5-9]. The initial steps of resuscitation are applicable to a huge number of newborn infants. Therefore, it is even more important that the initial steps be tested in clinical trials, as a small improvement may result in massive gains at the population level. The steps must be tested both for their necessity as well as the sequence in which they are done.

Given this background, Kumar, et al. [1] must be complimented for conducting a clinical trial on a question that- although apparently minor- could potentially have far-reaching consequences. The current version of the NRP recommends the initial steps of resuscitation for 3 situations- (*a*) preterm, (*b*) apneic or gasping, (*c*) poor muscle tone [2]. The authors have included infants who fulfilled criteria (*b*) and (*c*). There were preterm infants included in the study, who happened to fulfil the other criteria. Thus, the results of their study may not be generalizable to preterm infants who are neither apneic nor limp but who undergo the initial steps of resuscitation as per the current NRP protocol.

The authors conducted the randomization and concealment of allocation well. However, they should have given a justification why they opted to choose a composite outcome that included respiratory distress within 6 hours of birth. I have concerns about the sample size calculation in this trial. The sample size has been calculated for a single-group descriptive study designed to detect a 10% incidence of delivery room resuscitation. This has no relevance to the current study, where the sample size should have been calculated for an expected difference in the composite outcome between two groups. The baseline incidence could have been derived from the unit data of the authors. One can reasonably assume that the effect size in the study would be small, and I expect the true sample size would be much larger than that recruited by the authors.

The authors analyzed several clinically relevant short-term outcomes. There was no statistically signi-ficant difference in the composite outcome between the two groups, based upon which the authors concluded that it makes little difference to the outcome whether newborns are suctioned first or dried first, and either approach is acceptable. The conclusion is worded as if the trial had been conducted as a noninferiority trial or an equivalence study. Since the trial was not designed as a noninferiority trial, the absence of statistically significant difference does not necessarily imply equivalence of the two approaches, and it would have been more appropriate to conclude that the trial failed to detect a statistically significant difference between the two approaches.

The authors have correctly analyzed the issues related to hypothermia in their study and observed that body temperature in the labor room may have been a more relevant outcome, rather than at the time of admission into the NICU. They had a remarkably high

incidence of need for bag and mask ventilation, with almost every subject who underwent the initial steps of resuscitation, requiring bag and mask ventilation.

Not withstanding some of the limitations of this clinical trial and some of the atypical findings, the fact remains that this trial is probably one of the first of its kind. It focuses one's attention on the need to have uniform recommendations and clinical practices. It also demonstrates the urgent need for large, multicentric well-conducted randomized controlled trials on simple questions that affect day-to-day neonatology practice. Hypothermia at birth is a bigger issue in low- and middle-income countries than high-income countries, and countries like India must take the lead in conducting simple, large trials of this kind. The findings of the current clinical trial could form the basis of planning larger trials with adequate sample size.

Funding: None; *Competing interests:* None stated.

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PERSPECTIVE

Identifying Serious Bacterial Infections in Febrile Young Infants

VIKRAM BHASKAR,[1] PRERNA BATRA[1] AND PRASHANT MAHAJAN[2]

From [1]Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi, India; and [2]Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan, USA.

Correspondence to: Dr Prerna Batra, Professor, Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi 110 095, India. drprernabatra@yahoo.com

Fever is one of the most common presenting complaints among infants brought to pediatric emergency. Although most of the infants have benign, self-limiting viral infections, approximately 10% of all may have serious bacterial infection. Clinical examination alone is insufficient to detect serious bacterial infection in well appearing infants, and a standardized approach is always sought for. However, guidelines used in the United States or European countries may not be applicable in a tropical country like India. Deviation from these guidelines leads to challenges of unwarranted hospitalization and antibiotic usage, extra cost of care and risk of antimicrobial resistance. Various prediction rules can detect a low risk infant with negative predictive values ranging from 93.7-100%. While use of biomarkers such as C reactive protein and procalcitonin can be reliable, it is costly and may not be applicable to the local population. Validation studies over varied population are needed in future.

Keywords: *Blood culture, Diagnosis, Investigations, Management, Procalcitonin*.

Fever is one of the most common presenting complaints of children brought to pediatric emergency. Data from developing countries is lacking, but in the United States, fever accounts for almost 20% of the visits to the pediatric emergency department [1]. Fever may result from infectious (bacterial, viral, parasitic) or non-infectious (autoimmune, environmental, drugs) causes. Young infants (0-90 days) are particularly at risk of serious bacterial infections (SBI) that include bacteremia, meningitis, pneumonia and urinary tract infections, owing to their immature immune system and absence of localizing signs [2]. The incidence of SBI in young infants is reported to be 7-11% [3]. Our focus of discussion here includes neonates (0 to 28 days) and infants aged 29 to 90 days old, in whom the diagnosis and management of SBI is challenging, with a battery of tests being conducted alongwith administration of empirical antibiotics. The authors present a perspective on the dilemmas and current advances in the evaluation and management of febrile young infants.

GUIDELINES FOR IDENTIFICATION

Diagnosis of SBIs in young febrile infants has been challenging for years for clinicians and researchers globally. Clinical examination alone is insufficient to detect SBI as many infants appear well and do not show any localizing symptoms or signs. Results of many of the laboratory tests, like culture, take time. Thus, a standardized approach to identify these cases early, simultaneously avoiding over-investigation and over-treatment in this vulnerable age group is desirable.

Protocols for management of sick or toxic looking infants (defined as clinical picture consistent with the sepsis syndrome including lethargy, signs of poor perfusion, marked hypoventilation or hyperventilation or cyanosis) are relatively well defined, but there is a lack of consensus regarding guidelines for well looking febrile young infants [4]. Further, differentiating well appearing young infants with SBI from those having a benign viral infection remains a diagnostic challenge. Given the incidence of meningitis in neonatal age group is as high as 0.8-6 per 1000 live births [3], American College of Emergency Physicians (ACEP) recommended performing lumbar puncture even in well looking young infants (< 28 days) [5]. Updated ACEP guidelines in the year 2016 focused on key issues pertaining to well appearing febrile child less than 2 years of age and gave evidence-based recommendations after performing systematic review [2].

Guidelines used in the United States or European countries may not be applicable in a tropical country like India. Immunization status of infants also affects the differential diagnosis of fever in this age group. Mahajan, et al. [6] proposed an algorithmic approach for evaluation and management of a febrile child, applicable in India. These guidelines focused on the triage, assessment and management of a child presenting with fever in the emergency department. They recommended that, in all toxic looking infants and well appearing infants aged <28 days, comprehensive severe sepsis evaluation is to be, including complete blood count, quantitative C-reactive protein

(CRP), peripheral smear, blood culture, chest *X*-ray, urinary analysis including culture and lumbar puncture. For well appearing infants aged 29 days to 90 days, lumbar puncture was not advocated. Also, chest *X*-ray had to be performed only if TLC >20,000/cumm, temperature >39^{0}C or respiratory symptoms were present. These guidelines are consensus based, but reasonable to use in absence of strong evidence. However, more research is needed to understand the epidemiology of febrile children ≤90 days of age in India and for validation of the algorithm countrywide. Introduction of newer immunization policies incorporating *H. influenzae* and pneumococcal vaccines and development of antigen-based point-of-care rapid diagnostic tests for various bacterial and viral diseases, for example lateral flow immunochromatographic tests (LFIA) for *Gp A Strepto-coccus*, respiratory syncytial virus (RSV), nucleic acid amplification tests (NAAT) and nicking enzyme ampli-fication reaction (NEAR) for influenzae A and B, have led to a perceived need for change in these guidelines [7].

Although globally, pediatric emergency medicine physicians report following a set of published guidelines for the management of a well-appearing febrile infant, there is a wide variation in diagnostic testing and hospitalization across different sites for young infants aged less than 60 days, with rates of lumbar puncture and hospitalization ranging from 40-90% [8-12]. Non-adherence to these guidelines, results in unwarranted hospitalization, antibiotic usage, extra cost of care and risk of antimicrobial resistance.

CLINICAL PREDICTION CRITERIA

Various prediction rules or criteria have been established in the past to detect infants who do not require hospital admission or parenteral antibiotics. Boston [9], Philadelphia [10] and Rochester criteria [11] are few such well-established prediction rules with negative predictive values ranging from 93.7% to 100%. Application of Boston criteria [9] in 503 infants (28 to 89 days), having fever without focus, showed that 94.6% infants had no SBI if total leucocyte counts were < 20,000/cumm, CSF cell counts were < 10 cells/cumm, with normal urinalysis and normal chest *X*-ray (if done). Philadelphia rule [10] utilized clinical assessment and a set of extensive laboratory evaluation to categorize infants (29 to 56 days) as 'low risk' for SBI, who could be managed on out-patient basis without antibiotics. Rochester criteria were applied to infants who were term-born, without perinatal complications, nor any underlying disease and had not received antibiotics previously, excluding those who were 'too ill' to wait evaluation. Negative predictive value (NPV) of Rochester criteria for ruling out SBI was close to 99% [11]. These rules were created to safely identify infants who are at low risk of having a serious or invasive bacterial infection as the cause of their fever. However, these prediction rules have not been validated across cultural, geographic, socio-economic environ-ments and thus may not be applicable in all clinical settings. A comparison of these three commonly used criteria is given in **Table I**.

Cerebrospinal Fluid Examination

Missing SBIs like meningitis or bacteremia, may lead to serious consequences. The risk of missing SBI must be weighed against the cost of hospitalization, risk of hospital-acquired infections and probable misuse of antibiotics. A large study of 3,246 infants observed bacterial meningitis in only 0.2% of the well-appearing febrile infants >28 days old [13], thus raising doubts regarding the need for routine cerebrospinal fluid (CSF) examination in infants less than 60 days of age. [14,15], In

Table I Comparison of Different Clinical Prediction Criteria to Identify Febrile Young Infants at Low Risk of Serious Bacterial Infections

	Philadelphia criteria [10]	*Rochester criteria [11]*	*Boston criteria [9]*
Age (d)	29-60	<60	28-89
Laboratory parameters (for low risk status)	WBC <15,000/µL Band-neutrophil ratio <0.2 Urine analysis <10 WBC/hpf CSF <8 WBC/µL CSF Gram stain-negative Chest *X* ray – without infiltrates Stool-without blood, few/no WBCs	WBC >5000 and <15,000/µL Absolute band count <1500/µL Urine analysis <10 WBC/HPF Stool <5 WBC/HPF Chest *X*-ray negative	WBC <15,000/µL Urine analysis <10 WBC/HPF CSF <10 WBC/µL Chest *X*-ray negative
Recommendations for low-risk patients	Home care No antibiotics Follow-up	Home care No antibiotics Follow-up	Home care Antibiotics administered Follow-up

WBC: White blood cells; UA –, CSF: Cerebrospinal fluid; hpf: High power field.

another study, in infants with UTI, probable bacterial meningitis was seen in 0.8%, while none had confirmed bacterial meningitis, thereby prompting the authors to recommend a tier-based approach for the evaluation of febrile infants [16]. Such results were reiterated in a systematic review of low-risk febrile young infants with UTI, thus making lumbar puncture (LP) questionable in such infants [17]. Despite growing evidence, centers still perform CSF testing in this age group, because of risk of neurologic sequelae and mortality associated with bacterial meningitis [18,19]. The frequently used Rochester and modified Philadelphia criteria [14] do not require routine lumbar puncture to classify febrile infants as being at low or high risk for SBI. Aronson, et al. [20], found that the modified Philadelphia criteria had higher sensitivity than that of Rochester criteria (91.9% vs 81.5%; P=0.01), but the specificity was lower (34.5% vs 59.8%; P<0.001) to stratify apparently well febrile infants with invasive bacterial infection, without the use of LP. Thus, there is minimal risk of missing a child with meningitis or SBI if these criteria are used judiciously, avoiding unnecessary LP. Yale Observation Scale (YOS), an easily applied observational scale, without any investigations, compiled three decades back [21], was not found to reliably predict SBI in infants< 60 days [22]. On the contrary, a large number of infants aged 29-60 days old, were misclassified as having invasive bacterial infection using modified Boston and modified Philadelphia criteria [23].

In view of the low risk of meningitis, ACEP (2016) recommends that CSF examination can be deferred in full-term, well-appearing, febrile infants, between 29 and 90 days, diagnosed with a viral illness. Antibiotics are to be avoided, unless another bacterial source is identified. Admission, or quick follow-up visits is advisable. [2]. Previous guidelines by ACEP (1993) recommended giving single dose of parenteral ceftriaxone and outpatient management with re-evaluation in OPD 24 hours later, in low-risk febrile infants aged 29 to 60 days, after documenting normal CSF cytology and sepsis screen. In low-risk febrile infants between 61-90 days, additionally, the more conservative approach of withholding lumbar puncture and re-evaluation is to be considered [5]. In a recent study, Kuppermann, et al. [24] as a part of the 'Febrile infant working group of the pediatric emergency care applied research network (PECARN)' derived and validated a clinical prediction rule to identify febrile infants <60 days at low risk of SBI. They concluded that negative urinalysis result, absolute neutrophil count (ANC) of ≤4090/µL, and serum procalcitonin of ≤1.71 ng/mL can rule out SBI with 97.7% sensitivity and 99.6% negative predictive value [24]. The advantage of this rule is that it averts the need for CSF analysis.

Role of Biomarkers

Literature suggests promising role of newer biomarkers in early, reliable identification of children with SBI. Studies have suggested that markers like C-reactive protein (CRP), and procalcitonin (PCT) are useful in predicting SBI [25-30]. Procalcitonin had a greater area under curve than CRP in febrile infants with more invasive disease i.e. sepsis, bacteremia, and bacterial meningitis [31].

STEP-BY-STEP APPROACH

With the objective of avoiding unnecessary investigations, without the risk of missing cases of SBI, a middle path combining clinical criteria and statistically derived cut-offs of standard laboratory tests and newer biomarkers can be used to risk stratify infants and derive prediction rules. The 'step by step' approach is one such algorithmic approach developed by European group of pediatric emergency physicians [32]. This approach sequentially evaluates the general appearance, age, urinalysis and lastly, biomarkers, to identify a low-risk infant who could safely be managed as outpatient without the need of lumbar puncture or empirical antibiotic therapy. Gomez, et al. [33] validated the 'step-by-step' approach and concluded that the sensitivity and NPV of this approach to rule out SBI in infants <90 days was 92% and 99.3%, respectively, which was better than Rochester criteria and lab-score alone. Galleto Lacour, et al. [34] developed and validated a laboratory index score that utilized PCT, CRP and urinary dipstick and found it to be a reliable tool for identifying infants at risk of SBIs. However, prior to application of prediction rules such as the Step-by-Step rule or the PECARN Febrile Infant prediction rule, a robust analysis of the epidemiology of febrile infants as well as feasibility of implementation in the local population needs to be undertaken, because even robustly derived and validated rules may be difficult to apply/implement if found to be irrelevant to the local population.

FUTURE DIRECTIONS

Whenever any decision is taken regarding the management of a febrile child, parents or guardians must be included in the decision-making process. This includes, but is not limited to, clearly informing the risk of including or excluding components of evaluation (like lumbar puncture) and management, so that an informed, responsible decision can be taken. Since neither isolated clinical nor laboratory criteria can absolutely rule in or rule out SBIs in febrile young infants, development of prediction rules seem to be a promising option. Viral infections especially herpes simplex virus and respiratory

Box I Key Points for Identifying Serious Bacterial Infections in Febrile Young Infants

- Neither clinical examination nor individual investigations alone are sufficient to detect serious bacterial infections in well appearing febrile young infants.
- Derivation of prediction rules incorporating clinical prediction rules and investigations including quantitative C-reactive protein and procalcitonin are promising options.
- Multicentric validation studies are required to prove efficacy of these rules.

syncytial virus should also be considered as possible etiologies. Validation studies over varied population and derivation of the age-specific cut-offs of laboratory tests like quantitative CRP, procalcitonin and other biomarkers should be conducted to provide a definite plan for identification of SBI in febrile young infants.

The key messages are listed in **Box I**. Quantifying host immune response to presence of bacterial or viral pathogen using RNA bio-signatures forms an exciting area of future research, which has the potential to replace cultures as the reference standard [35].

Contributors: PB, PM: conceived the idea; VB, PB: drafted the manuscript; PM: reviewed it critically. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interest*: None stated.

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RESEARCH PAPER

Diversity in Child Mortality and Life Expectancy at Birth Among Major Tribes in Selected States of India

ARVIND VERMA[1], RAVENDRA K SHARMA[2] AND KALYAN B SAHA[1]

From [1]Indian Council of Medical Research (ICMR) – National Institute of Research in Tribal Health, Jabalpur, Madhya Pradesh; [2]ICMR-National Institute of Medical Statistics, New Delhi; India.

Correspondence to: Dr Arvind Verma, Principal Technical Officer, ICMR-National Institute of Research in Tribal Health, PO-Garha, Nagpur Road, Jabalpur 482 003, Madhya Pradesh, India. vermaarvind1@rediffmail.com
Received: January 27, 2020; Initial review: January 30, 2020; Accepted: September 26, 2020.

Objective: To provide tribe- specific child mortality rates and health indicators from selected states in India. **Methods**: We used Census 2011 data and Coale Demney methodology to estimate the infant mortality rate (IMR), under-five mortality rate (U5MR) and expectation of life at birth (LEB) for 123 tribes of selected states of India. **Results**: The estimated IMR and U5MR were higher in scheduled tribe population compared to respective state's total population. The IMR varied from 124 in the Birhore tribe of Chhattisgarh and Jharkhand, and the Bharias of Madhya Pradesh to 48 per 1000 live births in the Gamit tribe of Maharashtra. Similarly, the U5MR varied from the highest (203) in the Birhore tribe of Chhattisgarh to the lowest (57/1000 live births) in the Gamit tribe. The LEB varied from 72 years in the Gamit tribe of Maharashtra to 51 years in the Birhore tribe of Chhattisgarh. The study reveals that tribes have gross variation in child mortality rates and there is pressing need to prioritize tribe-specific action plans to improve their health indicators.

Key words: *Health, Indigenous population, Infant mortality, Neonatal care, Under-5 mortality rate.*

Published online: **October 12, 2020; *PII:*S097475591600252**

India has 705 Scheduled Tribal groups (ST) with a population of 104 million (8.6% of total population) as per 2011 census. These tribal groups constitute the second largest tribal population in the world, after the African continent. These tribal groups belong to different ethnic groups and are at different levels of development. The tribal population contributes considerably to infant and under five deaths. As per recent NFHS-4 survey in 2015-16, infant mortality rate (IMR) and under -five mortality rate (U5MR) were 44 and 57 among the ST population compared to national average of 32 and 38, respectively [1]. Poorer health and social outcomes for indigenous peoples than for non-indigenous populations have been reported from across the world [2].

The Indian population census in 2011 enumerated ST population in 30 states and union territories of the country. ST population residing in Chhattisgarh, Gujarat, Jharkhand, Madhya Pradesh, Maharashtra, Odisha and Rajasthan states accounts for two-third of the tribal population of rural India [3], and are in a critical state and consistently reporting poor vital parameters which varied in tribal sub-groups [4]. The mortality rates for STs of these states are much higher compared to tribes residing in the other states [1]. However, no data is available on tribe-specific child mortality and life expectancy in India. Hence, in the present analysis, we estimated the IMR, U5MR and life expectancy at birth (LEB) for major tribes residing in Chhattisgarh, Gujarat, Jharkhand, Madhya Pradesh, Maharashtra, Odisha and Rajasthan states of India.

Editorial Commentary: Pages 11-12.

METHODS

The census, 2011 of India enlisted 705 tribes/tribal groups in the country and out of them 75 tribes/tribal groups/ sub-groups were classified as particularly vulnerable tribal groups (PVTG), formerly known as primitive tribes [3]. Of these, 268 tribes, including 38 PVTGs, reside in the selected seven states. However, only 106 tribes/ tribal groups, each having at least 5,000 women, and 17 PVTGs, each having at least 1,000 women in the age group (15-49), are included in the study, so as to have relatively robust estimates. Overall, these selected tribes encompassed about 94-97% of the respective state's total ST population. The data on Children Ever Born (CEB) and Children Surviving (CS) are used for the estimation of IMR, U5MR and life expectancy at birth LEB, and compiled from tribes-specific tables of census, 2011 [5].

We used the Brass method for estimating the child mortality rates. The Brass method estimates the mortality q(x)-the probability of dying between birth and exact age x, from the proportion of children dead among those ever born by women in different age groups [8]. Trussell [8] version of Brass method which uses Coale Demeny south model life tables to simulate mortality was adopted to estimate the child mortality. The estimates of IMR, U5MR and LEB are calculated by MORTPAK 4.3 software (United Nation) [7]. The MORTPAK provides age group specific estimates of IMR, U5MR and LEB. The weighted average of estimates for women age groups 20-34 years are considered using CEB as weights and refer to 4.6 years prior to census reference date, i.e. 2006-07 year. The estimates of IMR, U5MR, and LEB were calculated for Indian total population and total ST Population, selected seven states' total population and total ST population, and 123 selected major tribes residing in these states.

RESULTS

The IMR, U5MR, and LEB estimates are summarized in **Fig. I** and **Table I**. The tribe specific estimates of IMR, U5MR and LEB for all 123 tribes are given in **Web Annexure I**.

The estimated IMR for India's total population was 65 compared to 76 per 1000 live births for country's total scheduled tribe (ST) population in year 2006-07. The IMR for total population varied from lowest (53) in Maharashtra to highest (76) in Madhya Pradesh, whereas in case of total ST population it varied from lowest (60) in Maharashtra to highest (89) in Madhya Pradesh. Overall, ST population in Chhattisgarh, Madhya Pradesh, Jharkhand, Odisha and Rajasthan states had 11-14 extra infant deaths per 1000 live births compared to respective state's averages. In the studied 123 tribes, 66 tribes had higher IMR than the national ST average (76 per 1000 live births). The mean (SD) of estimated IMR for 123 tribes/tribal groups was 80.9 (19.7) per thousand live births, ranging from highest 124 in the Birhore tribe of Chhattisgarh and Jharkhand states, and the Bharia tribe of Madhya Pradesh to lowest 48 in the Gamit tribe of Maharashtra, depicting that on an average 76 extra infants died during first year of life in the Birhors and the Bharia tribes compared to the Gamits of Maharashtra. The difference in IMR was not only observed between tribes residing in different states but also among tribes residing within the states. A difference of 49-62 extra infant deaths was observed among the tribes of Chhattisgarh, Madhya Pradesh, Jharkhand, Odisha, and Rajasthan states (**Table I**).

The U5MR for India as a whole was estimated at 82 deaths per 1000 live births, whereas it was 101 for total scheduled tribe (ST) of the country i.e., on an average 19 extra deaths among children under five years in ST population compared to the national average. The U5MR for total population varied from lowest (64) in Maharashtra to highest (100) in Madhya Pradesh. However, in case of total ST population U5MR varied from lowest (76) in Maharashtra to highest (123) in Madhya Pradesh. Overall, ST population in Chhattisgarh, Madhya Pradesh, Jharkhand, Odisha and Rajasthan states had 21-24 extra deaths per 1000 children under five years age compared to respective state averages (**Fig.1**). Among 123 tribes, 65 tribes had higher U5MR than the national average for ST population (101). The mean (SD) U5MR was 112.0 (36.5) per thousand live births ranging from highest (203) in the Birhore tribe of Chhattisgarh to the lowest (57) in the Gamit tribe of Maharashtra, reflecting 146 extra under five deaths in the Birhore compared to the Gamit tribe (**Table I**).

The estimated LEB for total population and total ST population of India was 67 and 65 years, respectively. This shows that on an average, a tribal individual survives two years lesser than the national average. Among the selected seven states, the LEB for total population varied from 65 years in Madhya Pradesh to 70 years in Maharashtra state. However, in case of total scheduled tribe population, the LEB varied from 61 years in Madhya Pradesh to 69 years in Maharashtra (**Fig. 1**). Among 123 selected tribes, 70 tribes had lower LEB than the national average for ST population (65 years).The mean (SD) of estimated LEB for 123 tribes was 63.0 (5.3) years, ranging from highest 72 years in the Gamit tribe of Maharashtra to lowest 51 years in the Birhore tribe of Chhattisgarh. The difference in LEB was not only very high between the tribes residing in different states, but also among tribes residing within the state. In Chhattisgarh state, the LEB varied from 51 years in the Birhore tribe to 68 years in the Oraon tribe. A difference of 13-17 years was observed in tribes of Chhattisgarh, Madhya Pradesh, Jharkhand, Odisha, and Rajasthan (**Table I**).

DISCUSSION

Vast difference was noted to prevail in child mortality by tribal groups. The IMR and U5MR was 44.4 and 57.7, respectively among STs compared to national averages of 40.7 and 49.7, respectively. These child mortality rates also vary considerably among ST population of different Indian states. However, there is dearth of information on different tribal communities, especially on demographic and health indicators. The expert group on tribal health, Government of India [8] and Saha, et al. [9] highlighted the

Table I Tribe-Specific Estimates of Infant Mortality Rate (IMR), Under-5 Mortality Rate (U5MR) and Life Expectancy at Birth in the States

State (Total tribes)[a]	*Total studied tribes*[b]	*IMR (per 1000 live births)*			*U5MR (per 100 live births)*			*Life expectancy at birth (y)*		
		Highest	*Lowest*	*Total*[c]	*Highest*	*Lowest*	*Total*[c]	*Highest*	*Lowest*	*Total*[c]
Chhattisgarh (42)	20	124.3 (Birhore)	62.0 (Oraon)	84	203.0 (Birhore)	80.3 (Oraon)	118	67.8 (Oraon)	51.2 (Birhore)	62
Madhya Pradesh (46)	14	123.8 (Bharia)	68.5 (Majhi)	89	194.8 (Bharia)	88.8 (Majhi)	123	66.4 (Majhi)	52.1 (Bharia)	61
Jharkhand (30)	22	124.3 (Birhore)	67.0 (Karmali)	81	195.8 (Birhore)	86.0 (Karmali)	109	66.8 (Karmali)	52.0 (Birhore)	63
Odisha (62)	24	112.6 (Koya)	58.5 (Bathudi)	87	171.4 (Koya)	72.9 (Bathudi)	120	68.9 (Bathudi, Sounti)	54.9 (Koya)	62
Rajasthan (12)	7	118.5 (Saharia)	69.8 (Dhanka)	83	183.5 (Saharia)	90.4 (Dhanka)	113	66.1(Dhanka)	53.4 (Saharia)	63
Gujarat (29)	19	76.3 (Dhanka)	49.5 (Rabri)	67	101.5 (Dhanka)	60.2 (Rabri)	86	71.3 (Rabri)	64.4 (Dhanka)	67
Maharashtra (47)	17	75.0 (Pradhan)	47.5 (Gamit)	60	99.4 (Pradhan)	57.2 (Gamit)	76	71.8 (Gamit)	64.7 (Pradhan)	69

[a]Total number of tribes/tribal groups enumerated in the state in census 2011; [b]Total number of tribes for which tribe-specific estimates computed; [c]Estimates for total scheduled tribe population of the state.

need to generate tribe-specific data to formulate developmental programs accordingly.

Our estimate of IMR for total ST population of the country is slightly higher as compared to previous reports [2], which estimate 74.3 deaths per 1000 live births. The difference between two rates of IMR based on census 2011 data is due to different methodologies adopted. Anderson, et al. [2] have used Coale-Demeny model (Palloni Heligman equation) with South Asian life-table and taken simple average of estimates for age groups 20-34 years. Whereas, we have used Coale-Demeny model (Trussell equation) with South Asian life-table and taken weighted average of estimates for age groups 20-34 years. The study has not only demonstrated the huge differences in child mortality and life expectancy at birth among tribes residing in different states, but also among tribes residing within the state. The tribes residing in economically backward states like Chhattisgarh, Madhya Pradesh, Jharkhand, Odisha and Rajasthan were having higher child mortality indicators compared to those residing in relatively well-off states of Gujarat and Maharashtra. The study also shows that most of the PVTGs residing in different states have relatively higher mortality rates and lower life expectancy compared to other tribal communities residing within the states. A gap of 76 in IMR and 146 in U5MR among tribal communities is a matter of serious concern and needs immediate attention. Similarly, a variance of 21 years in life expectancy at birth reflects an extremely poor health status among some tribal communities.

The child mortality rates may be higher among tribal communities because of their poor socio-economic status, geographical isolation, poor availability and inaccessibility, and underutilization of modern health services. Sahu, et al. [10] recorded high IMR and U5MR among scheduled tribes of rural India and reported that the factors associated with mortality remained more or less same over the period of 1992-2006. The NFHS-4 shows that one-third pregnant women from ST community in India did not receive any antenatal care during pregnancy and majority of the deliveries (73.2%) are performed with assistance of midwife at home; lack of proper training and low frequency of postnatal check-ups (68.6%) pose serious threat to the health of newborns [4]. Inequalities in the proximate determinants of child mortality, which vary according to their beliefs and multiplicity of cultures, and in turn influences antenatal care, delivery practices and postnatal care of infants [11]. Culture, ritual and traditional beliefs of the tribes also acts as hindrance in utilization of maternal and child health (MCH) facilities [4]. Many tribal communities still believe in various taboos and traditional practices.

WHAT THIS STUDY ADDS?

- We provide tribe-specific estimates of infant mortality rate, under-five mortality rate and life expectancy at birth for 123 tribes of seven states of India.

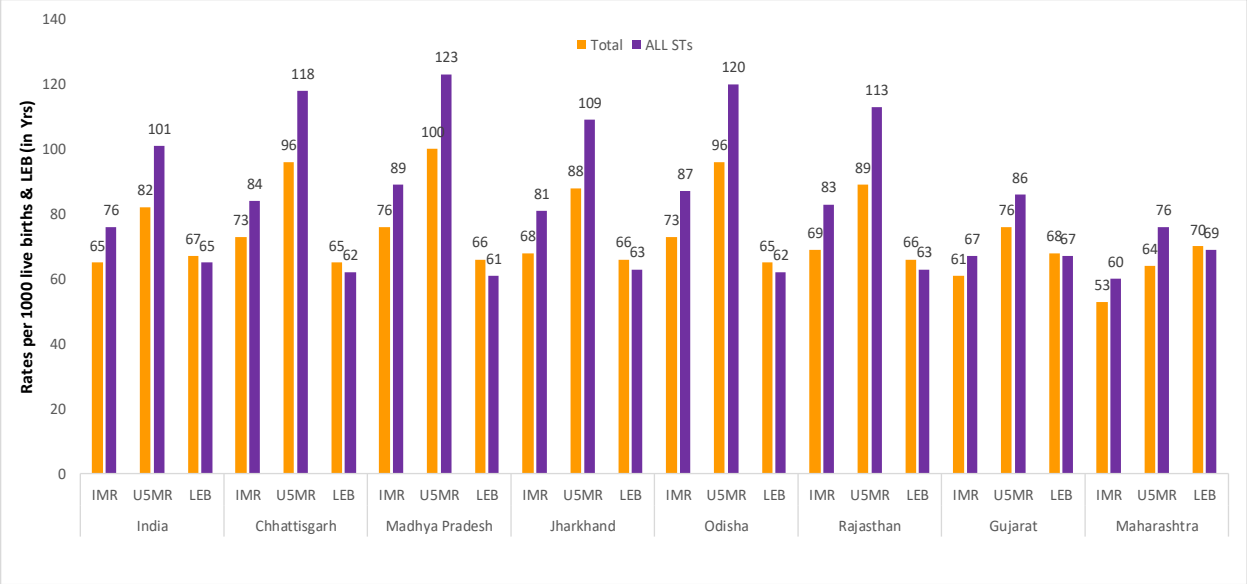

Fig. 1 Estimated infant mortality rate (IMR), under-5 mortality rate (U5MR), life expectancy at birth (LEB) for total and scheduled tribes population of India and selected states.

Delayed breastfeeding and pre-lacteal, supplementary feeding practices like honey and goat's milk are also widespread among them [12,13]. The presence of malnutrition, anemia, higher incidence of infectious diseases like malaria, tuberculosis and diarrheal diseases may further worsen the child mortality in these tribal communities.

These estimates are derived from census 2011 data using Trussell version of Brass method, which has its own limitations, as it assumes that age-specific fertility and mortality rates remained constant in the recent past, and no strong relation exists between the age of mother and infant mortality, etc., and these estimates are referred for the year 2006-07. In the absence of any other tribe- specific data source, these estimates will provide valuable information which may guide the program managers.

In India, tribes are classified as scheduled tribes and clubbed together for implementation of socio-development program for their upliftment. However, tribes are not a homogenous group and enormous variation is observed in the estimates of IMR, U5MR and LEB. Hence there is a need for tribe-specific approach to bridge the gap. The present study also affirms the need to generate tribe-specific data, prioritize the tribal group on the basis of their vulnerability, health and mortality parameters. Accordingly, tribe-specific developmental programs may be formulated to improve the childhood health and quality of life so that country can achieve SDGs targets within the stipulated time frame.

***Acknowledgments*:** Dr Aparup Das, Director, ICMR-National Institute of Research in Tribal Health, Jabalpur (MP) for his support and guidance. Prof Chander Shekhar, IIPS, Mumbai for his valuable suggestions to improve the quality of the paper.
Contributors:AV: Concept and design of study, data compilation and analysis, manuscript writing; RKS: Data analysis, literature review and manuscript writing; KBS: Data interpretation, manuscript writing and final editing. All authors have read final version of the manuscript.
Funding: None; *Competing interest*: None stated.

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RESEARCH PAPER

Suctioning First or Drying First During Delivery Room Resuscitation: *A Randomized Controlled Trial*

ASHOK KUMAR,[1] RAVI PRAKASH YADAV,[1] SRIPARNA BASU[1] AND TB SINGH[2]

From [1]Neonatal Unit, Department of Pediatrics and [2]Biostatistics Unit, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India.

Correspondence to: Dr Ashok Kumar, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India. ashokkumar_bhu@hotmail.com

Received: July 23, 2019; Initial review: November 05, 2019; Accepted: July 13, 2020.

Objective: To compare the effect of suctioning first or drying first on the composite outcome of hypothermia or respiratory distress in depressed newborns requiring delivery room resuscitation.

Design: Open-label, randomized, parallel-group, controlled trial.

Setting: Delivery room and neonatal intensive care unit of a tertiary-care teaching hospital.

Patients: Depressed newborns (*n*=154) requiring initial steps of resuscitation at birth.

Intervention: During delivery room resuscitation eligible newborns were randomly allocated to receive either suctioning first or drying first (77 newborns in each group).

Main outcome measure: Composite incidence of hypothermia at admission or respiratory distress at 6 hours of age.

Results: Both groups were comparable with regard to maternal and neonatal characteristics. Composite outcome was similar in both the groups [46 (59.7%) *vs* 55 (71.4%)] in suctioning first and drying first, respectively [RR (95% CI), 0.84 (0.66–1.05); *P*=0.13]. Incidence of hypothermia, respiratory distress at admission and oxygen saturation at 6 hours were also similar. On admission to NICU, hypothermia was observed in 26 (33.8%) neonates in suctioning first group and 33 (42.8%) neonates in drying first group but by one hour of age the proportion of hypothermic neonates was 13 (16.9%) and 14 (18.1%), respectively.

Conclusion: In newborns depressed at birth, the **s**equence of performing initial steps, whether suctioning first or drying first, had comparable effect on composite outcome of hypothermia at admission or respiratory distress at 6 hours of age.

Key words: *Hypothermia, Initial steps, Mortality, Newborn, Outcome, Respiratory distress.*

Clinical Trial Registration: CTRI/2017/04/008340

Approximately 10% of newborns require some assistance to initiate and sustain effective breathing at birth [1], and perinatal asphyxia accounts for 23% of 4 million neonatal deaths each year globally [2]. Skilled delivery room resuscitation can prevent many of these deaths and neurodevelop-mental handicaps in survivors.

All depressed newborns requiring delivery room resuscitation should receive 'initial steps' before initiating positive pressure ventilation. These essentially constitute temperature maintenance, positioning, suctioning, drying and tactile stimulation. Suctioning is done to clear the airway and drying is done to prevent heat loss. Though the sequence of suctioning followed by drying has been endorsed as the part of initial steps in neonatal resuscitation program (NRP) of the American Academy of Pediatrics (AAP) [3], it is based on expert opinion rather than evidence. It is not clear whether the same sequence should be followed in a resource-limited settings of lower and middle income countries, where the danger of hypo-thermia constitutes a bigger threat [4-6]. Due to this dilemma, the Indian NRP (first edition) [7], advocated for the sequence of drying followed by suctioning as initial steps in Indian scenario. However, in neonatal resus-citation module of Facility-based newborn care [8], the sequence has been changed to suctioning first, followed by drying. Contradictory recommendations have led to confusion among health professionals, with variations in practice and training. The objective of the present study was to compare the effect of suctioning versus drying as a first procedure during delivery room resuscitation on the composite outcome of hypothermia at admission or respiratory distress at 6 hours of age.

Editorial Commentary: Pages 13-14.

METHODS

This open-label, randomized controlled trial was conducted in the delivery room and neonatal intensive care unit (NICU) of a tertiary care teaching hospital of central India from March, 2016 to August, 2017. The study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from

the parents before delivery. The cases was excluded, if there was insufficient time to obtain informed consent.

Consecutively delivered inborn neonates who were depressed at birth and required initial steps of resuscitation were included. Depression at birth was defined as presence of apnea or gasping and/or limp or poor muscle tone. Neonates delivered through meconium stained liquor, major congenital anomalies and cases where there was insufficient time to obtain consent were excluded. Antenatal details of the mothers including maternal age, gravida, parity, receipt of antenatal care, complications of pregnancy, evidence of fatal distress, mode of delivery, and relevant investigations done in the pregnant mother, including ultrasonography were noted.

Eligible newborns were randomized into one of two groups (suctioning first or drying first) using random permuted blocks of 4, 6 or 8. The randomization sequence was prepared by an independent person not involved in the conduct of study. Allocation of newborns to different groups was done using serially numbered, opaque and sealed envelopes.

All deliveries were attended by two pediatric residents who were trained in neonatal resuscitation as per AAP guidelines. After delivery, if a newborn was found to be apneic or limp, the umbilical cord was clamped immediately and baby was placed under radiant warmer with neck slightly extended. By this time, one member of the team or a staff nurse opened the sealed envelope and further sequence of initial steps was performed as per randomization. During resuscitation, oxygen saturation was recorded from right hand or wrist, using hand-held Masimo pulse oximeter. For suctioning, wall mounted suction was used with a pressure not exceeding 100 mm of Hg. Each attempt at suctioning was limited to no more than 3 to 5 seconds, and care was taken to avoid vigorous or deep suctioning. We used a pre-warmed towel to dry the baby and removed wet towel to prevent further heat loss. After completing initial steps including tactile stimulation, if the baby continued to have apnea/gasping breathing or bradycardia (heart rate 100/minute), positive pressure ventilation was initiated. The remaining steps of resuscitation were similar in the two groups.

All neonates were admitted to NICU and were monitored and managed as per unit protocol. Babies were kept under radiant warmer with temperature set at 36.5ºC. Babies were monitored using a predesigned proforma for heart rate, oxygen saturation, temperature, capillary refill time, respiratory rate, and other signs of respiratory distress (chest wall retractions, grunting and bilateral air entry into the chest). Investigations included blood glucose, serum electrolytes, chest X-ray, sepsis workup (complete blood count, absolute neutrophil count, C-reactive protein and blood culture), if needed, arterial blood gas analysis and renal function tests. Other tests included echocardiography and cranial ultrasonography, as and when necessary. Respiratory support was given via oxygen hood, continuous positive airway pressure (CPAP), high flow nasal cannula (HFNC) or mechanical ventilation as per need. Intravenous fluids, parenteral nutrition, and feeding were provided. Complications were managed as per our unit protocol.

Primary outcome variable was composite outcome of admission hypothermia or respiratory distress at 6 hours of age. Hypothermia was defined as rectal temperature <36.5ºC. Rectal temperature was recorded using a low-reading rectal thermometer. Respiratory distress was defined as presence of at least one of the following: respiratory rate >60/minute, chest wall retractions and grunting. Secondary outcome variables included the need and duration of positive pressure ventilation, chest compressions and medication use during delivery room resuscitation, oxygen saturations during first 10 minutes of age, incidence of hypothermia and respiratory distress within 24 hours, development of complications and duration of hospital stay and outcome.

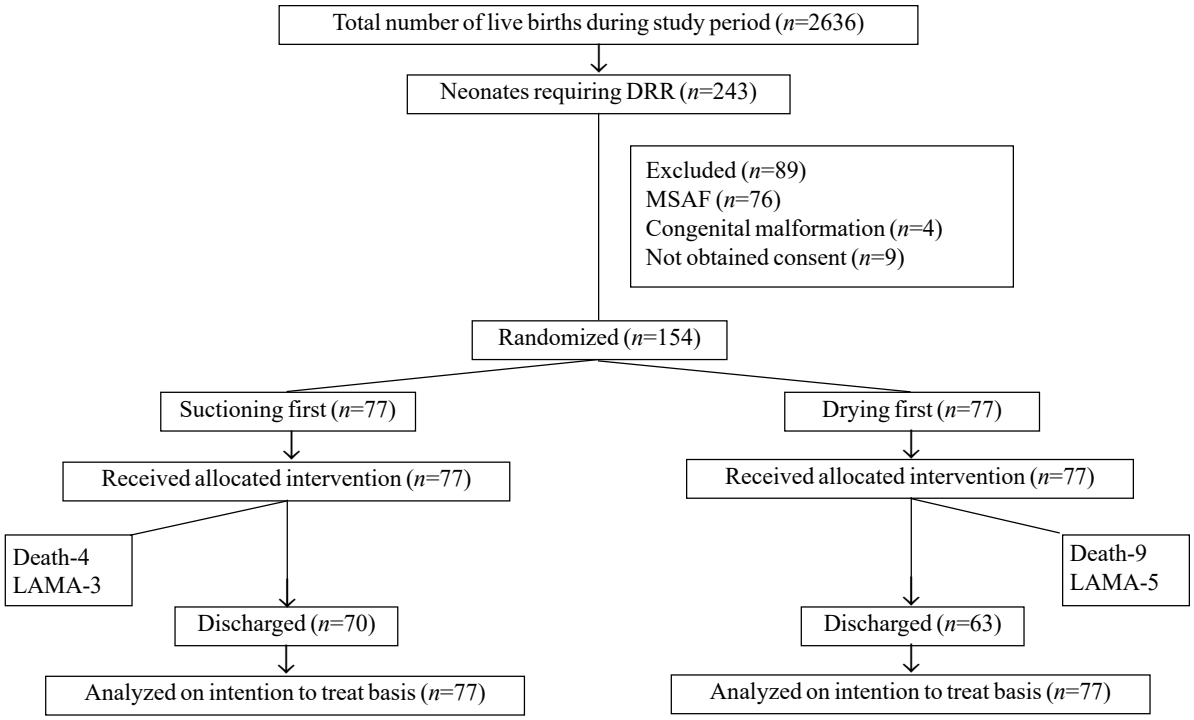
Assuming an expected incidence of the need for delivery room resuscitation of 10% [3], a precision (d) of 0.05 and level of confidence of 95%, the sample size calculated was 138. Considering 10 % attrition rate, the total sample size was 154 newborns, 77 in each group *(www.kck.usm.my/ppsg/statistical_resources/SSCPS version1001.xls).*

Statistical analyses: The statistical program SPSS version 16.0 was used for analysis. Independent samples t test/Mann Whitney U test and Fisher exact test were used as applicable to compare parametric and non-parametric variables. Risk ratios (RR) with 95% CI were calculated for outcome variables. The data were analyzed on intention to treat basis. A P value of <0.05 was considered statistically significant.

RESULTS

Each group included 77 neonates, and all neonates received their allocated intervention (**Fig. 1**). Both the groups were similar with respect to maternal and neonatal characteristics, except the incidence of eclampsia, which was significantly higher in suctioning first group (**Table I**).

The composite outcome of hypothermia at admission or respiratory distress at 6 hours of age was similar in suctioning first and drying first, respectively [46 (59.7%) vs. 55 (71.4%); RR (95% CI), 0.84 (0.66-1.05); P = 0.13]



DRR: Delivery room resuscitation; MSAF: Meconium stained amniotic fluid; LAMA: Left against medical advice.

Fig.1 Flow of participants in the study.

Table I Maternal and Neonatal Characteristics of Study Participants

	Suctioning first (n=77)	*Drying first (n=77)*
Maternal characteristics		
*Maternal age, y	26.2 (4.5)	25.9 (4.1)
#Gravida	2 (1 -3)	2 (1 -3)
PIH/ Pre-eclampsia	7 (9)	6 (7.7)
Eclampsia	21(27.2)	10 (12.9)
Antepartum hemorrhage	4 (5.1)	5 (6.4)
PV leak >18 h	11 (14.2)	16 (20.7)
Maternal fever	2 (2.6)	2 (2.6)
Fetal distress	10 (12.9)	15 (19.4)
Cesarean section	56 (72.8)	53 (68.9)
Neonatal characteristics		
*Gestation, wk	35.4 (3.5)	34.7 (3.1)
*Birthweight, g	2123 (67)	2131 (64)
Male gender	43 (55.8)	46 (59.7)
#APGAR score		
1 min	4 (3-5)	4 (3-6)
5 min	7 (6-8)	8 (7-9)

*Values in no. (%) except*mean (SD) or #median (IQR); PIH: Pregnancy induced hypertension; PV: Per vaginal; P>0.05 for all variables between the two groups.*

(**Table II**). Among the secondary outcome variables, oxygen saturation within 10 minutes after birth, incidence of hypothermia at admission, and respiratory distress at different time intervals during first 6 hours of age were also similar (P>0.05) (**Table II**). On admission to NICU, 26 (33.8%) neonates in suctioning first group and 33 (42.8%) neonates in drying first group experienced hypothermia (**Table II**). By one hour of age hypothermia was observed in 13 (16.9%) and 14(18.1%) neonates, respectively. The differences were not significant.

Resuscitation details for both the groups are summarized in **Table II**. No significant difference was observed in the extent of delivery room resuscitation received by both the groups. Four (5.2%) neonates expired in the suctioning first group, whereas 9 (11.7%) expired in the drying first group (P>0.05) (**Table II**).

DISCUSSION

The present study demonstrated that suctioning first or drying first during initial steps of delivery room resuscitation result in comparable rates of composite outcome of hypothermia at NICU admission or respiratory distress at 6 hours of age in depressed newborns. We could not find any study in literature which investigated the comparative efficacy of drying versus suctioning as a first intervention during delivery room resuscitation.

WHAT IS ALREADY KNOWN?

- During delivery room resuscitation, the sequence of performing suctioning and drying is based on expert opinion rather than any evidence.

WHAT THIS STUDY ADDS?

- Suctioning first or drying first during delivery room resuscitation has comparable effect on the composite outcome of admission hypothermia or respiratory distress at 6 hours of age in newborn infants.

Table II Outcome Variables in Neonates in the Two Study Groups

Variable	*Suctioning first (n =77)*	*Drying first (n=77)*	*Relative risk (95% CI)*
Composite outcome, *n* (%)	46 (59.7)	55 (71.4)	0.84 (0.66-1.05)
Hypothermia at admission	26 (33.8)	33 (42.8)	0.79 (0.52-1.18)
Respiratory distress at 6 h	34 (44.2)	38 (49.4)	0.89 (0.64-1.25)
Oxygen saturation (%)[a]			
At 1 min	60 (56-63)	59 (54-63)	-
At 2 min	68 (64-72)	68 (64-72)	-
At 5 min	84 (82-87)	84 (81-86)	-
At 10 min	94 (92-95)	93 (92-95)	-
Bag and mask ventilation	73 (94.8)	75 (97.4)	0.97 (0.91-1.04)
Duration, s[a]	30 (30-30)	30 (30-60)	-
Bag and tube ventilation	50 (64.9)	43 (55.8)	1.16 (0.89-1.50)
Duration, min[a]	5 (5-10)	5 (1-10)	-
Chest compressions	0	4 (5.1)	0.11 (0.01-2.03)
Adrenaline usage	0	2 (2.5)	0.20 (0.01-4.10)
Death	4 (5.2)	9 (11.7)	0.44 (0.14-1.38)

All values in no (%) except [a]median (IQR); RR: Relative risk; Composite outcome - hypothermia at admission or respiratory distress at 6h of age; P>0.05 for all variables between the two groups.

The incidence of hypothermia was quite high in our study cohort, as compared to previous data from India [9-11]. Although newborns were resuscitated under radiant warmer, they were transported to NICU without any additional source of heat, which might have led to higher incidence of admission hypothermia in our study population. Preponderance of preterm newborns in study population might have added to the burden of hypothermia in study cohort. We did not measure the temperature of newborns in delivery room before transporting them to NICU. The possibility that some babies developed hypothermia during resuscitation cannot be excluded. It is well known that hypothermia at admission is associated with poor outcome [4-6]. We did not use polyethylene wraps to maintain temperature of extremely preterm newborns at birth, which obviates the need for drying in these cases, as drying was applied as one of the comparator interventions in the present study.

We observed no difference in the extent and duration of resuscitative interventions between the two groups. The mortality rates were also comparable in the two groups.

To conclude, it makes little difference to the outcome whether newborns are suctioned first or dried first and either approach is acceptable. However, to bring uniformity and consistency among health professionals and to avoid confusion in the implementation of NRP guidelines, we should follow an approach which is in agreement with standard guidelines unless there is a definite evidence of preferring one approach over the other.

Contributors: AK, SB: conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript; RPY: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript; TBS: analyzed the data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical clearance: Institutional Ethics Committee of Institute of Medical Sciences, BHU; No. Dean/2014-15/EC/1455 dated 17 October, 2015.
Funding: None; *Competing interests*: None stated.

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RESEARCH PAPER

Mutation and Phenotypic Spectrum of Patients With RASopathies

MEENAKSHI LALLAR,[1] SUNITA BIJARNIA-MAHAY,[1] IC VERMA,[1] KAUSHIK MANDAL[2] AND RATNA DUA PURI[1]
From [1]Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi; [2]Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Correspondence to: Dr Ratna Dua Puri, Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi, India.
ratnadpuri@yahoo.com
Received: March 30, 2020;
Initial review: April 29, 2020;
Accepted: July 27, 2020.

Objective: To examine the common and specific clinical features, mutation spectrum and genotype-phenotype correlation in Noonan syndrome and related RASopathies. **Participants**: Records of 30 patients with clinical diagnosis of Noonan syndrome and related RASopathies presenting over a six-year period at a tertiary care medical genetics centre were reviewed. Detailed clinical phenotype evaluation and genetic testing (*PTPN11* sequencing or next generation sequencing) was done. The genetic results were used to classify the patients. **Results**: Noonan syndrome was confirmed in 22 patients, 5 had cardiofaciocutaneous syndrome and 3 had Noonan syndrome like disorder with loose anagen hair. The molecular diagnosis was confirmed in 27 patients. Mutations in *PTPN11* gene were confirmed in 57.8 % patients. Developmental delay, cardiac defects, ectodermal abnormalities and coarse face was the predominant phenotype. Noonan syndrome like disorder with loose anagen hair was clinically identifiable by the sparse, slow growing hair and caused by one recurrent SHOC2, c.4A>G mutation. **Conclusions**: Noonan syndrome and other RASopathies should be suspected in patients with short stature, cardiac defects, typical facial dysmorphism with or without ectodermal involvement.

Keywords: *Cardio-facio-cutaneous syndrome, Noonan syndrome, PTPN 11 gene, RAS/MAPK pathway.*

Published online: **August 06, 2020;** ***PII:*****S097475591600221**

RASopathies are a group of clinically defined genetic disorders with a prevalence of 1 in 1000. The patients present with a varying combination of craniofacial, cardiac, skin and skeletal phenotypes. RASopathies include neurofibromatosis type 1 (NF1), Noonan syndrome (NS), Noonan syndrome with multiple lentigines, Noonan syndrome like disorder with loose anagen hair (NSLAH), Legius syndrome, Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC) and capillary malformation arteriovenous malformation (CMAVM) [1]. All these disorders have an autosomal dominant pattern of inheritance with variable expression and penetrance.

In this study, we report on common phenotypes, diagnostic features, clinical differentiation, mutation spectrum and genotype – phenotype correlation in patients with Noonan syndrome and related RASopathies seen over a six-year period.

METHODS

In this medical record review the clinical data of patients presenting with Noonan syndrome and related disorders in our genetic clinic from 2014 through 2019 was collected on a structured defined proforma. We excluded patients with neurofibromatosis as they form a distinct, easily identifiable, group. Informed consent was taken at the time of evaluation and molecular testing from all patients/ parents included in the study. The *PTPN11* gene was sequenced or next-generation sequencing (NGS) using a panel/clinical-exome approach on Illumina HiSeq2500 was performed. All the molecular variants were classified according to the recommended method of the American College of Medical Genetics and Genomics [2]. Patients who did not undergo molecular testing were classified according to the predominant phenotype. The clinical data is represented as proportions for frequency of phenotypic features and mutations.

RESULTS

The study cohort included 30 patients, (23 males); 22 of which (16 males) were diagnosed with Noonan syndrome, five patients with CFC and three patients with NSLAH. The mean age of patients in the cohort was 7 years [range 4 months to 23 years]. Mutations were identified in 27 patients. In two patients only *PTPN11* sequencing was done, which was negative and one patient did not consent for molecular testing.

The age of diagnosis of Noonan syndrome patients ranged from 4 months to 23 years. The predominant clinical features were cardiac disease (82%), short stature (77%),

facial dysmorphism (64%), skeletal features like scoliosis, webbed neck, chest defects (pectus and wide space nipples) (45%), mild developmental delay (27%), coagulation abnormalities (23%) and cryptorchidism (14%) (**Table I**). The commonest cardiac defect was pulmonary stenosis (39%, 7/18) followed by hypertrophic cardio-myopathy (33%, 6/18). Skin features like *café au lait* macules (size varying from 5-10 mm, more than three) and hyperkeratosis were present in 27% patients. One child presented at 3 months of age with juvenile myelo-monocytic leukemia (JMML) syndrome (**Table I**). Antenatal features of cystic hygroma, bilateral choroid plexus cyst and dilated single lymphatic sac were documented in one child with Noonan syndrome related short stature.

Facial dysmorphism was present in 14 (64%) patients. (**Fig.1 a, b**). The four most characteristic features (hypertelorism, down-slanting palpebral fissures, ptosis, and low-set, posteriorly rotated ears) were present together in only four patients; 10 had atypical facies with one or two of the above dysmorphic features. Down-slanting palpebral fissures were seen in 64% and hypertelorism in 57%. Two patients had coarse facies and ectodermal features and were initially suspected as CFC syndrome but were later diagnosed as Noonan syndrome based on genetic testing (*RAF1* and *SOS2,* respectively) (**Fig. 1b**).

Table I Genotype Phenotype Correlation in 22 Patients with Noonan Syndrome

Phenotype	*N=22*	*Genes involved (genotype)*
Facial dysmorphism	14 (65%)	*RIT1* (1), *SOS2* (1) and *SOS1* with 45,
Typical gestalt, with all three cardinal features	4	X mosaic karyotype (1), *PTPN11* (1)
(hypertelorism, downslant palpebral fissure, ptosis		*PTPN11* (8)
and posteriorly rotated, low set ears)		*SOS1* (1), *RIT1* (1), *RAF* (1), *SOS1* (1),
Isolated hypertelorism	8	*PTPN11 (5)RIT1* (1),
Isolated downslant palpebral fissure	9	
Isolated ptosis	5	*SOS2* (1), *PTPN11* (3)*SOS2* (1),
Coarse facies	2	*RAF1* (1)*RAF1 (1)*
Relative macrocephaly	1	
Short stature[a]	17 (77%)	*PTPN11* (11). *SOS1* (2), *RAF1* (1),
		KRAS (1) and two mutation negative NS patients.
Cardiac defects	18 (82%)	
Pulmonary stenosis	7	*PTPN11* (3) and *SOS1 (2), RIT1* (1), *RAF1* (1)
Hypertrophic cardiomyopathy (HCM)	6	*PTPN11* (5) and *RIT1* (1)
Atrial septal defect	3	*PTPN11* (3)
Atrioventricular canal defect	1	*PTPN11 (1)*
Double outlet right ventricle with VSD	1	*SOS2 (1)*
Skeletal defects	9 (41%)	
Chest deformities (pectus, and wide space nipples)	4	*PTPN11*(3), *KRAS* (1)
Webbed neck	3	*PTPN11* (3)
Scoliosis	2	*PTPN11* (1), *SOS2* (1)
Developmental delay/intellectual disability	6 (27%)	*SOS2* (1), *RIT1* (1), *KRAS* (1),
Mild	6	*PTPN11* (3).
Cryptorchidism	3 (14%)	*PTPN11* (2), *SOS2* (1)
Renal anomalies	2 (9%)	
Vesico ureteric reflux with hydronephrosis	1	*KRAS* (1)
Renal echogenicity on fetal scan	1	*PTPN11* (1)
Coagulation abnormalities	5 (23%)	
Prolonged APTT/PT	2	*SOS1*(1), *SOS2* (1)
Factor IX deficiency	1	*PTPN11* (1)
Epistaxis	2	*PTPN11*(2)
Skin anormalites	6 (27%)	
Multiple cafe au lait	3	*PTPN11* (2), *RAF* (1)
Multiple nevi	2	*SOS1* and 45, X mosaic (1) and *PTPN11* (1)
Hyperkeratosispilaris, keloid and ulerythemaophryogenes	1	*SOS2* (1)
Juvenile myelomonocytic leukemia (JMML)	1 (5%)	*PTPN11* (1)

NS: Noonan syndrome; VSD: ventricular septal defect ; [a]Patients with SOS2 and RIT1 mutation had normal height.

Five patients of CFC syndrome were identified. All had developmental delay, coarse facies and ectodermal findings (**Web Table I**) (**Fig. 1c**). All the three patients with NSLAH had mild developmental delay, coarse facies and sparse, slow growing hair (**Fig. 1 d, e**). One patient additionally had a history of thrombotic stroke (**Web Table I**).

Of the 22 Noonan syndrome patients, mutations were present in 19 (86%) patients. These were present in *PTPN11* (11/19), *SOS1* (2/19), *SOS2* (2/19), *RIT 1* (2/19), *KRAS* (1/19) and *RAF1* (1/19) genes. The mutations and related information are listed in **Web Table II**. All the identified mutations are previously reported. The two CFC syndrome patients had the most common *BRAF* mutation, c.770A>G, p.Gln257Arg. All three NSLAH patients harbored the recurrent *SHOC2*, c.4A>G, p.Ser2Gly mutation (**Web Table I***).*

DISCUSSION

The clinical diagnosis of Noonan syndrome is traditionally on a gestalt recognition of the characteristic facial dysmorphism, cardiac malformations and short stature. Associated ectodermal features suggest CFC and NSLAH as the probable diagnosis [3,4]. In this cohort, Noonan syndrome was the commonest RASopathy (73%), followed by CFC (17%) and NSLAH (10%). The most consistent and typical facial features in the Noonan syndrome cohort were down-slanting palpebral fissures, ptosis and hypertelorism, similar to previous reports [5]. However, we also observed *PTPN11* mutation positive Noonan syndrome with atypical facies, including only hypertelorism, down-slanting palpebral fissures or ptosis. Another set of patients with mutations in uncommon Noonan syndrome genes like *RIT1, SOS1* and *SOS2* had the typical NS facial phenotype. A CFC like phenotype was seen with mutations in *RAF1* and *SOS2* associated NS suggesting a phenotypic overlap between NS and CFC. As the facial profile in NS evolves with age, it alone may be insufficient to predict the genotype, but along with other systemic features, it can aid in the clinical diagnosis [6].

The predominant cardiac lesions in NS are pulmonary stenosis (PS) and hypertrophic cardiomyopathy (HCM). Early suspicion and echocardiography is important for appropriate management as PS and HCM in *PTPN11* related NS are seldom rapidly progressive and fatal [7]. Short stature was another predominant phenotype observed in this study, which may be due to growth hormone (GH) deficiency, neurosecretory dysfunction, or GH resistance. GH therapy is approved for Noonan syndrome and should be initiated early [8].

Renal abnormalities are described in 10-11% of cases of Noonan syndrome [9]. In the present study one patient with *KRAS* associated NS (NS-3) had bilateral grade 5 vesicoureteric reflux (VUR) with hydronephrosis. VUR leading to hydronephrosis is previously unreported in Noonan syndrome. It reiterates the need for multi-organ screening in malformation syndromes for early detection and management, and prevention of related morbidity [10]. In one patient (NS-9, *SOS2* mutation) with abnormal gait and brisk deep tendon reflexes, MRI brain showed bilateral thalamic hyperintensities. MRI changes in RASopathies are previously reported, but MRI brain is recommended only if there is abnormality neurological examination [12]. Bleeding abnormalities are reported in almost 43% patients of NS while on laboratory testing abnormal coagulation profile is described in upto 90% patients [13]. One patient with NSLAH had a history of thrombotic stroke. This previously unreported association is either incidental or a disease association and needs to be addressed in additional patient cohorts. Specific *PTPN11* gene mutations predispose to an increased risk of JMML in NS patients [14], but they have a favorable prognosis and better outcomes, highlighting the importance of this

Fig. 1 Variable facial dysmorphism in Noonan syndrome: (a) Boy with Noonan Syndrome with hypertelorism, ptosis, downslant palpebral fissures, low set posteriorly rotated ears (PTPN11, exon 3, c.218C>T), (b) Boy with Noonan syndrome with cardio-facio-cutaneous syndrome like phenotype – coarse face, woolly hair, ptosis, hypertelorism, low set posteriorly rotated ears, (SOS2, Exon 6, c.800T>G), (c) Boy with cardio-facio-cutaneous syndrome - coarse face, hypertelorism, downslant eyes, low set ears, coarse hair (BRAF, exon 15, c.1802A>T) and (d), (e) Boy with Noonan syndrome like disorder with loose anagen hair - coarse face, hypertelorism, downslant eyes, relative macrocepahly and the distinct sparse slow growing hair.

WHAT THIS STUDY ADDS?

- Most Noonan syndrome patients may not have all the typical facial gestalt findings, and Hypertrophic cardiomyopathy is as prevalent as pulmonary stenosis.
- More than half of Noonan syndrome patients have mutations in exon 3, 8, 12 and 13 of *PTPN11* gene.

correlation in management protocols [15].

A previous Indian study reported exons 3 and 13 of *PTPN11* gene as the mutation hot spot in 11 Noonan syndrome patients [16]. Another study identified exons 3, 8 and 13 of *PTPN11* gene with the maximum pathogenic variants in 107 Indian patients [17]. Exons 3, 8, 12 and 13 were the hotspots exons and the commonest mutation was a previously reported, c.218C>T in exon 3 in this series. Additionally, the recurrent *SOS2*, c.800T>A mutation of NS-9 was also present in two patients [18]. We observed that most mutations in Indian patients were similar to those reported in worldwide literature.

Limitations of this study include a small number of predominantly NS patients with less representation of CFC and NSLAH. Also the absence of longitudinal follow up data limits information on management outcomes and prognosis of the patients.

Noonan syndrome should be suspected in patients with short stature (cardiac malformations, primarily pulmonary stenosis and hypertrophic cardiomyopathy), skeletal defects and facial dysmorphism (usually includes hypertelorism and down slanting palpebral fissures). *PTPN11* hot spot exon testing identifies mutations in more than half of Noonan syndrome patients.

Contributors: ML: study design, article writing, data collection; ICV: article review, critical input, study design, data collection; RDP: article critical review and writing, data collection, study design; SBM: article critical review, data collection; KM: article critical review, data collection, PTPN11 test. All authors approved the final version of manuscript.
Funding; None; *Competing interest*; None stated.

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Web Table I Genotype Phenotype Correlation in Cardio-facio-cutaneous Syndrome (CFC) and Noonan Syndrome – Like Disorder With Loose Anagen Hair (NSLAH)

Disease	*Mutation,*	*No.*	*Age, sex*	*Face, skin and hair*	*Cardiac*	*Cognition and development*
CFC(*n*=5)	*BRAF,* exon 6, c.770A>G, commonest, CFC-1	2	1 y, F	Coarse face, Curly hair bulbous nose tip	Pulmonary stenosis	Severe developmental delay, failure to thrive, feeding difficulty developmental
			5 y, M	Coarse face, curly hair, ichthyotic skin hypopigmented facial macules	Pulmonary, stenosis Septal hypertrophy	delay, failure to thrive
	BRAF, exon 15, c.1802A>T, CFC-1	1	2 y, M	Coarse face, curly hair,		Developmental delay, failure to thrive
	MAP2K1, Exon 3 . 389A>G, Pathogenic reported CFC-3	1	6 y, M	Coarse face, curly hair , hyperkeratosis Papilloma	Atrial septal defect	Developmental delay
	MAP2K2 Exon 6, c.619G>A, likely pathogenic CFC-4	1	13 y, M	Coarse face Hyperkeratosis Curly hair Squint operated		Developmental delay, behavioral abnormalities
NSLAH (*n=3*)	*SHOC2,* c.4A>G	3	3 y, 4 y and 5 y,	Coarse facies Ptosis, sparse slow growing hair, hyper-keratosis, Café au lait spots, Thick gums, Thrombotic stroke Chin hemangioma,	Atrial septal defect (*n*=2)	Mild developmental delay

Web Table II Mutation Spectrum of Noonan Syndrome (*N*=19)

Gene	*No. of cases*	*Mutation*	*ClinVarId, Accession date – (23.5.2020)*	*OMIM*
PTPN11 (*n*=11; 56%) ENST00000351677	3	Exon 3, c.218C>T	VCV000013334.6	NS-1(163950)
	1	Exon 3, c.179G>T	VCV000055797.2	
	1	Exon 2, c.124A>G	VCV000040482.3	
	1	Exon 8, c.923A>G	VCV000013327.8	
	1	Exon 8, c.922A>G	VCV000013326.12	
	2	Exon 12, c.1403C>T	VCV000013331.11	
	1	Exon 13, c.1510A>G	VCV000040562.15	
	1	Exon 13, c.1528C>G	VCV000040566.7	
SOS1(*n*=2; 11%) ENST00000426016	2 (one Turner mosaic)	Exon 16, c.2536G>A Exon 11, c.1654A>G	VCV000040706.6 VCV000012871.7	NS-4(610733)
RIT1 (*n*=2; 11%) ENST00000368323	2	Exon 4, c.221C>G Exon 5, c.321G>A	VCV000060506.8 VCV000190305.2	NS-8 (615355)
SOS2 (*n*=2; 11%) ENST00000216373	2	Exon 6, c.800T>A Exon 6, c.800T>G	VCV000209092.3 VCV000577079.2	NS-9(616559)
KRAS (*n*=1; 6%) ENST00000311936	1	Exon 2, c.13A>G	VCV000012596.3	NS-3(609942)
RAF1 (*n*=1; 6%) ENST00000251849	1	Exon 17, c.1837C>G	VCV000013960.5	NS-5(611553)

RESEARCH PAPER

Karyotype-Phenotype Correlation in Turner Syndrome at a Single Center in Eastern India

Sunetra Mondal, Rana Bhattacharjee, Subhankar Chowdhury and Satinath Mukhopadhyay

From Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India.

Correspondence to: Dr Satinath Mukhopadhyay, Department of Endocrinology and Metabolism, IPGME&R and SSKM Hospital, Kolkata, West Bengal 700 020, India. satinath.mukhopadhyay@gmail.com

Received: November 25, 2019; Initial review: January 27, 2020; Accepted: September 28, 2020.

Objective: To describe clinical features in Indian girls with Turner syndrome along with the phenotype-karyotype correlation. **Methods**: 103 girls with Turner syndrome were divided into karyotype-groups: Classic (45X), 45,X/46,XX mosaics, isochromosomeXq (46,X,iXq and 45,X/46,X,iXq mosaics), 45,X/46,XYmosaics and structural defects, and analyzed for phenotypic differences. **Results:** Majority (44.1%) had classic karyotype followed by isochromosome-Xq (26.5%). Classic Turner syndrome had higher prevalence of most skeletal and cutaneous stigmata, cubitus valgus (68.3%) and multiple nevi (68.2%) being the commonest. Bicuspid aortic valve was most common in 45,X/46,XX mosaics (5/15, 33.3%), and aortic coarctation in classic TS (3/42, 7.2%). Congenital renal anomalies occurred mostly in classic TS (6/42,14.3%). Overt hypothyroidism, conductive deafness and recurrent otitis media were commonest in isochromosomes (P<0.03). 45,X/46,XY mosaics had highest IQ (P<0.005). **Conclusion:** We report some novel associations of karyotype with non-endocrine parameters in Turner syndrome. In resource-limited settings, underlying karyotype may help prioritize screening investigations in girls with Turner syndrome.

Keywords: *Congenital anomalies, Karyotype, Skeletal stigmata, Turner syndrome.*

Turner syndrome is characterized by short stature and multiple skeletal deformities, gonadal failure, congenital anomalies of cardiovascular and urinary system, neurocognitive abnormalities, autoimmune diseases, metabolic abnormalities and osteoporosis [1]. There is variability in the clinical manifestations of Turner syndrome depending on the karyotype and other factors like parental origin of the X chromosome and epigenetic modification [2]. The extra-endocrine manifestations in Turner syndrome like the cardiac or renal deformities and autoimmune disorders are important to detect early for timely intervention and improving longevity. Results of studies trying to correlate genotype with phenotype in Turner syndrome have often been inconsistent although there are some established associations like increased autoimmune disorders in isochromosomes, mental retardation in ring chromosomes and an overall milder presentation in 45,X/46,XX mosaics compared to classic Turner syndrome (45,X) [3-5].

There are few studies on Turner syndrome from India [6,7]. The current study reports the skeletal stigmata and different congenital anomalies, otologic and neurocognitive aspects of Turner syndrome in India and analyzes inter-karyotype phenotypic differences.

METHODS

Karyotype analysis was performed according to the International System for Human Cytogenetic Nomenclature (ISCN, 2005) guidelines [8] on 20-30 metaphase cells. Ethical clearance for this study was obtained from the institutional ethics committee of IPGME&R, Kolkata. Skeletal stigmata were assessed as per standard definitions [9]. Echocardiography with color doppler assessment was used to detect congenital cardiac malformations and assessment of aortic root diameter. For girls older them 15 years, Weschler adult intelligence Score (WAIS IV) was used whereas for those aged between 5-15 years, the Malin intelligence scale for Indian children (MISIC), a validated Indian adaptation of Weschler intelligence scale for children (WISC), was used for intelligence testing [10].

The patients were grouped into categories depending on their karyotype including classic-Turner syndrome (45,X), 45,X/46,XX mosaics, 45,X/46,XY mosaics, isochromosome-Xq (46,X,iXq or 45,X/46,X,iXq), structural defects of X (del-Xq or ring chromosomes) and complex karyotypes. The results obtained for the parameters were analyzed for differences between classic and non-classic Turner syndrome and among the first four karyotypes.

Statistical analyses: Statistical analyses were done using GraphPad Prism v.6e. Differences between karyotypes were assessed using unpaired t-test, ANOVA, or Chi-square test as applicable. *P* value <0.05 was considered as significant.

RESULTS

Of 103 patients with Turner syndrome, majority (44.1 %) were classic Turner syndrome followed by those with isochromosome-Xq (26.2%) and 45,X/46,XX-mosaics (17.6%). The mean (SD) age of presentation was 14.8 (3.97) years, upto 98% of the patients presenting due to gonadal failure (74%) or short stature (24%). Only 2% of the girls presented due to associated comorbidities or complications, chiefly cardiac. The youngest age of diagnosis was 6 years; diagnosed during evaluation for coarctation of aorta.

Cubitus valgus (68.3%) and multiple nevi (68.2%) were the most prevalent stigmata. Classis TS had a significantly higher prevalence of short fourth meta-carpals/metatarsals, high arched palate, edema of hands/feet, low posterior hairline, low set ears and shield chest. We also noted some atypical stigmata like absent terminal phalanges of digits and terminal transverse defect of lower limb.

Congenital cardiac malformations were found in 21.5% patients, most common malformation being bicuspid aortic valve (*n*=6) followed by septal defects (ASD/VSD) (*n*=6) and coarctation of aorta (CoA) (*n*=4). Others included root dilatations with regurgitation of aortic and tricuspid valve and mitral valve prolapse. Four patients had multiple cardiac malformations. 45,X/46,XX mosaics had higher prevalence of BAV (5, 33.3%), (*P*=0.004 vs classic Turner Syndrome). Most cases of aortic coarctation occurred in those with classic Turner syndrome (75%) (**Table I**). Classic Turner syndrome had the highest aortic root diameter (27.55 mm +/- 4.03). ECG abnormalities were seen in 11.2% - mostly left-ventricular-hypertrophy (LVH) or Right-axis-deviation (RAD) secondary to coarctation of aorta or septal defects, or non-specific ST-T wave changes. Hypertension was seen in seven patients, out of which three had coarctation of aorta. Neither hypertension nor ECG changes had any karyotype preponderance.

Classic Turner syndrome had a slight majority of congenital anomalies of kidney and urinary tract (CAKUT) (19 % vs 6.1 % vs non-classic TS, *P*=ns). Renal anomalies were mostly seen in classic TS (14.3% vs 2.4%, *P*=0.04). Horseshoe kidneys (9.5%) were commonest, followed by unilateral fused kidneys (4.8%). Duplicated pelvicalyceal system, PUJ abnormalities occurred equally in classic and non-classic karyotypes.

Upon pure tone audiometry testing, 11% had conductive hearing loss (HL) whereas sensorineural hearing loss (SNHL) was seen in 18.2% and mixed HL in 7.3%. Upto 18.4% had recurrent otitis media. There was a significantly higher prevalence of recurrent otitis media and conductive deafness in isochromosomes (both 47.3%, P_{both}<0.03). Classic TS had slightly higher prevalence of sensorineural hearing loss (SNHL) (27.3%, *P*> 0.05).

Celiac screening with serum tissue-transglutaminase IgA-antibody were negative in fifty asymptomatic patients tested (with normal total IgA levels). One patient with malabsorptive symptoms revealed villous atrophy and lymphocytic infiltrates on duodenal biopsy.

Thyroid antibodies (anti- TPO Ab and/or anti-Tg Ab) were found in 52.9% of the girls, 28.2% had overt hypothyroidism and 23.5% had subclinical hypothyroidism. One patient with classic TS had Graves' disease.

Table I Prevalence of Phenotypic Abnormalities in Different Karyotype of Turner Syndrome (*N*=103)

Karyotype group (n)	*Classic TS (n=43)*	*Non-classic TS (n=55)*	*XO/XX mosaics (n =18)*	*Iso-chromosome Xq (n=25)*	*XO/XY mosaics (n=6)*
Cardiac malformations, *n* (%)	23.8	20	46.7[a]	4.1	16.7
Aortic root diameter (mm)	23.8 (2.4)[a]	23.5 (2.5)	24.8 (3.1)	22.5 (1.8)	23.8 (2.4)[a]
Congenital anomalies of kidney and urinary tract, *n* (%)	19	6.1	6.7	0	0
Conductive hearing loss	10.8	31.6[a]	23	47.3[b]	0
Verbal IQ	88.2 (10.4)	87.7 (19)	71.1 (17)[c]	91.8 (13.8)	107.3 (11.6)[a]
Performance IQ	75.6 (8.4)	75.2 (14.9)	62.3 (12.2)[c]	78.9 (12.9)	89 (2.2)[a]
Arithmetic scores	79.9 (10.3)	77.9 (17.7)	62.9 (17.1)[c]	81.4 (12.5)	96.8 (8.1)[a]

All values in mean (SD) or as stated; TS: Turner syndrome; IQ: Intelligence quotient; [a]significant difference from classic TS (P<0.004); [b]significantly higher than classic TS (P=0.02); [c]significantly lower than classic TS (P<0.005).

WHAT THIS STUDY ADDS?

- This study provides data on clinical features of Turner syndrome from a large cohort of Indian patients.
- Karyotype may help prioritize some screening investigations in resource-constrained settings.

There were no significant differences in anti-thyroid antibody positivity or prevalence of autoimmune thyroid disease (AITD) [TPO/Tg positive and not euthyroid] among the karyotypes. Overt hypothyroidism was significantly higher for isochromosomes (52%, P=0.002) whereas subclinical hypothyroidism and euthyroidism with TPO/Tg-Ab positivity were both slightly higher in XO/XY mosaics (50% and 16.7%,P_{both}=ns).

Out of fifty patients studied, 42% had normal VIQ, only one patient had normal PIQ. 58% had a discordance between VIQ and PIQ (VIQ–PIQ>10). 45,X/46,XY mosaics had the highest and 45,X/46,XX mosaics the lowest Verbal and Performance IQ as well as arithmetic scores (P_{both}<0.005). We had a single case of ring chromosome in our cohort who had extremely low PIQ as well as extremely low VIQ. Of those with extremely low PIQ (PIQ<70), 28.6% were classic TS while 50% were 45,X/46,XX mosaic TS.

DISCUSSION

Though several studies have reported an increased severity of stigmata in classic TS, the differences of Turner's stigmata in different karyotypes have less clinical relevance. We had similar findings and in addition, we found some atypical skeletal stigmata like absent terminal phalanges of digits and terminal transverse defect of lower limb which might have a biologically plausible explanation related to compression of the developing limb bud by in-utero lymphedema or SHOX haploin-sufficiency.

CoA was seen almost exclusively in classic TS which is also reported in the Turkish registry [11] and cardiac malformations were overall more in classic TS in a study from Saudi Arabia [5]. There are predominantly two mechanisms leading to CCMs in TS. The first is jugular lymphatic-sac obstruction causing distension of the thoracic-duct which compresses the ascending aorta leading to coarctation. The other mechanism is haploinsufficiency of X chromosomal genes like *CASK* and *USP9X* which are important in regulating TGF-β-SMAD signalling pathway [12,13]. This leads to altered migration of neural crest cells into vascular smooth muscle and altered regulation of matrix proteins causing defective valve formation and root dilatation. It might be that the former mechanism is more important for coarctation, which is therefore more prevalent in classic TS who are more prone to in-utero lymphedema formation. The second mechanism probably explains the valvular/septal abnormalities. We also found a significantly higher aortic root diameter in classic TS. Developmental defects of the kidney but not collecting duct anomalies were higher in classic TS. Whether factors like obstruction of the tract of ascent of kidneys by distended lymphatic sac has any role to play in this is unknown.

The higher prevalence of conductive hearing loss in isochromosomes and classic Turner syndrome is explained by the fact that both these groups have a haploinsufficiency of Xp specific genes like *SHOX* which is expressed in the first two branchial arches. This leads to altered eustachian tube mechanics and abnormal shape of the palate which predispose to fluid accumulation in the ear leading to secondary infections and conductive hearing loss.

Though the prevalence of anti-thyroid antibodies was similar in all groups, an increased severity of autoimmune responses of the thyroid could explain an earlier onset and hence higher prevalence of overt hypothyroidism in isochromosomes. Interestingly, in a UK-based TS registry including adult TS only, isochromosomes had a lower prevalence of hypo-thyroidism whereas in an Iranian study, hypothyroidism was high among 45,X/46,XX and mosaic isochromosomes [3,14].

Almost all the girls tested had low PIQ. 45,X/46,XY mosaics had the highest and 45,X/46,XX mosaics the lowest VIQ, PIQ and arithmetic scores. Ours is the only Indian study on IQ in TS girls.There have not been many systematic studies on separate VIQ and PIQ assessment across different karyotypic variants in TS and age-appropriate battery of tests were not used. Individuals with TS are known to have an increased risk of selective impairment of non-verbal skills and performance IQ. A review by Ross, et al. [15] suggests that apart from hypoestrogenism, haploinsufficiency of genes on the short arm of the X chromosome (Xp) could be responsible for the hallmark features of the TS cognitive phenotype.

A limitation of our study was that cardiac MRI was not done to measure aortic size index. For celiac disease, we analyzed only anti-Ttg IgA and total IgA and did not

detect any positive case. The possibility exists that duodenal biopsies would have yielded more cases.

In developing nations like India, frequent monitoring for all comorbidities in Turner syndrome is difficult. Echocardiographic screening for congenital cardiac malformations should be done for all, but cardiac MRI with aortic size index estimation is a must for classic Turner syndrome patients, who have the highest prevalence of aortic coarctation and the largest aortic root diameter. IQ (verbal and performance) testing is most important for 45,X/46,XX mosaics. Similarly, frequent pure tone audiometry is most essential in the classic and isochromo-some Xq group. While annual thyroid function testing is recommended for all karyotypes of Turner syndrome, more frequent monitoring for overt hypothy-roidism may be necessary for Turner syndrome with isochromosome-Xq. We do not intend to underemphasize the importance of following existing guidelines for screening [20], but we suggest that our findings may help prioritize the most essential investigations in different karyotype groups.

Acknowledgements: Dr Dinesh Munian, Assistant Professor, IPGME&R, Kolkata and Dr Ajanta Halder, Professor, Department of Genetics, Vivekananda Institute of Medical Sciences, Kolkata for their opinion on karyotypes of the patients. Dr Pradip Mukhopadhyay for his support with the statistical analysis.

Ethics clearance: Institutional ethics committee of IPGME&R, Kolkata; No. IPGME&R/IEC/2017/098, dated February 16, 2017.

Contributors: SM: acquisition of data, analysis of raw data with interpretation and formulating the initial draft; RB: contributed to data collection, analysis and revising the draft; SC: contributed to the concept and design of the project and critical analysis of the data and draft; SM: was chiefly involved in data analysis, revising the data and draft critically for important intellectual content. All authors approved the final version of the manuscript.

Funding: None; *Competing interest*: None stated.

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RESEARCH PAPER

Economic Burden of Juvenile Idiopathic Arthritis in India

MOKSUDA KHATUN,[1] DEBADYUTI DATTA,[2] AVIJIT HAZRA,[3] PRAMIT GHOSH,[4] MUHAMMAD BIN SELIM,[5] AND RAKESH MONDAL[1]

From Departments of [1]Pediatrics and [4]Community Medicine, Medical College Kolkata; Department of Pediatrics, [2]NB Medical College and [5]Kakdwip Super Speciality Hospital; and [3]Department of Pharmacology, IPGMER and SSKM Hospital, Kolkata; West Bengal, India.

Correspondence to: Dr Rakesh Mondal, Pediatric Rheumatology Unit; Department of Pediatrics, Medical College Kolkata, West Bengal, India. ivanrakesh2001@gmail.com
Received: November 15, 2019; Initial review: December 11, 2019; Accepted: August 31, 2020.

Background: Published Indian studies on the economic burden of juvenile idiopathic arthritis (JIA) are lacking. **Methods**: A prospective observational study recruited pediatric patients aged from 1 to 12 years with JIA in the pediatric rheumatology clinic of a public sector tertiary care hospital. Direct healthcare costs and indirect costs for transportation, accommodation of the caregivers, and productivity loss for work absenteeism were assessed. **Results**: The proportions of direct annualized cost assessed in 60 patients (mean (SD) age 8.46 (2.24) year) spent on outpatient visits, blood tests, imaging investigations, other tests, medications and hospitalization were 0.85%, 12.8%, 9.0%, 2.9%, 41.7% and 32.7%, respectively. Direct healthcare costs for blood tests and medicine were lowest in oligoarticular JIA and highest in systemic onset JIA and (P=0.043 and 0.001 respectively). The direct and indirect costs were higher with the use of biologic agents (*n*=9) than in those without (*n*=51). **Conclusions**: JIA imposes considerable economic burden with the largest share attributable to medicines, and maximum in those with systemic onset JIA.

Keywords: *Cost analysis, Biologic agents, Pharmacoeconomic study, Financial burden, Medication cost.*

Published online: **September 16, 2020; *PII:*S097475591600246**

Juvenile idiopathic arthritis (JIA), the commonest rheumatic disorder in children, imposes a formidable burden on patients and caregivers in terms of reduced quality of life and economic hardship [1,2]. The financial burden is attributable to the cost of multiple clinic visits, laboratory tests, imaging investigations, expensive medications (biologics), occasional hospitalization, and work-absenteeism. The burden is particularly severe for patients with systemic onset JIA (sJIA) [1]. Literature on the economic burden of JIA are available from other countries [2,3] but are lacking from India. We, therefore, conducted this pharmaco-economic study of JIA patients attending a public sector hospital.

METHODS

This observational study was conducted between April, 2017 and March, 2018, in the pediatric rheumatology clinic of a tertiary-care teaching hospital in Eastern India. Patients aged 1-12 years and diagnosed with JIA were included after taking written informed consent from either parent. The study protocol was approved by the institutional ethics committee. The sampling strategy was purposive as children not accompanied by caregivers within the family and those with limited follow-up visits for at least 12 months were excluded. JIA subgroups were categorized as oligoarticular, polyarticular, systemic onset (sJIA), enthesitis related and undifferentiated.

Data were collected over a period of 12 months for direct healthcare costs and indirect costs. Direct healthcare costs covered six elements; out-patient clinic (OPD) visits, blood tests, imaging investigations, other tests, medications, and hospitalization. Most of the medications, investigations and hospitalization did not incur any costs as per the hospital's policy. The medication cost was calculated from the centralized procurement cost of the generic medicines supplied. The market prices of the brands supplied were considered at 20% discount for medicines supplied through local purchase. The cost of laboratory and imaging investigations were imputed from the government approved rates when offered by authorized public-private partnership units. The actual cost of investigations was recorded if done from outside. OPD visit costs were calculated at actuals which included the OPD registration charges and the expenditure on food and drink during the waiting time. Cost of hospitalization was applicable for only a proportion of patients and was inferred from the

bed charges (general pediatric ward) of three nearby not-for-profit hospitals in the non-governmental organization (NGO) sector. The costing was estimated to derive annualized costs and compared between different subgroups of JIA.

Indirect healthcare costs included transportation expenses for initial and follow-up visits for patients and their caregivers, and accommodation costs of the caregivers if from out-station. The productivity loss was calculated from the number of days of work-absenteeism and the loss of daily wages for daily wage earner caregivers or deduction from salary for salaried caregivers as declared.

Statistical analyses: Numerical variables were compared between biologic and no-biologic subgroups by Student unpaired *t* test or Mann-Whitney *U* test, depending upon whether normal distribution assumption was satisfied or not. Normality assumption was tested by Kolmogorov-Smirnov goodness-of-fit test. One-way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA, as applicable, was applied for comparison between the multiple JIA subgroups. Statistical significance was inferred if *P* value was less than 0.05.

RESULTS

A total of seventy children were approached which excluded three who didn't consent, four with unreliable records and three who were lost to follow-up, to finally include 60 (53.5% males) children in the study with mean (SD) age 8.46 (2.24) years. The mean (SD) of number of OPD visits were 12.5 (2.56) (range 7-20) and inpatient admissions ranged from 0-6. The mean (SD) number of OPD visits in sJIA subgroup was 13.2 (2) which was the maximum among all subgroups with most hospital admissions [median (IQR) 3 (0-6). The proportions of the total annualized cost incurred on OPD visits, blood tests, imaging investigations, other tests, medication and hospitalization were 0.8%, 12.8%, 9%, 2.9%, 41.7% and 32.7%, respectively.

The direct and indirect costs in the whole JIA cohort have been presented in **Table I**. The mean (SD) medication costs and hospitalization costs were Rs. 9011.5 (4217.53) and Rs. 8489.3 (4789.88) in patients with sJIA, which were highest than all other subgroups; P =0.001 and 0.090 respectively. The mean (SD) medication cost was lowest at Rs. 3225.1 (1046.96) in the oligoarticular subgroup as compared to sJIA subgroup; *P* <0.001. Children with oligoarticular did not require hospitalization. The medication and hospitalization costs were comparable between polyarticular, enthesitis related and undifferentiated types; *P* >0.05 (data not shown).

The median (IQR) transportation cost was highest for patients with sJIA and lowest in oligoarticular JIA [Rs. 2737 (2230-6040) and 1280 (1120-2000); *P* = 0.05]. The median (IQR) accommodation cost was Rs. 1585 (0-2876) in sJIA which was the highest among all subgroups; *P*=0.001. Self-declared income loss was comparable between subgroups. **Table II** compares the costs in JIA patients who received treatment with biologics (*n*=9) and those who did not.

DISCUSSION

The provisional cost analysis of JIA in a public-sector hospital revealed considerable economic burden, majorly for the cost of medicines. The burden was highest in patients with sJIA and was higher with uses of biologics.

The type of JIA and active joint count are predictors of direct costs, with higher costs for patients with

Table I Healthcare Related Costs (INR) for Children With Juvenile Idiopathic Arthritis (N=60)

Category	*Cost*
Direct costs	
OPD visits	120 (110-140)
Blood tests	1555 (1350-2340.5)
Imaging	772.5 (460-1453)
Other tests	312.5 (145-630)
Medicines[a]	6185.2 (2984.34)
Hospitalization	3168 (1522-5216)
Indirect costs	
Transport	2155.5 (1275-3000)
Accommodation	0 (0-1705)
Income loss	5195 (2890-7229)

Cost in median (IQR) or [a]mean (SD); OPD-Outpatient department.

Table II Healthcare Costs (INR) for Children With JIA According to Usage of Biologic Agents

Cost (INR)	*Treatment with biologics (n=9)*	*Treated without biologics (n=51)*
OPD visits	120 (120-120)	120 (110-140)
Blood tests	1350 (1247-1845)	1624 (1365-2465)
Imaging	550 (260-780)	825 (460-1467)
Medicines[a,b]	11737.14 (4518.74)	5844.47 (2107.93)
Hospitalization[b]	11956 (11210-12040)	2390 (1325-3268)
Transport[b]	2970 (2230-5132)	1722 (1270-2970)
Accommodation[b]	2400 (1600-3428)	0 (0-1257)

Data shown as median (IQR) and [a]mean (SD); [b]P value <0.05.

WHAT THIS STUDY ADDS?

- A provisional costs analysis of juvenile idiopathic arthritis in a public-sector teaching hospital revealed considerable economic burden, which was higher in systemic onset JIA and with the use of biologics.

polyarthritis (rheumatoid factor positive or negative) or sJIA [4]. The cost increases with disease activity, disease duration, and time period from symptom onset to first pediatric rheumatologist visit [5].

The major share of the total direct healthcare cost burden was accounted for by medicines in the present study, similar to other studies [4-6]. The investigation costs tend to be relatively higher in the developed countries. With the increasing availability and use of biologics for more severe disease, medication costs can be expected to further increase.

A study [7], from New England reported that out-patient cost in JIA was 3.3 times higher than the inpatient costs. The mean in-patient cost comprising hospitalization and medicine cost was higher than the outpatient cost in the present study when all the cases were pooled together. The direct healthcare costs accounted for 46% of total costs, direct non-healthcare costs for 26.4% and productivity losses for 27.6% in another study in the United Kingdom [6]. A German study [5] also indicated considerable proportion of indirect cost due to time lost from work.

In India, studies on economic burden of childhood diseases are scarce. The growth velocity is significantly reduced in seropositive JIA subjects [8]; treatment for which is costly. A recent systematic review [10], also concluded considerable economic impact of JIA with data largely reflecting European and North American costs.

The present study was conducted in a government hospital where the salary of professional personnel and other logistical costs were not accounted for. The estimated costs would be invariably less than the costing in private set-ups. The expenditure on evaluation and management before coming to the index hospital were not accounted. The sample size was limited and children only up to twelve years were included which may also affect generalizability of the study findings.

More studies on the economic impact of juvenile idiopathic arthritis in the Indian scenario are needed from different regions and health-settings before a plea for social support to these children can be made to the public health authorities.

Contributors: MK: primary investigator, data collection, draft preparation; DD: patient management, literature search; AH: literature search, draft review, statistical analysis; PG: study design, patient management, draft review and interpretation; MBS: technical inputs, data collection and interpretation; RM: conception of study, draft review, study design and literature search. All authors approved the final manuscript.
Ethical clearance: Institutional Ethics committee of Medical College Kolkata; No. 368/11-2016 dated November 19, 2016.
Funding: None; *Competing interest*: None stated.

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RESEARCH PAPER

High Flow Nasal Cannula Therapy as a Primary Mode of Respiratory Support in a Pediatric Intensive Care Unit

Sachin Shah, Amita Kaul, Rupesh Bhosale and Ganesh Shiwarkar

From Department of Neonatal and Pediatric Intensive Care Services,Surya Mother and Child superspecialty Hospital, Pune, Maharashtra, India.

Correspondence to: Dr Amita Kaul, Surya Mother and Child Superspecialty Hospital, Pune Octroi Naka, Sr. No. 8, Bhujbal Chowk, Near Wakad, Pune, Maharashtra 411 057, India. amitakaul@hotmail.com
Received: November 20, 2019; Initial review: February 05, 2020; Accepted: July 25, 2020.

Objective: To assess efficacy and safety of High flow nasal cannula therapy (HFNC) as primary mode of treatment for children with respiratory distress. **Methods:** Consecutive patients (1 mo-16 years) with respiratory distress were assessed for respiratory clinical score, COMFORT score and saturation to FiO_2 (SF) ratio. **Results:** A total of 188 (91.7%) patients out of 205 responded to HFNC alone. The respiratory clinical score and COMFORT score were lower with higher SF ratio in these than 17 patients who required ventilation (P<0.001). Median (IQR) time to failure was 2 (1.75-24) hours. Air leak was seen in 2 (1%) patients. **Conclusions:** HFNC is an effective and safe primary mode of respiratory support in children with respiratory distress. Children who succeed on HFNC show a favorable clinical response within first few hours.

Keywords: *Comfort score, Mechanical ventilation, Non-invasive ventilation, SaO2/FiO2 ratio*.

***Published online*: September 16, 2020; *PII*: S097475591600247**

Humidified flow nasal cannula (HFNC) delivers heated and humidified gas mixture at a flow greater than patient's inspiratory flow demand and can provide intermediate level of support between low-flow oxygen delivery and non-invasive ventilation (NIV) in critically ill children [1]. Retrospective studies have shown that HFNC is useful for conditions like bronchiolitis, asthma, pneumonia and congenital heart disease [2]. The evidence for its safety or usefulness in children is limited [3]. There is paucity of prospective clinical trials on the effectiveness of HFNC in respiratory failure (not due to bronchiolitis) in pediatric intensive care unit (PICU).

This study aimed at assessing the efficacy and safety of HFNC as a primary mode of treatment in respiratory distress in children.

METHODS

This cross-sectional study was undertaken at an urban tertiary care hospital of Western India from 1 January, 2018, to 31 December, 2018. The study was approved by the institutional ethics committee and informed consent from parents was taken prior to enrollment. Consecutive patients with respiratory distress necessitating admi-ssion to PICU, in the age group of 1 month to 16 years of age were included. Children requiring immediate non-invasive (NIV) or invasive ventilation and those with contraindications to HFNC, altered sensorium (GCS <12), apnea and catecholamine resistant shock were excluded.

Respiratory distress was defined as hypoxia (SpO2 <94% in room air), tachypnea (as per age) and increased work of breathing (chest wall retractions, use of accesssory muscles of breathing and nasal flaring/grunting). HFNC was started as the first line treatment if all the above clinical signs were present. Primary outcome measure was need for 'NIV' or invasive ventilation.

Bronchiolitis was defined as a clinical syndrome of respiratory distress in children less than two years with rhinorrhea followed by lower respiratory infection resulting in wheezing and crepts. Children with fever, respiratory distress, tachypnea and infiltrates on chest radiograph were classified as pneumonia. Children with fever, respiratory distress, tachypnea and chest signs of wheezing and crepts but without infiltrates on chest radiograph were classified as LRTI with wheeze.

A respiratory clinical score with the following parameters was calculated: age specific respiratory rate scores 0 to 3, retractions 0 to 3, dyspnea 0 to 3, and wheeze 0 to 3. Total score ranged between 0 for normal and 12 at the extremes [4]. FiO2 was adjusted to keep arterial oxygen concentration between 92-97% to calculate saturation to FiO2 (SF) ratio. HFNC tolerance

was assessed using modified COMFORT scale [5]. The scale estimates eight parameters with a 1 (low) to 5 (high) score: alertness, calmness, respiratory response, physical movement, mean arterial pressure, heart rate, muscle tone, and facial tension. The total score can range between 8-40 (score of 17-26 suggesting good comfort). Respiratory clinical score, SF ratio and modified COMFORT score were calculated before starting HFNC treatment, at 60 to 90 minutes and 12-24 hours afterward.

HFNC system (Fisher and Paykel Healthcare, New Zealand) with junior circuit 900PT501 was used. Infant OPT316 or Pediatric OPT318 nasal prongs were selected as per child's age. Flow was initiated at 1-2 L/kg/min for infants and 1 L/kg/min for pediatric patients and adjusted according to patient response and tolerance (max 2 L/kg/min). Failure on HFNC was defined as need for NIV or invasive ventilation, when clinical deterioration was present. Criteria for intubation were respiratory arrest, refractory hypoxia (SpO2 <90% on 100% FiO2), exhaustion due to increased work of breathing and inability to protect airway. Criteria for switching to NIV were left to discretion of the attending intensivist.

For calculation of sample size, a baseline risk for need of ventilation as 16% was assumed in children with respiratory distress presenting to the emergency. We hypothesised that HFNC would reduce the risk by 50% (absolute reduction of 8 percentage points). Using alpha error of 0.05 and for 90% power, we calculated a sample size of 178. To allow for potential 10% recruitment failure rate, required sample size was increased to 200.

Statistical analyses were performed using IBM SPSS 23 version (IBM 2015), and significance was assessed at 0.05 level. Comparisons between two groups were made using independent sample Mann Whitney U test and Kruskall Wallis test for continuous measurements. Univariable and multivariable Cox regression models were used to assess the association of HFNC failure with various clinical parameters.

RESULTS

A total of 205 (71 girls) children were commenced on HFNC therapy. HFNC failure occurred in 17 (8.3%) children at a median (IQR) time of 2 (1.75-24) hours. Thirteen of these children required invasive ventilation. Three children developed local erythema and two developed airleak on HFNC. Clinical characteristics of responders and non-responders to HFNC are presented in **Table I**.

Table I Characteristics of Children as per Response to High Flow Nasal Cannula (HFNC)

	HFNC responders (n=188)	*Non-responders (n=17)*	*P value*
Age, n (%)			
<6 mo	38 (90.4)	4 (9.6)	0.01
6-23 mo	60 (90.9)	6 (9.1)	0.001
2-5 y	73 (94.8)	4 (5.2)	0.001
6-12 y	15 (83.3)	3 (16.7)	0.001
13-16 y	2 (100)	0	0.001
Diagnosis, n (%)			
Bronchiolitis	37 (97.3)	1 (2.6)	0.001
Pneumonia	54 (79)	14 (21)	0.001
LRTI with wheezing	17 (94.5)	1 (5.5)	0.001
Acute severe asthma	15 (100)	0	0.001
Congenital heart disease	7 (100)	0	0.001
Septic shock	41 (93.1)	3 (6.9)	0.001
Others	15 (100)	0	0.001
FiO2 (%)[a]	40 (35-45)	60 (55-70)	0.08
Flow (L/min)[a]	15 (11-20)	16 (13-22)	0.45
PIM2 score (%)[a]	2.7 (1.1-6.4)	5 (4-14.3)	0.01
Mortality	0	3 (17.6)	0.001
Duration of HFNC (h)[a]	48 (41-75)	2 (1.75-24)	0.001
Respiratory clinical score[a]			
On admission	10 (9-11)	12 (11-12)	0.001
At 60-90 min	9 (8-10)	12 (11-12)	0.001
At 12-24 h	7 (6-8)	12 (11-12)	0.001
SF ratio[a]			
On admission	316 (262-330)	260 (236-323)	0.03
At 60-90 min	333 (281-346)	245 (217-246)	≤0.001
At 12-24 h	360 (306-374)	245 (196-252)	≤0.001
COMFORT score[a]			
On admission	31 (29-33)	33 (32-35)	≤0.001
At 60-90 min	29 (27-30)	33 (32-35)	≤0.001
At 12-24 h	25 (24-26)	34 (32-35)	≤0.001

[a]*Data presented as median (IQR); SF: Saturation to FiO2 ratio; LRTI: Lower respiratory tract infection; Maximum HFNC parameters – Oxygen flow rate (FiO2); PIM 2 score: Pediatric index of mortality score.*

In univariate regression analysis, respiratory clinical score [Hazard ratio (95% CI) 4.9 (2.1-11.2), *P*=0.001]; SF ratio [HR (95% CI) 0.94 (0.97-0.99), *P*=0.012]; and COMFORT score, [HR (95% CI)1.99 (1.4-2.8), *P*= 0.001] on admission were associated with HFNC failure. In multivariable regression analysis, none of these parameters were associated with increased risk of HFNC failure, respiratory clinical score [HR (95% CI) 2.26 (0.84-7.7), *P*=0.09], SF ratio, [HR (95% CI) 0.99 (0.97-1.00), *P*=0.29] and COMFORT score [HR (95% CI) 1.39 (0.88-2.21), *P*=0.15].

WHAT THIS STUDY ADDS?

- HFNC is an effective mode of respiratory support in children with respiratory distress with heterogenous etiologies.

DISCUSSION

HFNC was effective in preventing intubation in children with respiratory distress in the present study with low failure rate in patients with various respiratory etiologies. The low failure rate on HFNC could be because was started relatively early and preemptively, even in cases of mild to moderate illness.

Patients with shock were also managed successfully on HFNC in this study. The contribution of HFNC in recovery of these patients cannot be quantified since multimodal monitoring and management plays a more important role. However, HFNC helps in decreasing work of breathing in these patients by maintaining functional residual capacity.

Patients who responded on HFNC had lower respiratory clinical score and COMFORT score with higher SF score at 60-90 minutes and at 12-24 hours. These parameters suggest that patients who are likely to succeed on HFNC would show favorable response within first few hours which was sustained over 24 hours. Non-responders had lower SF ratio, higher respiratory clinical score and COMFORT score on admissions suggesting that these children were sicker and more likely to need NIV or invasive ventilation.

The complication rate was low with airleak seen in only two patients with ARDS. The lower incidence of airleaks may be due to the standard flow rates being used in the study.

HFNC use requires additional treatment modalities before invasive ventilation which can be associated with adverse events [6] and additional costs. It may also be associated with delay in intubation, which however, was not seen in the present study.

The present study used easily reproducible tools for assessment and monitoring of severity of illness in children with heterogenous conditions making this relevant in daily clinical practice. This was however, a single center study using prespecified protocol, thereby limiting its external validity. A control arm without HFNC was not compared for ethical concerns.

To conclude, HFNC is an effective and safe primary mode of respiratory support in children with respiratory distress due to various causes. Children who succeed on HFNC show favourable response within first few hours and response is sustained over the next few days.

Contributors: SS: conceptualized the study, analysed the data and wrote the manuscript; AK: assisted with the concept made the study protocol and reviewed the manuscript; RB,GS: were involved in data collection and reviewed the literature.
Funding: None; *Competing interests*: None stated.

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Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP): Recommended Immunization Schedule (2020-21) and Update on Immunization for Children Aged 0 Through 18 Years

Srinivas G Kasi,[1] S Shivananda,[2] Sanjay Marathe,[3] Kripasindhu Chatterjee,[4] Sunil Agarwalla,[5] Shashi Kant Dhir,[6] Sanjay Verma,[7] Abhay K Shah,[8] Sanjay Srirampur,[9] Srinivas Kalyani,[10] Harish Kumar Pemde,[11] S Balasubramanian,[12] Bakul J Parekh,[13] GV Basavaraja,[14] and Piyush Gupta[15]

[1]Kasi Clinic, Jayanagar, Bengaluru, Karnataka; [2]Fortis Hospital, Banneraghatta Road, Bengaluru, Karnataka; [3]Marathe Child Care Hospital, Nagpur; [4]Department of Pediatrics, Gouri Devi Institute of Medical Science and Hospital, Durgapur, Paschim Bardhaman, West Bengal; [5]Department of Pediatrics, MKCG MCH, Berhampur, Odisha; [6]Department of Pediatrics, Guru Gobind Singh Medical College, Faridkot, Punjab; [7]Division of Infectious Diseases, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh; [8]Dr Abhay K Shah Children Hospital, Ahmedabad, Gujarat; [9]Department of Pediatrics, Aditya Super speciality Hospital, Hyderabad, Telangana; [10]Department of Pediatrics, Niloufer Hospital, Osmania medical College, Hyderabad; [11]Department of Pediatrics, Lady Hardinge Medical College, New Delhi; [12]Department of Pediatrics, Kanchi Kamakoti Childs Trust Hospital, Chennai, Tamil Nadu; [13]Bakul Parekh Hospital for Children, Mumbai; [14]Department of Pediatrics, IGICH, Bengaluru, Karnataka; [15]Department of Pediatrics, University College of Medical Sciences, New Delhi; India.

Correspondence to: Srinivas G Kasi, Convener, ACVIP, Kasi Clinic, 2nd Cross, 3rd Block, Jayanagar, Bengaluru 560011, Karnataka, India. sgkasi@gmail.com

Justification: In view of new developments in vaccinology and the availability of new vaccines, there is a need to revise/review the existing immunization recommendations. **Process:** Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics (IAP) had a physical meeting in March, 2020 followed by online meetings (September-October, 2020), to discuss the updates and new recommendations. Opinion of each member was sought on the various recommendations and updates, following which an evidence-based consensus was reached. **Objectives:** To review and revise the IAP recommendations for 2020-21 and issue recommendations on existing and new vaccines. **Recommendations**: The major changes include recommendation of a booster dose of injectable polio vaccine (IPV) at 4-6 years for children who have received the initial IPV doses as per the ACVIP/IAP schedule, re-emphasis on the importance of IPV in the primary immunization schedule, preferred timing of second dose of varicella vaccine at 3-6 months after the first dose, and uniform dosing recommendation of 0.5 mL (15 µg HA) for inactivated influenza vaccines.

Keywords: *Guidelines, Inactivated polio vaccine, Pneumococcal vaccine, Rabies vaccine, Varicella vaccine.*

Published online: **November 29, 2020; *PII:*S097475591600258**

The Advisory Committee on vaccines and Immunization Practices (ACVIP) of the Indian Academy of Pediatrics met on 7 March, 2020, in Kolkata. ACVIP members and invitees who attended the meeting are listed in **Annexure I**. The aim of the meeting was to discuss and debate recent developments in the field of vaccinology, to issue the relevant recommendations based on them, and to revise IAP Immunization Timetable for the year 2020-21. This document presents the consensus recommendations, arrived at after detailed literature review, debates and discussions, held during the first physical meeting and subsequent meetings held online (dIAP platform), in view of the prevailing corona virus disease 19 (Covid-19) pandemic and inability to have physical meetings.

PROCESS

The process for issuing recommendations included review of recent published literature including standard indexed journals, vaccine trials, recommendations of reputed international bodies like Advisory Committee on Immunization Practices, Center for Disease Control and Prevention (CDC), USA, World Health Organization (WHO) and unpublished data from vaccine manufacturers. Data generated by studies done in India was specifically looked at and available local information was given preference. The summary of the key updates of ACVIP 2020-2021 recommendations is given in **Box I**.

RECOMMENDATIONS

The ACVIP-IAP recommendations for the year

Box I Key Updates and Major Changes in Recommendations for IAP Immunization Timetable 2020/21

Polio immunization

- A booster of the injectable polio vaccine (IPV) is recommended at 4-6 years.
- The importance of IPV in the immunization schedule is re-emphasized.

Inactivated influenza vaccines

- A uniform dosing of 15 mcg (0.5 mL) of inactivated influenza vaccines is recommended for all children older than 6 months.

Varicella vaccine

- The second dose of varicella vaccine should preferably be administered 3-6 months after the first dose.

New vaccines introduction

- DTaP/IPV combination vaccine: Tetraxim
- Quadrivalent conjugate meningococcal vaccine: Menveo
- Monoclonal antibody cocktail for post exposure prophylaxis of rabies: Twinrab
- Conjugate (CRM 197) typhoid vaccine: Typhi BEV
- 10-valent pneumococcal conjugate vaccine: Pneumosil

2020-21 are being given in **Table I** and **Fig. 1**. The recommendations about the newly introduced vaccines are summarized in **Box II** and vaccines for high risk children are summarized in **Box III**.

Booster Dose of Injectable Polio Vaccine (IPV)

The last case of wild polio virus (WPV) in India was reported on 13 January, 2011 and on 27 March, 2014, India along with the rest of Southeast Asia was declared polio-free [1]. It needs to be emphasized that until worldwide polio eradication is achieved, cases of imported WPV from endemic neighboring countries or cases of circulating vaccine derived poliovirus (cVDPV), remains a real threat unless population immunity is maintained by vaccinating children adequately in their early years of life. Outbreaks of cVDPVs have occurred in countries which have been polio free for several years [2]. In the absence of inapparent infection, universal vaccination of infants and children is the only way to establish and maintain population immunity against polio. In 2018, the ACVIP had recommended an all IPV schedule at 6-10-14 weeks followed by an IPV booster at 15-18 months, and the recommendation for the OPV booster at 4-6 years was dropped [3]. A birth dose of OPV continues to be recommended.

IPV is immunogenic in an EPI schedule (6-10-14 weeks), but the titers achieved and the seroconversion rates are reported to be lower, compared with vaccination of infants at older ages (2-4-6 months) [4]. Studies examining the long-term persistence of antibodies following IPV vaccination, have shown persistence of antibodies only up to the school-entry age, with the highest titers observed with the 3+1 schedule [4], as all IPV using countries recommend a school age booster [5]. A pre-school booster resulted in SPR rising to 100% for

Box II IAP-ACVIP Recommendations on Newer Vaccines

- Approves the use of Menveo vaccine in the 2-55 years age group. It reiterates the use of this vaccine only in special situations, as published before [45].
- Approves the use of Typhibev vaccine for age >6 months and up to 45 years as single dose. There is no recommendation for a booster dose.
- Recommends the use of rabies mAbs over RIGs in the management of category 3 bites. Human monoclonal rabies antibody (Rabishield) and murine cocktail monoclonal rabies antibodies (Twinrab), both are available in India and approved for the post-exposure management of suspected rabies exposure.
- Approves the use of Tetraxim for the second booster of DPT/IPV at 4-6 years of age.
- Approves the use of Pneumosil till 2 years of age in a 3+1 schedule, with the booster administered between 12-18 months.
- In the absence of studies in the 2-5 years age group, the ACVIP does not presently recommend the use of Pneumosil beyond 2 years of age.

Box III IAP Recommended Vaccines for High-risk Children

Vaccines

1. Meningococcal vaccine
2. Japanese Encephalitis (JE) vaccines
3. Oral Cholera vaccine
4. Rabies vaccine
5. Yellow fever vaccine
6. Pneumococcal Polysaccharide vaccine (PPSV 23)

High-risk conditions

1. Congenital or acquired immunodeficiency (including HIV infection, immunosuppressive therapy, radiation)
2. Chronic cardiac conditions
3. Chronic pulmonary conditions (including asthma if treated with prolonged high-dose oral corticosteroids),
4. Chronic systemic diseases: Renal (including nephrotic syndrome), hematological, hepatic diseases, diabetes mellitus
5. Functional/ anatomic asplenia/hyposplenia
6. Cerebrospinal fluid leaks, cochlear implants; for pneumococcal infections

Specific high-risk groups

1. Children having pets in home: Rabies vaccine
2. JE endemic areas: Japanese encephalitis vaccine
3. During outbreaks: Oral cholera vaccine
4. For travelers Rabies vaccine, meningococcal vaccine, yellow fever vaccine

Table I IAP Immunization Timetable 2020/21: IAP Recommended Vaccines for Routine Use

Age	*Vaccine*	*Comments*
Birth	BCG OPV Hepatitis B-1 (BD)	BCG: before discharge OPV: as soon as possible after birth Hep B should be administered within 24 hours of birth
6 week	DTwP/DTaP-1 IPV-1 Hib-1 Hep B-2 Rotavirus-1 PCV-1	DTwP or DTaP may be administered in primary immunization IPV: 6-10-14 weeks is the recommended schedule. If IPV, as part of a hexavalent combination vaccine, is unaffordable, the infant should be sent to a government facility for primary immunization as per UIP schedule.
10 week	DTwP/DTaP-2 IPV-2 Hib-2 Hep B-3 Rotavirus-2 PCV-2	RV1: 2 -dose schedule; all other rotavirus brands: 3-dose schedule
14 week	DTwP/DTaP-3 IPV-3 Hib-3 Hep B-4 Rotavirus-3 PCV-3	An additional 4th dose of Hep B vaccine is safe and is permitted as a component of a combination vaccine
6 month	Influenza (IIV)-1	Uniform dose of 0.5 ml for DCGI approved brands
7 month	Influenza (IIV)-2	To be repeated every year, in pre-monsoon period, till 5 y of age
6-9 month	Typhoid conjugate vaccine	As of available data, there is no recommendation for a booster dose
9 month	MMR -1	
12 month	Hepatitis A	Single dose for live attenuated vaccine
15 month	MMR-2, Varicella -1, PCV booster	
16-18 month	DTwP/DTaP-B1, Hib-B1, IPV-B1	
18-19 month	Hep A-2, Varicella-2	Only for inactivated Hep A vaccine
4-6 year	DTwP/DTaP-B2, IPV-B2, MMR-3	
10-12 year	Tdap, HPV	Tdap is to be administered even if it has been administered earlier (as DTP-B2) HPV: 2 doses at 6 mo interval between 9-14 y; 3 doses: from 15 y or immunocompromised of any age (0-1-6 mo for HPV2, 0-2-6 mo for HPV4)

Age in completed weeks/months/years.

all 3 serotypes and GMTs rising 32-fold to 55-fold for the 3 serotypes [6,7]. Following a pre-school booster, almost 100% SPR and high antibody titers persist for at least 5 years [8].

In the absence of a booster at 4-6 years, the seroprotection rates (SPR) against PV 1 and PV2 had fallen to 91% and 91.2% compared to a SPR of 100% in those who had received a school entry booster at 4-6 years [9]. There is low scientific evidence for ≥80% long-term (>5-10 years) persistence of protective antibodies following ≥3-4 doses of IPV before school age [10]. There are no studies regarding the long-term persistence of antibodies with the EPI schedule of 6-10-14 weeks or 2 doses of fractional doses intradermal IPV [4].

Some studies have suggested an inverse correlation between circulating levels of preexisting homotypic antibodies and excretion of poliovirus types 1, 2, and 3 following the administration of trivalent OPV, indicating better mucosal immunity with higher serum antibody titers [11]. There are no conclusive studies to demonstrate that the booster response occurs sufficiently rapidly to prevent re-infection or paralytic disease and that it is as effective as pre-existing immunity [12]. It has been recommended that "a minimal position

would be to recommend four to five doses of an IPV-containing vaccine with the last one administered at school-entry age" [4].

In a country like India, where risk of importation of polio virus (wild and cVDPV) is high, ACVIP re-emphasizes the use of OPV during national and subnational pulse polio days for all children. At this stage, these additional OPV doses in IPV primed children, will help in augmenting their gut immunity, which could be crucial for preventing circulation of polio virus.

ACVIP Recommendation

- A booster dose of IPV at 4-6 years of age for children who have received the initial IPV doses as per the ACVIP/IAP schedule.
- In case of non-availability of standalone IPV, this dose can be administered as a combination with DPT vaccines.

IPV in the Primary Immunization Schedule

In April 2016, a synchronous global switch was implemented from trivalent OPV (tOPV) to bivalent OPV (bOPV) in routine immunization programs. Simultaneously, IPV was introduced in the routine Immunization in all OPV-only using countries. Introduction of IPV was a risk mitigation strategy to overcome the risk associated with this switch. The switch was preceded by high quality SIAs with tOPV, to raise population immunity against type 2 PV [13]. Modelling studies done prior to the switch suggested that the risk of cVDPV would not last beyond a year and a half of the switch [14].

With a massive surge in requirements for IPV, a shortage resulted. According to the data published by the WHO, global coverage with one dose of IPV was about 50% in 2016, 60% in 2017, and only 72% in 2018 [15]. Thus, population immunity against PV type 2 has decreased, with resultant increase in cVDPV cases/outbreaks [16,17]. In 2017, there were two countries with cVDPV2 outbreaks with 96 cases; whereas, as of 13 October, 2020, worldwide there were 449 cases of cVDPV2 [18]. This data suggests that India is not free from the risks of cVDPV. In fact, India comes under the category of countries at high risk for cVDPV. Moreover, India has a long border with Pakistan, a country which is still endemic for WPW type 1. There is an imperative need to maintain population immunity against type 2 PV, which can only be achieved by administering IPV either in the IAP schedule or 2 doses of fractional dose intradermal IPV at 6 weeks and 14 weeks or a single dose of full-dose intramuscular IPV at 14 weeks. No child born after the switch should be left unprotected against type 2 PV.

ACVIP Recommendation

- No child should be administered only pentavalent vaccine and bOPV in infancy without IPV (two doses of fractional dose intradermal IPV at 6 weeks and 14 weeks or a single dose of full-dose intramuscular IPV/ hexavalent combination at 14 weeks). If hexavalent vaccines are unaffordable/unavailable, the infant must be referred to a government healthcare facility for the primary immunization as per UIP schedule.
- Infants and young children, born after the switch (25 April, 2016), who have not received IPV in any schedule, should receive at least one dose of an IPV/ IPV combination vaccine, intramuscularly, at the earliest opportunity.

Uniform Dosing for Inactivated Influenza Vaccines

Since the 1970s, when whole virion vaccines were in use, the standard-dose of IIVs in children less than 3 years of age has been 7.5 mcg per antigen, which is half the dose, given to older children and adults. As higher dose increased the reactogenicity, the lower dose was adopted to reduce reactogenicity and febrile convulsions observed with the whole virus vaccines that were in use at that time [19]. However, the immune response in young children was very variable, especially against the B strains in the vaccine. This was particularly significant in children younger than 3 years of age, who were vaccine-naïve [20]. Higher dose of 0.5 mL (15μg) in the 6-23 months age group is expected to result in higher levels of post vaccination HI antibody titer, which may result in increased efficacy [21]. Since, the complications of influenza are much higher in infants, studies were done to evaluate the safety, immunogenicity and superiority of full dose (0.5 ml; 15 μg) in the age group of 6-35 months to have uniform dosage recommendations in all age groups.

Studies have generally shown comparable reactogenicity and non-inferior immunogenicity with the full dose, in comparison with the half dose, in children 6-35 months of age [22-25]. Statistically superior immunogenicity was seen only in infants between 6-11 months of age, for H3N2 and B/Yamagata and not for H1N1 [25]. Superior GMTs were demonstrated against both vaccine B strains in children 6-17 months of age and unprimed children 6-35 months of age [24].

In children 6-35 months of age, the quadrivalent vaccine in a dose of 0.5 ml, demonstrated an efficacy of 63% (97·5% CI 52-72) against moderate-severe influenza, in a season when there was a 68% mismatch between the vaccine strains and the strains isolated in the study [25].

Several countries including USA, Finland, Australia,

UK, New Zealand and Canada have adopted a uniform dosage schedule for all age groups.

ACVIP Recommendation

- ACVIP endorses the use of a uniform dosing schedule of inactivated influenza vaccines (15 µg/0.5 mL) for all children older than 6 months.

So far, two brands, Influvac Tetra (Abbott) and Fluarix Tetra (Glaxo Smithkline) have received DCGI approval for this uniform dosage recommendation [26,27]. ACVIP endorses a dose of 0.5 mL per dose in children older than 6 months for these brands. Uniform dosage recommendations shall be extended to other brands also, once they get approval from the licensing authority (DCGI) in India. Till then, the manufacturer's age specific recommendations regarding dosage may be followed.

Second Dose of Varicella Vaccine

The timing of the second dose would depend on the relative contributions of primary and secondary vaccine failure to the incidence of breakthrough varicella. Primary vaccine failure could be defined as the failure to seroconvert or the failure to mount a protective immune response after vaccination despite seroconversion, whereas secondary vaccine failure is the gradual waning of immunity over time. Primary vaccine failure will favor an early second dose (few months after dose 1), whereas secondary vaccine failure will favor a delayed second dose (few years after dose 1).

Studies examining the immunological response to the second dose given after 6 weeks and given after 4-5 years have shown that the SPR (>5 U/mL by gpELIZA) are similar with both schedules, while the GMTs are higher with the longer interval schedule. However, the mean Stimulation Index (SI), which is a marker of the CMI is superior when the second dose is administered at 4-5 years [28,29]. Increases of GMTs by > 10-fold is observed following the second dose, irrespective of the interval between doses [30,31]. This is not seen with other viral vaccines. Such large increases suggest an inadequate priming and that the second dose is for completing the immune response initiated by the first dose.

Persistence of antibody in children after 1 dose of varicella vaccine has been demonstrated in both short-term and long-term follow-up studies [32-34], for periods as long as 9-20 years, with titers rising during the period of follow-up [32,34], indicating an absence of waning of antibody titers with time especially when there are occasions for natural boosting, thus suggesting a primary vaccine failure rather than waning immunity.

The highest incidence rate of breakthrough varicella was seen in the first 4-5 years after vaccination [35]. Vaccine effectiveness dropped from 97% in the first year post-vaccination to 86% in the second year and then remained stable till 8 years [36]. In a study from China, effectiveness was also shown to drop after the first year and then remain stable over the next 5 years [37]. These patterns are seen in primary vaccine failure, rather than waning immunity.

A single retrospective study has demonstrated an increasing incidence and severity over 10 years [38]. Some outbreak studies, which do not represent the entire population, have suggested waning immunity as a cause of vaccine failure [39].

Globally, as of end 2018, about 36 countries had included the varicella vaccine in their NIPs, about 23 have introduced a 2-dose schedule [40]. Approximately half of these 23 have preferred the shorter interval between doses.

Generally, there is more robust evidence for a primary vaccine failure following 1 dose of varicella vaccine and very limited evidence for secondary vaccine failure. A short interval between 2 doses of the varicella vaccine might be preferable to reduce breakthrough varicella, especially in countries with poor coverage and where the wild-type virus circulates predominantly. In India, in the bigger cities, 2-3 years is the usual entry age for pre-school. This may result in breakthrough varicella before the receipt of a delayed second dose. In India, varicella vaccine is not in the NIP and is recommended only by the IAP and the overall uptake is low and exposure to varicella following 1 dose may give rise to breakthrough varicella. Since the aim of varicella vaccination, in office practice, is the best possible protection for the individual child, an earlier second dose will be beneficial over a delayed second dose.

ACVIP Recommendation

- The second dose of varicella vaccine should be preferably administered 3-6 months after the first dose.

New Vaccines

The newly introduced vaccine products are detailed below and the ACVIP recommendations for these are given in **Box II**.

Quadrivalent Conjugated Meningococcal Vaccine

The quadrivalent conjugate meningococcal vaccine, Menveo (Glaxo SmithKline) has been licensed by the Drug Controller General of India (DCGI). Menveo contains *N. meningitidis* serogroup A, C, Y, and W-135

Vaccine	Age in completed weeks/months/years															
	Birth	6w	10w	14w	6m	7m	9m	12m	13m	15m	16-18m	18-24m	2-3 Y	4-6 Y	9-14 Y	15- 18 Y
BCG																
Hepatitis B	HB 1[a]	HB 2	HB 3	HB 4[b]												
Polio	OPV	IPV 1[c]	IPV 2[c]	IPV 3[c]							IPV[c]B1			IPV[c]B2		
DTwP/DTaP		DPT 1	DPT 2	DPT 3							DPT B1			DPT B2		
Hib		Hib 1	Hib 2	Hib 3							Hib B1					
PCV		PCV 1	PCV 2	PCV 3				PCV B								
Rotavirus		RV 1	RV 2	RV 3[d]												
Influenza					Dose 1[e]	Dose 2	Annual Vaccination									
MMR							Dose 1			Dose 2				Dose 3		
TCV																
Hepatitis A								Dose 1				Dose 2[f]				
Varicella										Dose 1		Dose 2[g]				
Tdap[h]/Td																
HPV															1 & 2[i]	1, 2 & 3[j]
Meningococcal[k]							Dose 1	Dose 2								
JE								Dose 1	Dose 2							
Cholera								Dose 1	Dose 2							
PPSV 23																
Rabies																
Yellow Fever																

Recommended age **Catch up age range** **Vaccines in special situations**

(a)To be given within 24 h after birth. When this is missed, it can be administered at first contact with health facility; (b) An extra dose of Hepatitis B vaccine is permitted as part of a combination vaccine when use of this combination vaccine is necessary; (c) IPV can be given as part of a combination vaccine; (d) 3rd dose of Rota vaccine is not necessary for RV1; (e) Influenza vaccine should be started after 6 mo of age, 2 doses 4 wks apart, usually in the pre-monsoon period. At other times of the year, the most recent available strain should be used. Annual influenza vaccination should be continued, for all, till 5 y of age; after the age of 5y, this vaccine is recommended in the high-risk group only; (f) Single dose is to be given for the live attenuated Hepatitis A vaccine. The inactivated vaccine needs two doses; (g) 2nd dose of Varicella vaccine should be given 3-6 mo of age after dose 1. However, it can be administered anytime 3 mo after dose 1 or at 4-6 y; (h) Tdap should not be administered as the second booster of DPT at 4-6 y. For delayed 2nd booster, Tdap can be given after 7 y of age. A dose of Tdap is necessary at 10-12 y, irrespective of previous Tdap administration. If Tdap is unavailable/unaffordable, it can be substituted with Td; (i) Before 14 completed years, HPV vaccines are recommended as a 2-dose schedule, 6 mo apart; (j) From 15th y onwards and the immunocompromised subjects at all ages, HPV vaccines are recommended as a 3-dose schedule, 0-1-6 (HPV2) or 0-2-6 (HPV4); (k) Menactra is approved in a 2-dose schedule between 9-23 mo. Minimum interval between two doses should be 3 mo. Menveo is recommended as a single dose schedule after 2 y of age.

Fig. 1 ACVIP recommendations 2020-21.

oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM197 protein. Each dose of vaccine contains 10 µg MenA oligosaccharide; 5 µg of each of MenC, MenY, and MenW- 135 oligosaccharides; and 32.7 to 64.1 µg of CRM197 protein [41].

In general, in pooled cohort of 2–10 years and 11-18 years age group, non-inferiority of MENVEO to MenACWY-DT (Menactra-Sanofi Pasteur Inc)was demonstrated for all serogroups. Persistence of antibodies were demonstrated in children and adolescents up to 5 years post-vaccination. Menveo demonstrated a favorable tolerability profile in all the age groups [42,43].

In the Indian licensure study, 72%, 95%, 94%, and 90% of subjects achieved a post-vaccination hSBA >8, for serogroups A, C, W, and Y, respectively, which were similar across all the 3 age groups [4]. Post-vaccination GMTs showed increases of 17-fold against serogroup A, 42-fold against serogroup C, 7-fold against serogroup W, and 15-fold against serogroup Y, compared to pre-vaccination GMTs. Post-vaccination GMTs were generally somewhat higher with increasing age. The vaccine was well tolerated with no safety concerns [44]. This vaccine is recommen-ded for use only in special situations, as published before [45].

Typhoid Conjugate Vaccine

Typhibev (Biological E vaccines) is a typhoid conjugate vaccine where the source of the Vi antigen is *C. frenundii*, which is in conformity with WHO specifications. Each dose of 0.5 ml contains Typhoid Vi Polysaccharide (produced from C. Freundii sensu lato 3056): 25 µg conjugated to 16.7 µg to 100 µg of CRM197 [46].

A multicentric phase II/III study showed that seroconversion (anti-Vi IgG >2 ug/ml) was obtained in 99% subjects (95%CI: 97.06, 99.79) in Typhibev compared to 99.4% in comparator group Typbar-TCV (Bharat Biolech India Limited). Non inferiority was established with comparator TCV. Anti Vi IgG >4.3 ug/ml (criteria defined for having sustained protection for at least 4 years) also fulfilled predefined non inferiority criteria. The side effects profile was comparable with the comparator vaccine [47].

Typhibev was licensed for use in India by DCGI in February, 2020; approved for those aged older than 6 months to 45 years, to be given in 0.5 mL single dose, intramuscular injection [46].

Monoclonal Antibody Cocktail for Post Exposure Prophylaxis Of Rabies

In the 2018-19 recommendations, the ACVIP, strongly endorsed the use of monoclonal antibodies (mAbs) for rabies post-exposure prophylaxis (PEP) [3,48]. Twinrab (Zydus Vaxxicare) is the second rabies mAb to receive DCGI approval. Twinrab is a combination of two murine anti-rabies mAb, docaravimab (62-71-3) and miromavimab (M777-16-3). The two mAbs individually bind to and neutralize both rabies and rabies-like virus strains isolated from canine, human, and bovine sources, preventing their entry into the neighboring cells [49].

In a phase 3, randomized study, comparing anti-rabies monoclonal antibody cocktail (Twinrab) against Human Rabies Immunoglobulin (HRIG), the GMTs of the antibodies induced with Twinrab were shown to be non-inferior to the antibodies induced with HRIG, with no statistically significant difference in the two groups and a similar adverse effect profile was seen in the two groups [50].

The recommended dose of Twinrab is 40 IU/kg of body weight. Twinrab is indicated for post exposure prophylaxis in individuals with suspected rabies exposure. Twinrab must always be used in combination with rabies vaccine as part of post-exposure prophylaxis in line with the recommendation of WHO [3,48].

DTaP/IPV Combination Vaccine

Tetraxim (Sanofi Pasteur) is a fully liquid, DTaP/IPV combination vaccine to be administered by intramuscular route. Each 0.5 ml dose contains: Diphtheria toxoid (≥30 IU), Tetanus toxoid (≥40 IU), *Bordetella pertussis* antigens: pertussis toxoid and filamentous haemagglutinin (25 µg each), inactivated poliomyelitis virus (type 1: 40 D antigen Units (DU), type 2:8 DU, type 3:32 DU [51].

In a review done over 619 subjects in five clinical studies, it was found the DTaP-IPV combination vaccine was highly immunogenic [52]. Tetraxim booster at 4-6 years of age has been shown to be associated with strong anamnestic responses to all antigens [6] and has been shown to be as immunogenic as DTwP-IPV when given as a school-entry booster [7]. The vaccine induced seroprotective titers (>0.01IU/mL) against diphtheria and tetanus, persist till at least 5 years after the pre-school booster [8].

10-Valent Pneumococcal Conjugate Vaccine

Pneumosil (Previously SIIPL-PCV) (Serum Institute of India Pvt Ltd Pneumococcal Conjugate Vaccine) is a pneumococcal polysaccharide conjugate vaccine that has been pre-qualified for use by WHO on 18 December, 2019 [53]. This is the third pre-qualified PCV vaccine after Prevenar-13 (Pfizer) and Synflorix (GSK vaccines).

Pneumosil is a pneumococcal polysaccharide

conjugate vaccine containing saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F, conjugated using CDAP (1-cyano-4-dimethylamino pyridinium tetrafluoroborate chemistry) and chemically activated. Each dose of 0.5 ml vaccine contains 2 µg each of serotypes 1, 5, 9V, 14, 19A, 19F, 23F, 7F, 6A and 4 µg of serotype 6B conjugated to non-toxic diphtheria CRM197 carrier protein: 19-48 mcg [53]. It is available as a ready to use vial containing vaccine in liquid form with a vaccine vial monitor [54].

In the phase 1/2 study done in Gambia, in infants, seroprotection rates (SPR) of >90% was observed for all serotypes with PCV 13 following the primary immunization, whereas SPR of > 90% was observed for all serotypes except serotypes 6A and 6B, following SIIPL-PCV. Serotype-specific IgG GMCs estimates after the primary series were above 1 mg/mL for all serotypes following both vaccines. The serotype-specific OPA GMTs following the primary series were comparable for the two vaccines for six (1, 5, 6B, 14, 19F, and 23F) of 10 serotypes, while the responses were lower following SIIPL-PCV^{TM} for the remaining 4 serotypes [55].

A significant booster response (except for type 5) was noted with both vaccines in children primed at 6-10-14 weeks with the SIIPL-PCV and the comparator vaccines. The magnitude of the booster response was higher for 1, 6B, 9V, 19A, and 23F with SIIPL-PCV, while it was higher for 5, 19A and 19F with PCV 13. The OPA GMTs following the booster vaccination in toddlers were generally comparable with both vaccines [55].

In comparison with Synflorix, both vaccines elicited a significant booster immune response for all 10 serotypes except serotype 5, while the OPA GMTs showed a booster response for all 10 serotypes. Persistence of antibodies was seen for all serotypes till 1 year of follow up [56].

The DCGI has approved it for active immunization against invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in infants from 6 weeks of age group for three dose regimen (dosing schedule: 6, 10 and 14 weeks) [57]. The WHO has approved it for active immunization against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F, till the age of 2 years [58].

Competing interests: Representatives of a few vaccine manufacturing companies also presented their data in the consultative meetings. None were involved in formulating the recommendations. *Funding*: None. The first physical meeting was held during Vaccicon 2020 at Kolkata. The organizers provided the premises for the meeting. Indian Academy of Pediatrics provided the online platform for subsequent online meetings.

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ANNEXURE I

Members Who Attended the Physical Meeting in Kolkata (7 March, 2020)

(in alphabetical order)

Abhay K Shah, Bakul J Parekh, G V Basavaraja, Kripasindhu Chatterjee, S Balasubramanian, S Shivananda, Sanjay Marathe, Sanjay Srirampur, Shashi Kant Dhir, Srinivas Kalyani, Srinivas G Kasi, Sunil Agarwalla, Rohit Aggarwal (*Special invitee*).

Piyush Gupta and Sanjay Verma could not attend the meeting.

Association of Child Neurology (AOCN) – Indian Epilepsy Society (IES) Consensus Guidelines for the Diagnosis and Management of West Syndrome

Suvasini Sharma,[1] Jaya Shankar Kaushik,[2] Kavita Srivastava,[3] Jyotindra Narayan Goswami,[4] Jitendra Kumar Sahu,[5] Kollencheri Puthenveettil Vinayan[6] and Rekha Mittal[7]

*From Department of Pediatrics, [1]Lady Hardinge Medical College, New Delhi; [2]Department of Pediatrics, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India; [3]Department of Pediatrics, Bharati Vidyapeeth Deemed University Medical College, Pune, Maharasthra, India; [4]Department of Pediatrics, Army Hospital – Research and Referral, New Delhi, India; [5]Division of Pediatric Neurology, Advanced Centre of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [6]Department of Pediatric Neurology, Amrita Institute of Medical Sciences, Kochi, Kerala, India; [7]Department of Pediatric Neurology, Madhukar Rainbow Children's Hospital, Delhi, India; for the AOCN-IES Expert Committee.**

**Full list of members provided in Annexure I*

Correspondence: Dr. Suvasini Sharma, Associate Professor, Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children Hospital, New Delhi, India. sharma.suvasini@gmail.com

Justification: West syndrome is one of the commonest causes of epilepsy in infants and young children and is a significant contributor to neurodevelopmental morbidity. Multiple regimens for treatment are in use. **Process:** An expert group consisting of pediatric neurologists and epileptologists was constituted. Experts were divided into focus groups and had interacted on telephone and e-mail regarding their group recommendations, and developed a consensus. The evidence was reviewed, and for areas where the evidence was not certain, the Delphi consensus method was adopted. The final guidelines were circulated to all experts for approval. **Recommendations:** Diagnosis should be based on clinical recognition (history/home video recordings) of spasms and presence of hypsarrhythmia or its variants on electroencephalography. A magnetic resonance imaging of the brain is the preferred neuroimaging modality. Other investigations such as genetic and metabolic testing should be planned as per clinico-radiological findings. Hormonal therapy (adrenocorticotropic hormone or oral steroids) should be preferred for cases other than tuberous sclerosis complex and vigabatrin should be the first choice for tuberous sclerosis complex. Both ACTH and high dose prednisolone have reasonably similar efficacy and adverse effect profile for West syndrome. The choice depends on the preference of the treating physician and the family, based on factors of cost, availability of infrastructure and personnel for daily intramuscular injections, and monitoring side effects. Second line treatment options include anti-epileptic drugs (vigabatrin, sodium valproate, topiramate, zonisamide, nitrazepam and clobazam), ketogenic diet and epilepsy surgery.

Keywords: *Epileptic spasms, Hypsarrhythmia, Infantile spasms, Treatment.*

West syndrome (WS) is one of the commonest types of epilepsy in infants and toddlers and is a significant contributor to neurodevelopmental morbidity in children. Common co-morbidities include global developmental delay/intellectual disability, autism spectrum disorder, cerebral palsy, and visual and hearing impairment. The currently preferred term for infantile spasm is epileptic spasm.WS is now understood to be an age-dependent epileptic encephalopathy, an expression of brain injury to any cause; which may be pre-natal, perinatal or postnatal. The pathophysiological mechanisms are not well understood.

In India, the situation is compounded by a huge time lag from onset to diagnosis – reported median lag is almost 6-12 months as compared with a few weeks in the developing countries. There is also a lack precise knowledge on the disease among pediatricians. Other challenges include paucity of trained personnel to report pediatric electroencephalograms (EEG), high cost of investigative work up, and availability issues with first line treatments such as adrenocorticotropic hormone (ACTH) and vigabatrin. The plethora of regimens mentioned in the literature adds to the confusion. A consensus guideline for the diagnostic evaluation and management of children with WS in India has been a long felt need.

PROCESS

The process of preparing a consensus document on the diagnosis and management of WS was initiated by the members of Association of Child Neurology (AOCN). In association with Indian Epilepsy Society (IES), a

consensus document was envisaged on the same. The invited experts included pediatricians, pediatric neurologists, neurologists, and epileptologists (**Annexure 1**), who were categorized into one of five groups: definitions, etiology, early diagnosis and prognosis; diagnostic evaluation; hormonal treatment; vigabatrin and other drugs; and diet, surgery and supportive care. First the evidence was reviewed. For areas where the evidence was not certain, the Delphi consensus method was adopted [6]. The writing group members of each group identified a set of open- ended questions which were discussed in their respective groups. These open-ended questions were administered using Google form to all experts. In this process, the experts gave their opinions to the moderator, who anonymized the responses and sent them back to all experts. A guarantor ensured that responses were blinded and the methodology of Delphi was adopted.

The responses to the open-ended questions obtained were qualitatively analyzed, and similar responses were categorized, clubbed and converted into closed ended responses. Based on these responses, new questions with close-ended responses were framed. These questions were again sent to experts in the second round. Their responses were collated and presented in the meeting of experts. Categorical responses where more than 75% of experts agreed on single response were considered to have reached a consensus. The concerns, discrepancies and responses where consensus was not reached (<75% agreement) were polled again using audience response system. Questions where polling did not reach 75% consensus were re-polled. Any question where second polling also failed to establish a consensus were considered as having failed to reach the same, and the data was presented as a range rather than a definitive response.

A final consensus meeting was held on 1 September, 2019 at Delhi. The coordinator of each group made a presentation of the draft document for consensus. Deliberations were held, and inputs and suggestions by the various participating members were incorporated into the document. The final document was prepared and circulated to all the participating members for inputs and approval.

RECOMMENDATIONS

Definition

As per the 2004 International Delphi consensus statement on WS[1], definitions of clinical spasms, epileptic spasms, and WS were framed (**Box 1**). Spasms may be confused with myoclonic seizures but the longer duration, presence of a tonic phase, occurrence in clusters and the relationship with the sleep wake cycle help to differentiate spasms from myoclonic seizures [1]. Differentiation from paroxysmal non-epileptic phenomena in typically developing children such as benign myoclonus, benign myoclonic epilepsy of infancy, Sandifer syndrome, etc may require video telemetry with concurrent surface electromyography. As per the International League Against Epilepsy (ILAE) 2017 seizure and epilepsy classification, epileptic spasms may be of focal, generalized or unknown onset [2].

1. *Consensus Statement: Definitions*

- WS is defined as the presence of epileptic spasms (usually in clusters) and the presence of hypsarrhythmia or variant hypsarrhythmia on EEG [7].
- Children with clinical spasms but EEG not showing hypsarrhythmia or its variants should have an overnight EEG and be referred for expert evaluation. A repeat EEG may be considered in such patients as an early EEG may miss hypsarrhythmia. Specialist may also consider treating these children similar to West syndrome.

Box I Terms Related to Infantile Spasms and West Syndrome

- *Clinical spasms*: Brief, synchronous movements involving head, trunk, and limbs, or sometimes of the head, trunk, or limbs alone occurring for around 1 second (0.5-2 sec). These may be flexor/extensor/ mixed and may be symmetric/ asymmetric [8]. Spasms typically occur in clusters and are seen before falling asleep or when waking up from sleep [8].
- *Subtle spasms*: Episodes of activities such as head-nod, facial grimacing, eye movements, yawning, gasping associated with hypsarrhythmia.
- *Infantile spasms – single spasm variant (ISSV):* Infantile spasms occurring singly and not in clusters [8].
- *Epileptic spasms*: Clinical spasms associated with an epileptiform electroencephalogram [EEG].
- *Epileptic spasms without hypsarrhythmia*: Presence of clinical spasms and epileptiform abnormalities other than hypsarrhythmia or its variants on EEG [8].
- **West syndrome*: Children with epileptic spasms in clusters with EEG showing hypsarrhythmia or its variants [7].

**Some definitions include the presence of pre-morbid or co-morbid developmental delay or regression, but in the West Delphi 2004 consensus, the development criterion has not been included.*

- Children who have hypsarrhythmia on EEG but no clinical spasms must be referred for expert evaluation. Such children may have subtle spasms, which may be missed by parents and may be picked up on a video EEG recording. Home videos may also assist in picking up subtle spasms.

Etiology

Most recent studies classify spasms into two broad categories- known and unknown etiology. Known causes can further be classified into pre-natal, perinatal and postnatal, depending on the timing of central nervous system insult. Another classification scheme is as per the new ILAE 2017 classification [2], wherein the etiology is classified into structural-metabolic, genetic, infectious, etc. However, this can be a bit confusing as there may be overlaps; e.g. tuberous sclerosis may be classified as both structural and genetic. For practical purposes, the etiology should be classified as known or unknown. If known, the exact etiology should be mentioned.

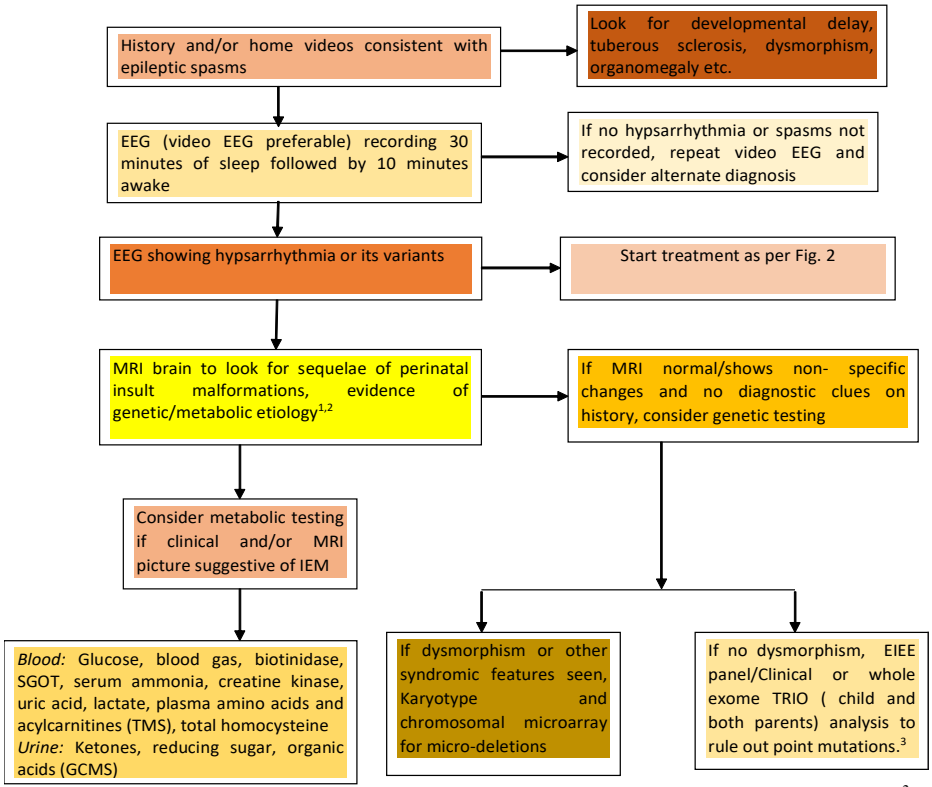
The etiological profile of WS in India is different, as compared with the developed world, where genetic and presumed genetic (unknown etiology) is higher. In India, the etiology is known in 80-85% of affected children [3,4]. Perinatal causes, including perinatal hypoxia and neonatal hypoglycemia are the most predominant [3,4].

Diagnosis of WS

Clinical suspicion remains the cornerstone of diagnosis of epileptic spasms. An evaluation including a thorough history, examination and EEG are important in the diagnosis of infantile spasms. As etiology is the most important predictor of outcome, efforts should be made to establish the underlying etiology, as this may also affect the treatment decisions and prognosis; e.g. children with tuberous sclerosis complex are more likely to respond to VGB, while most with unidentified etiology may respond better to steroids. The evaluation should follow a step wise process to avoid unnecessary tests, due to the costs involved **(Fig. 1)**.

Electroencephalography (EEG)

An EEG (preferably video-EEG) is the most important tool in diagnosis and management of epileptic spasms, and the following protocol may be followed:



[1]In low resource settings, CT may be considered as initial investigation, especially if the etiology is likely perinatal asphyxia; [2]If initial MRI normal, consider repeating after the age of 2 years, with MRS, if unknown etiology and persisting spasms. In case of refractory spasms, especially if asymmetric, consider FDG PET to look for focal cortical dysplasia, in consultation with expert; [3]Detailed pedigree should be drawn although family history may or may not be contributory as many variants are de novo; IEM: Inborn error of metabolism, EIEE: Early infantile epileptic encephalopathy; TMS: Tandem mass spectrometry; GCMS: Gas chromatography mass spectrometry; SGOT: Serum glutamic oxaloacetic transaminase.

Fig. 1 Diagnostic algorithm for child with West syndrome.

Basic level: Recording for sufficient length to capture sleep is strongly recommended and if achieved, further recording for at least 10 minutes after awakening should be attempted, as epileptic spasms occur very often in that period. The EEG should be planned preferentially during spontaneous sleep and after feeding. This may require planning arrangements with parents. In infants whose EEG is abnormal and the epileptic spasms have not been captured during the EEG, a home video is suitable to establish presence of clinical spasms.

Advanced level: If there is diagnostic uncertainty e.g. if EEG is not diagnostic or spasms are not observed, a prolonged overnight inpatient video EEG recording for 24 hours with polygraphic (with neck and bilateral deltoid EMG) parameters is desirable as it will capture awake as well as all sleep stages and possibly also capture spasms. However, if inpatient facilities are not available, a prolonged EEG record for 2-4 hours to capture stage 2 of non-REM sleep followed by 30 minutes after awakening should be considered [5]. Long term video EEG may also pick up other coexisting seizure types, as noted in 22% of infants with epileptic spasms in a study; especially in those who had etiology of preterm birth or birth asphyxia [6].

Depending on the clinical and EEG findings, the level of diagnostic certainty can be classified as confirmed, probable and possible WS according to following criteria [1,5]:

a) *Confirmed WS:* When interictal EEG shows hypsarrhythmia (or its variants) along with either electroclinical documentation (ictal EEG showing electrodecremental response) or home video showing cluster of spasms.

b) *Probable WS (High diagnostic certainty):* When clinical history is suggestive of spasms but EEG shows multifocal discharges but not hypsarhythmia or its variants.

c) *Possible WS (Low diagnostic certainty):* When history of spasms is doubtful, and EEG shows multifocal discharges and not hypsarhythmia or its variants

Depending on the clinical and EEG findings, the level of diagnostic certainty can be classified as confirmatory, probable and possible WS [1,5]. In probable or possible cases, parents should be encouraged to bring home video of the spasms. Repeat EEG at advanced level can be planned to record hypsarrhythmia or spasms.

Following the initiation of any first line treatment, the efficacy of therapy should be assessed within 2-3 weeks; in terms of cessation of spasms and resolution of hypsarrhythmia on EEG [4]. If no/partial response to treatment is seen, a repeat EEG may be considered to plan the next level of treatment. EEG should also be repeated after 2 weeks if the first EEG **is** normal or inconclusive, or if there is a suspicion of additional/change in seizure type, which may occur in 12-42.3% of cases [6]. If focal abnormalities are identified in infants with additional focal seizures, further investigations like high resolution multi-modality magnetic resonance imaging (MRI)/ positron emission tomography (PET) can be planned to search for a resectable lesion [6].

2. *Consensus statement: EEG for Suspected West Syndrome*

- EEG evaluation with standard 10-20 system of electrode placement with preferably 3 additional surface EMG electrode channels (over the neck and bilateral deltoids) is recommended within 24-48 hours of suspected diagnosis. Video-EEG recording of at least 30 minutes of sleep followed by brief awake state should be attempted to capture hypsarrhythmia and ictal correlate of spasms.
- Prolonged video EEG recording may be required if the EEG is not diagnostic or the spasms are not observed or there is uncertainty regarding the diagnosis.
- Sleep may be induced using chloral hydrate, triclofos, or melatonin; although, natural sleep is preferred. The diagnostic patterns include inter-ictal pattern of hypsarrhythmia or its variants and ictal patterns of spasms.
- Repeat EEG may be considered:
  - After clinical cessation of spasms, to document resolution of hypsarrhythmia on EEG;
  - If the first EEG was normal/ inconclusive;
  - If there is suspicion of additional/change in seizure type; and
  - If the there is no/partial clinical improvement.

EEG Patterns of WS

EEG background is mostly abnormal during both wakefulness and sleep. The inter-ictal patterns vary according to the underlying pathology, age and stage of sleep.

Inter-ictal patterns:

a. Hypsarrhythmia: This term describes a characteristic high voltage, completely disorganized and chaotic pattern consisting of random high voltage slow waves and spikes. These spikes vary from moment to moment,

both in location and duration. At onset, hypsarrhythmia may be present only during drowsiness and light sleep, but soon becomes abundant during wakefulness. During stage 2 and 3, there is an increase in the spikes and polyspikes; which become more synchronous, causing fragmentation of the hypsarrhythmic activity, giving a quasi-periodic appearance [5,7]. The hypsarrhythmia pattern usually attenuates in REM sleep. Capturing wakefulness after sleep is crucial to demonstrate the chaotic background activity considered typical of hypsarrhythmia.

b. Hypsarrhythmia variants/ modified hypsarrhythmia: Up to 33% patients do not show hypsarrhythmia [7]. Several variants have been described: rapid, slow, asymmetric, unilateral and even suppression burst like patterns [8]. Many of these variations correlate with neuropathology. Asymmetric hypsarrhythmia constituted 23% of cases with hypsarrhythmia in a study and indicates the importance of identifying focal hemispheric abnormalities like cortical dysplasia; more so if in infants with asymmetric spasms [9]. Also, hypsarrhythmia may not be seen in late onset spasms [9].

Ictal EEG pattern (during spasms): The most common pattern seen in 72% of the attacks is a brief duration (1-5 sec) three phased pattern: *a*) diffuse high amplitude slow wave, *b*) low amplitude fast activity, and *c*) short lasting diffuse flattening of ongoing activity (electro-decremental response) [10]. In asymmetric spasms, there may be focal discharges preceding, during or following it; indicating the side with focal cortical lesion.

Evolution of EEG: On effective treatment, rapid improvement in EEG is seen, which may even completely normalize. However, resolution of hypsarrhythmia with persistence of background abnormalities occurs more frequently, as a reflection of underlying abnormalities. In most symptomatic cases, there is return of spike wave discharges with development of other seizure types [11]. The chaotic pattern gradually becomes more organized and disappears by 2-4 years and may evolve into other abnormal patterns [12].

Neuro-imaging Studies

If available and feasible, MRI is preferred over Computed Tomography (CT) scan in view of higher yield of abnormalities. Early MRI (T2, T1, FLAIR) with epilepsy protocol should be considered to reach an etiologic diagnosis. However, treatment should not be delayed if MRI cannot be done immediately due to lack of availability or need of anesthesia.

One third of cases considered idiopathic on clinical assessment enter the symptomatic category of structural-metabolic following the MRI scan. In the National Infantile Spasms Consortium, a causal abnormality was identified in 40.9% of infants who underwent MRI with epilepsy protocol, making it the highest yield test [13]. Common abnormalities picked up in Indian scenario include sequelae of perinatal asphyxia and hypoglycemia.

Timing of MRI: Ideally MRI should be obtained prior to initiation of therapy, as Adrenocorticotropic hormone (ACTH) therapy may cause transient abnormalities that may be falsely misinterpreted as brain atrophy. Also, Vigabatrin (VGB) can induce T2 signal abnormalities [14]. On the other hand, MRI done in early infancy may miss cortical dysplasias in view of immature myelination [15].

Repeat MRI: If initial MRI is normal, and seizures persist, MRI may be repeated after 6 months, and certainly at 24-30 months age when myelination is more mature [11].

Additional neuroimaging studies: Magnetic resonance spectroscopy (MRS) can help to delineate a possible metabolic or mitochondrial cause. Areas of hypo metabolism on a Positron emission tomogram (PET) may indicate a cortical malformation. PET may be important in a child with asymmetric spasms, focal EEG changes and a normal MRI of the brain. Positive PET localization has led to seizure remission following the resection surgery done (based on the PET finding) even with a normal MRI [16]. Ictal and interictal single photon emission computed tomography (SPECT) has been used to aid in the localization of the epileptic focus in children with asymmetric infantile spasms who are being evaluated for surgery.

3. *Consensus Statement: Neuroimaging in WS*

- MRI is the neuroimaging modality of choice, and should be considered for etiologic diagnosis in children with WS. However, if it is delayed for any reason, treatment should be started without waiting for the imaging.
- In low-resource settings, if there is clear history of perinatal asphyxia or neonatal hypoglycemia, an initial CT scan may suffice. However, if the CT is normal, an MRI must definitely be considered.
- If the first MRI is normal, repeat MRI (preferably 3 Tesla, with epilepsy protocol incorporating 3D FLAIR, STIR, SPGR sequences and optionally diffusion weighted MRI with post processing) should be considered after the age of 24 months (when the myelination is complete) to pick up any cortical dysplasia missed on early MRI or any additional findings which may help to suspect a genetic/ metabolic etiology.

- If previous MRI with epilepsy protocol is normal, additional studies like MRS, PET and SPECT may be considered if there are asymmetric spasms, focal features on EEG with spasms refractory to treatment, especially in children with tuberous sclerosis. However, the patient should be referred to an expert for planning these studies.

Metabolic Evaluation of West Syndrome

More than 25 IEM have been found to be associated with WS, with frequency of metabolic disorders in epileptic spasms estimated to be 4.7% [13]. A wide range of metabolic disorders, including mitochondrial disorders, such as Leigh's disease, aminoacidopathies, such as non-ketotic hyperglycinemia, can present with infantile spasms. Other metabolic conditions include glucose transporter defects, pyridoxine deficiency, pyridoxal-5-phosphate deficiency, disorders of cerebral folate metabolism, Menkes' disease, and biotinidase deficiency. At the very least, disorders treatable at low cost-e.g. pyridoxine dependency and biotinidase deficiency should be ruled out, if required, by a therapeutic trial.

Clues to the presence of IEM include a positive family history, consanguinity, previous sibling deaths, failure to thrive, fluctuating course, deterioration after a period of apparent normalcy, tone abnormalities or movement disorders. Ophthalmological examination, unusual odors and visceromegaly may provide other clues. MRI may show non-specific or specific patterns (for few disorders). However, if none of these features are present, the yield of metabolic investigations is very low [17].

4. *Consensus Statement: Metabolic Testing*

- Metabolic evaluation should be considered if
  - No specific etiology can be identified on examination and MRI; or
  - Clinical clues to the presence of underlying metabolic etiology including coexistent movement disorder, failure to thrive; or systemic findings; or
  - There is poor response to conventional treatment.
- First tier investigations:
  - Blood: Glucose, blood gas, biotinidase, Serum glutamate oxaloactetate Transaminase (SGOT), serum ammonia, creatine kinase, uric acid, lactate, plasma amino acids and acylcarnitines (Tandem Mass Spectrometry) total homocysteine
  - Urine: Ketones, reducing sugar, organic acids (Gas Chromatography Mass Spectrometry)
- Second tier investigations: Depending on the results of the first-tier tests and clinico-radiological clues.
  - Blood: Lysosomal enzymes, very long chain fatty acids,
  - Urine: oligosaccharides,
  - CSF: glycine, lactate/pyruvate, neuro-transmitters.
- Plasma / CSF glucose ratio after a 4 hour fast is a low-cost test to diagnose a treatable disorder (Glucose transporter defect), hence it can be done even as a first line test.

Genetic Evaluation

Genetic causes are being increasingly recognized in epileptic encephalopathies of unexplained etiology. A timely genetic diagnosis has potential for precision treatment decisions, which can improve seizure and development outcomes. It also helps to counsel the parents regarding prognosis and recurrence risk in future pregnancies. A combination of genetic tests provided a definitive diagnosis in more than 40% of children presenting with new-onset spasms without an obvious cause after clinical evaluation and MRI [4,13,18].

Copy number variants (CNVs) are deletions and duplications of stretches of DNA ranging from 1 kb to an entire chromosome. These CNVs can be detected by chromosomal microarrays (CMA) which include comparative genomic hybridization (CGH). Pathogenic CNVs were detected in 3.6-11.8% of children with epileptic encephalopathies [17]. The yield is likely to be higher in case of associated dysmorphism, intellectual disability, developmental delay disproportionate to seizure etiology/frequency, and presence of behavioral issues including autism in non-consanguineous families.

The applications of NGS include targeted gene panel, whole exome (WES) and whole genome sequencing (WGS). However, WES has shown to have higher diagnostic yield compared to gene panels, as it sequences the entire coding genome. The current diagnostic yield of genetic tests is below 60%; and a substantial number of patients may still remain undiagnosed.

In one Indian study, in 36 patients with WS with presumed genetic etiology, genetic causes were identified in 17 children [4]. In a multicentric study, out of 100 infants with epileptic spasms of unknown cause undergoing whole exome sequencing, pathogenic mutations were identified in 15 [19]. Etiology was more

likely to be identified in those children who had abnormal development (32.5%) vs. those with normal development (8.3%) [19].

5. *Consensus Statement: Genetic Testing*

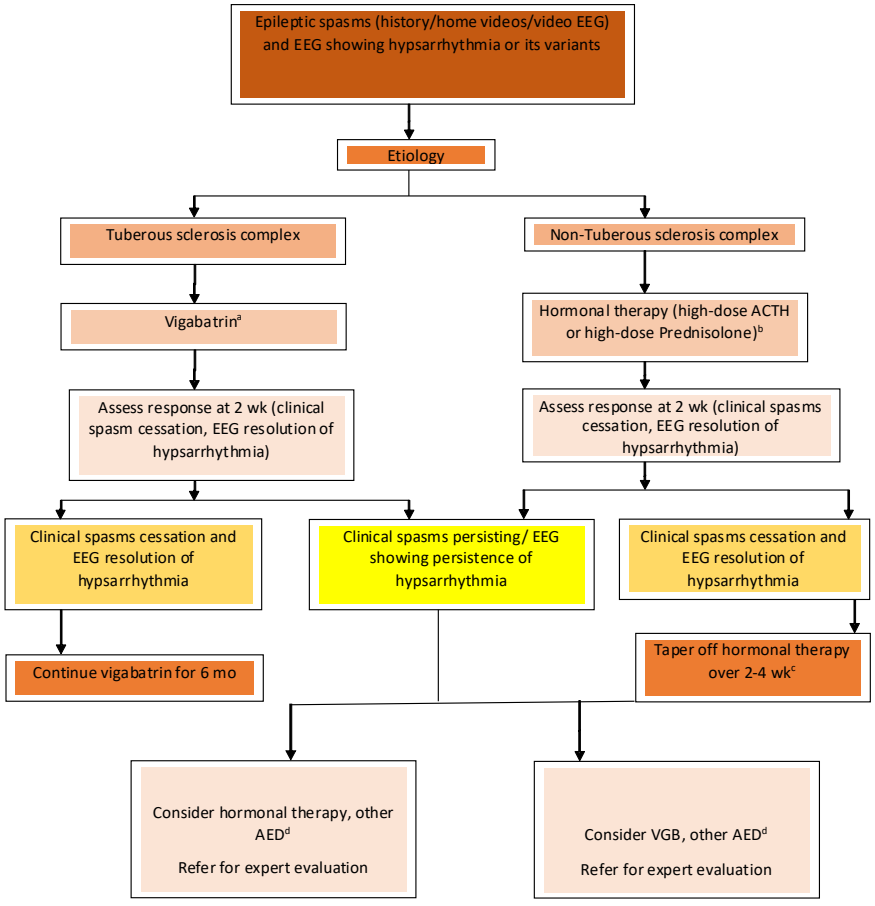
- Genetic testing should be considered if history, clinical examination or MRI suggests an unknown or a known genetic etiology.
- It should also be considered in children with dysmorphism
- Pre and post-test counselling of parents to explain what to expect from the test and the implications of pathogenic/ likely pathogenic/VUS/negative results is recommended.
- In children with dysmorphism, karyotype and CGH microarray florescent in-situ hybridization (FISH) should be the first-line tests.
- WES in trios with parental samples to enable variant segregation should be done if first line tests are negative. American College of Medical Genetics and Genomics (ACMG) criteria should be used in consultation with a geneticist to ascertain the pathogenicity of an identified variant [20].
- In children without dysmorphism, clinical/whole exome sequencing trio testing should be the first line genetic testing.

Treatment

The treatment algorithm for WS is shown in **Fig. 2**.

First-line Treatment Options

High-quality evidence is available for hormonal therapy (adrenocorticotropic hormone or oral steroids), VGB and combination of hormonal therapy with VGB in the treatment of WS. The United Kingdom Infantile Spasms



[a]Vigabatrin dose: Start with 50 mg/kg/d and hike by 50 mg/kg every 3-7 d interval as tolerated to a maximum dose of 150 mg/kg/d; [b]ACTH Dose: 150 IU/m^2 or 6 IU/Kg IM daily for 2 wk, Oral Prednisolone dose: 4 mg/kg/d for 2 wk; [c]If EEG shows continued presence of epileptiform abnormalities despite the resolution of hypsarrhythmia, consider starting sodium valprote, topiramate or zonisamide for 12-24 mo; [d]Other AEDs which may be considered include topiramate, zonisamide, benzodiazepines, or sodium valproate. Pyridoxine trial may be considered in cases with unknown etiology.

Fig. 2 Treatment algorithm for West syndrome.

Study compared hormonal treatment with VGB for epilepsy and development outcome at short-term (14 months and four years of age). It was observed that hormonal therapy was superior in terms of an initial cessation of epileptic spasms, but not at 14 months and four years of age [21]. However, successful initial control of epileptic spasms was associated with better long-term developmental outcome [22].

Recently, the effectiveness of the combination of hormonal therapy with VGB was studied in comparison with hormonal therapy alone [23,24]. Initial results demonstrated that the combination therapy was significantly superior to the hormonal therapy for the cessation of epileptic spasms as a short-term response. However, the combination therapy did not significantly improve epilepsy or neurodevelopmental outcome at 18 months of age. Pyridoxine, as an adjunct with steroid therapy was not been found superior to steroid therapy alone [25].

6. *Consensus Statement: First-line treatment for WS*

The first-line treatment options are hormonal therapy (adrenocorticotropic hormone or oral steroids) and VGB. Hormonal therapy should be preferred for cases other than tuberous sclerosis complex and VGB should be the first choice for tuberous sclerosis complex. Regarding combination treatment, in view of limited literature, the group suggested the need for more data, before recommending as it as routine first line treatment.

Hormonal Therapy

Hormonal therapy in the form of ACTH and oral steroids has been widely used. ACTH has disadvantages of parenteral route and cost. Oral steroids have advantages of ease in administration due to oral route and low-cost. It is difficult to summarize evidence comparing these two modalities of treatment, as different preparations (synthetic and natural ACTH), different doses of ACTH and prednisolone, and different regimens have been used in various studies. Also, many of the studies were underpowered or used varying outcomes. The most important outcomes would be electroclinical resolution and neurodevelopmental outcomes. However, many studies have only used clinical spasm cessation, or surrogate markers such as EEG improvement.

In the 2004 United Kingdom Infantile Spasms study, spasm freedom was achieved in 70% of children taking high dose oral prednisolone (40-60 mg/day) and 76% of children taking ACTH (40 IU/alternate day) [21]. A few recent studies [26,27]used high-dose oral steroids as initial management of WS, and subsequent treated failed cases with ACTH and demonstrated a response rate of 40% and 33% respectively, with high-dose ACTH therapy among non-responders with high-dose oral steroids [26,27]. Two recent systematic reviews have suggested equivalent efficacy of high dose prednisolone as ACTH [28,29].

Dosage schedule for ACTH: Typically, in the high dose schedule, 150 IU/m^2/BSA has been used, and in the low dose schedule, 20-30 IU/day has been used [30]. There is a need of high-quality studies and evidence to conclude the optimum dosing protocol of ACTH.

Dosage schedule for prednisolone: In the previously mentioned UK Infantile spasms study, 40-60 mg/day of oral prednisolone was used [21]. However this dose may be too high for our smaller size infants. Chellamuthu et al have studied high dose (4 mg/kg) vs. 2 mg/kg daily oral prednisolone in a randomized controlled trial and demonstrated the higher effectiveness (52% versus 25%) of high-dose prednisolone with similar adverse event profile [31]. Some centers advocate very high 8mg/kg/day as initial dosing protocol [26]. There are concerns of infection and tolerability issues with very high dose of oral steroids.

7. *Consensus Statement: Hormonal therapy in WS*

- Both ACTH and high-dose prednisolone have reasonably similar efficacy and adverse effect profile for the treatment of WS.
- The initial choice depends on the preference of the treating pediatrician/neurologist and family, based on factors of cost, availability of infrastructure and personnel for daily intramuscular injections.
- High-dose ACTH therapy may also be considered in cases who failed to response with oral steroids.
- High-dose ACTH is a preferred therapeutic option as compared to low-dose ACTH. Suggested dose is 150U/m^2/BSA or 6U/kg intramuscular once daily for two weeks to assess therapeutic response.
- High dose prednisolone (4 mg/kg/day) is recommended in view of better efficacy and similar tolerability to the usual dose (2 mg/kg/day). This treatment should be given for 2 weeks to assess response.
- If there is clinical spasms cessation, EEG should be performed to look for resolution of hypsarrhythmia. If there is EEG resolution as well, i.e. electroclinical cessation, then the first line drug (ACTH/prednisone) should be tapered off over 2-4 weeks.
- In case there is no clinical spasms cessation or persistence of hypsarrhythmia on EEG, then the first line drug should be tapered off and second line treatment should be started.

Further treatment after electroclinical resolution

There is no published evidence on what treatment the child should be started after there is clinical cessation of spasms and EEG resolution of hypsarrhythmia or its variants. There is no evidence that anti-epileptic drug treatment will prevent relapses or further development of epilepsy.

8. *Consensus Statement: Further Treatment After Electroclinical Resolution*

After clinical cessation of spasms, if the EEG shows resolution of hypsarrhythmia, the following actions are recommended:

- If the EEG is normal, or shows background abnormalities such as slowing but no epileptiform abnormalities, then the hormonal therapy can be tapered off and there is no need to start any other anti-epileptic drug treatment.
- If the EEG shows epileptiform abnormalities such as multifocal or focal spike wave discharges, the patient may be started on an anti-epileptic drug such as topiramate, sodium valproate and/or zonisamide for a period of 12-24 months (there is no evidence to prefer any one of these AEDs).

Treatment of Relapses

Relapse of epileptic spasms is frequent and constitute major challenge as it is an adverse prognostic variable for long-term epilepsy and neurological outcome [32]. There is a paucity of evidence on how to manage these patients. Options include a second trial of hormonal therapy or starting VGB.

9. *Consensus Statement: Treatment of Relapses*

The treatment of children who have initially responded with hormonal therapy should be individualized. Options include a repeat trial of hormonal therapy or vigabatrin.

Monitoring and Precautions on Hormonal Therapy

There are no published guidelines or recommendations on the plan of investigations before and during steroid or ACTH therapy in children with WS. The dwelling environment and socioeconomic strata would determine the risk of exposure to pathogens and subsequent infection.

Both ACTH and oral steroid treatment are commonly associated with adverse effects such as irritability, increased appetite, hypertension, weight gain, hyper-pigmentation and risk of infections. Adverse effects are associated with high dose and longer duration of therapy. It is routine to monitor blood pressure, blood sugar and urine sugar. There is variability in frequency of monitoring for these adverse effects.

10. *Consensus Statement: Pre-Hormonal Therapy Investigations, Monitoring and Precautions on Hormonal Therapy*

- Screening with chest *X* ray and Mantoux test is recommended in children at high risk, i.e. positive family history of contact and suspected immunodeficiency.
- Children with WS on hormonal therapy should be monitored for adverse effects. Parents should be counseled regarding the adverse effects.
- Clinical surveillance for infections should be done.
- At least weekly blood pressure monitoring needs to be done while the child is on therapy.
- No live vaccines (e.g. oral polio or measles) should be given while child is on hormonal treatment and for 1 month after stopping the therapy.
- Children on systemic corticosteroids for more than 2 consecutive or 3 cumulative weeks within last 6 months are at risk for adrenal insufficiency. Hence in case of inter-current illness, oral intolerance or surgical procedures, hydrocortisone should be administered in a stress dose of 25-100 mg/m^2 in divided doses.

Vigabatrin

Vigabatrin (VGB) is a GABA agonist that acts by inhibiting 4-aminobutyrate transaminase, the enzyme for catabolism of GABA. VGB is the drug of choice for epileptic spasms in tuberous sclerosis [18]. VGB is less effective that hormonal therapy as first line drug in treatment of infantile spasm. In terms of short term efficacy, cessation of spasm ranges from 27.3-55.3% with the use of VGB [21]. However, there is a considerable variation in the definition of spasm cessation among various studies. Apart from TSC, there are few etiological predictors of favorable response to VGB. Data from the International Collaborative Infantile Spasms Study (ICISS) [23] study revealed that children with stroke and infarcts responded well to combination of VGB and steroids when compared to those with other etiology. However, there is limited data on predictors of clinical response to VGB among non-TSC patients with epileptic spasms.

There is limited number of studies on long term efficacy of VGB in infantile spasms. The United Kingdom Infantile Spasms Study (UKISS) included non-tuberous sclerosis infants aged 2–12 months who were

followed up to determine the long term developmental outcome at 12-14 months of age. It was observed that mean Vineland adaptive behaviour scales (VABS) score were comparable between the high dose steroid group and VGB group [22].

There is a considerable variation in the dose and regimen for treatment of children with epileptic spasms. Doses from 18 mg/kg/day to 150 mg/kg/day have been used by many authors for infantile spasm. The dose is increased by 50 mg/kg/day every 3-7 days, to a maximum of 150 mg/kg/day [33].

Visual field defects have been reported with use of VGB [34]. Other side effects reported with use of VGB include sedation, irritability, and hypotonia. There are no standard methods to detect visual field loss among young children. A 30 HZ flicker electroretinography (ERG) has been used to monitor ocular toxicity. The proportion of patients with visual field defects in adults (52%) was noted to be higher than children (34%) in a systematic review of 1678 exposed patients to VGB [34].

11. *Consensus Statement: Vigabatrin in WS*

- VGB is the first line treatment among infantile spasm with tuberous sclerosis complex.
- Among patients with infantile spasm (non-tuberous sclerosis), VGB should be considered for treatment where hormonal therapy/steroids are either contraindicated or has failed.
- VGB is started at a dose of 50 mg/kg/day and hiked by 50 mg/kg every 3-7 days interval as tolerated to a maximum dose of 150 mg/kg (max within 14 days) or cessation of clinical and electrophysiological spasm has been achieved, whichever is earlier.
- If effective, the duration of therapy should generally be limited to six months.
- Parents should be explained the risk of possible visual side effects with use of VGB, and its minimal risk in infants and among those with less than six months of drug.
- Baseline and six-monthly ophthalmological evaluation including fundus examination is recommended for all children on VGB.
- Electroretinography (ERG) is optional at 6 monthly intervals in case of prolonged VGB therapy.

Treatment After Failed Hormonal Therapy and VGB

Other antiepileptic drugs which may be tried in children with epileptic spasms who have failed hormonal therapy and VGB include topiramate, sodium valproate, zonisamide, levetiracetam, and benzodiazepines such as nitrazepam, clobazam and clonazepam. Nitrazepam has been approved by Central Drugs standard Organization (India) for its use in epilepsy. There have also been small studies on the use of pyridoxine (other than when treating pyridoxine-dependent seizures), thyrotropin releasing hormone (TRH), hydrocortisone, sulthiame, and magnesium sulphate. However, considering limited literature with insufficient evidence, none of these drugs are deemed effective in treatment of infantile spasms [35].

12. *Consensus Statement: Treatment After Failure of Hormonal Therapy and Vigabatrin*

- Among children who failed hormonal therapy and VGB, use of benzodiazepines, sodium valproate, topiramate, or zonisamide may be considered.
- A trial of pyridoxine, pyridoxal phosphate, folinic acid and biotin may be considered for a minimum duration of seven days among those with epileptic spasms of unknown etiology and failed response to first line agents.

Dietary Therapies

The ketogenic diet (KD) is a high-fat, low-carbohydrate, and restricted protein diet that has been found useful in the management of WS [36]. KD administration in infants needs hospitalization, monitoring and availability of a trained dietician as the diet must be carefully titrated to achieve seizure reduction and provide calories and proteins for growth [37]. This may be difficult to achieve in a low resource setting. Also, ketogenic formula, which makes KD administration easier for infants, is not easily available in India, and is costly. The modified Atkins diet, which is a simpler and easier to administer version of the KD, has also been found to be effective and well-tolerated in children with infantile spasms [38].

13. *Consensus Statement: Dietary therapies for WS*

- Dietary therapy should be considered in children with WS after the failure of hormonal therapy and/or vigabatrin and one more AED, provided a center providing this therapy is accessible.
- KD is preferable, but in low resource settings, the modified Atkins diet may be used.
- Considerations while starting the diet include family education/motivation, and availability of a trained dietician.
- For infants <18 months of age, in-patient initiation is recommended, lower fat: protein ratios should be used, fine tuning of the diet is needed to maintain growth

- Dietary therapy should be tried for at least 3 months before considering it ineffective
- If effective in controlling spasms, it should be continued for a period of at least 2 years

Epilepsy Surgery

In the recent years, there have been studies on epilepsy surgery in refractory epileptic spasms [25]. The various surgeries reported include total hemispherectomy, subtotal hemispherectomy, multilobar resection, lobectomy and tuberectomy. Curative epilepsy surgery has the best outcomes with EEG-concordant lesional abnormalities on MRI [25]. The advances in neuroimaging and invasive monitoring have facilitated patient selection, presurgical evaluation, and ultimately, resection planning [39].

14. *Consensus Statement: Epilepsy Surgery in WS*

Children should be evaluated for epilepsy surgery after failure of the first line treatments (hormonal treatment and/or vigabatrin), if there is presence of surgically resectable lesions e.g., cortical dysplasias, hemimegalencephaly, Sturge Weber syndrome, tuberous sclerosis, and if there is presence of focal features on clinical semiology of spasms and EEG.

EARLY DIAGNOSIS

As mentioned earlier, the diagnosis of WS is significantly delayed in India, adversely impacting the treatment response and neurodevelopmental outcome [3,4]. In one study, the mean age at diagnosis was 13.1 months and the mean lead time to treatment was 7.9 months [3].

Pre-Symptomatic Diagnosis and Treatment of WS

Certain populations are at high risk of developing WS, such as infants with perinatal brain injury and tuberous sclerosis. There is evidence that asymptomatic infants with tuberous sclerosis complex at high risk of developing spasms and epilepsy can be identified in the pre-symptomatic stage using serial surveillance EEGs. All pre-symptomatic patients with tuberous sclerosis showing epileptiform abnormalities detected on serial surveillance EEGs went on to develop epilepsy [40]. Presence of epilepsy in tuberous sclerosis is an important association for mental retardation/intellectual disability. Antiepileptic treatment with VGB in this high-risk group, identified on serial EEGs, can significantly reduce the rates of evolution of asymptomatic EEG abnormalities to epilepsy and give a much better neuro-developmental outcome (nearly 80% normal development vs 20%, with standard treatment) Furthermore, the rates of drug resistant epilepsy were 7 % vs 42 % in the preventive vs standard groups [40].

There are also a few retrospective studies with small numbers of patients on the EEG findings preceding the onset of epileptic spasms and hypsarrhythmia in infants with perinatal asphyxia and periventricular leukomalacia. More evidence is needed before routine serial surveillance EEGs are recommended for presymptomatic diagnosis of WS in at-risk infants with perinatal brain injury.

15. *Consensus Statement: Early Diagnosis*

- Health professionals dealing with follow up and early intervention of high-risk infants should be trained to ask about and recognize epileptic spasms.
- Parents of high-risk infants should be made aware about the risk of epileptic spasms and educated to recognize spasms and report to a health facility early in case spasms occur.
- In every infant with developmental delay, the presence of epileptic spasms must be enquired for, especially at the 10 week and 14 week immunization visit.
- If spasms are suspected, an EEG should be urgently obtained within 24-48 hours.
- Infants diagnosed with tuberous sclerosis complex antenatally or at birth should be referred to a pediatric neurologist for consideration of surveillance EEGs, monthly from 2 mo of age, and presymptomatic treatment with VGB.

Supportive Care

Key facets of supportive care in WS include issues pertaining to nutrition, sleep, dental care, behavior, cognition and schooling.

16. *Consensus Statement: Supportive care in WS*

Anticipatory evaluation and appropriate management of co-morbidities (specifically related to feeding, oral hygiene, neuromotor delays, constipation, sleep, and growth retardation) should be ensured. Schooling, as per cognitive abilities, should be ensured. Disability certification, if eligible as per government guidelines, should be proactively arranged, so as to facilitate financial and other support.

CONCLUSION

In this article, the guidelines for the diagnosis and management of West syndrome are provided. These are based on the current evidence and where-in the evidence is insufficient, expert opinion. The neurodevelopmental outcomes of children with West syndrome are likely to improve with timely diagnosis and early appropriate management. As there is on-going research on the many facets of treatment, and there are still many unanswered

questions, an update of these guidelines will be provided when new evidence emerges.

Acknowledgment: Dr Sushma Goyal and Dr Chaitanya Datar for helpful inputs in the EEG and genetic testing sections, respectively.

Contributors: SS and RM: conceptualized the idea; SS, JSK, KS, JS, JNG, RM, KPV: constituted the writing committee and drafted the manuscript; JSK devised and conducted Delphi process. All the authors approved the final version of the manuscript.

Funding: The logistics of faculty travel for the West syndrome Delphi Consensus meeting was funded by Intas Pharmaceutical Ltd. and Ferring Pharmaceuticals. The venue support was provided by Army Hospital, Research and Referral, Dhaula Kuan, New Delhi. None of the funding sources had any role in content of the discussion during meeting, or in report or manuscript preparation. They did not have access to any version of the manuscript.

Competing interests: None stated.

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Annexure 1

Association of Child Neurology – Indian Epilepsy Society Expert Committee (*alphabetically arranged*)

Razia Adam (Hyderabad, Telengana); Satinder Aneja (Noida, Uttar Pradesh); Biswaroop Chakrabarty (Delhi); Arijit Chattopadhyay (Kolkata); Saurabh Chopra (Delhi), Rajni Farmania (Delhi); Pradnya Gadgil (Mumbai, Maharashtra); Divyani Garg (Delhi); Jatinder Singh Goraya (Ludhiana, Punjab); Sheffali Gulati (Delhi); Aparajita Gupta (Kolkata, West Bengal); Rachana Dubey Gupta (Indore, Madhya Pradesh); Vineet Bhushan Gupta (Delhi); Anaita Udwadia Hedge (Mumbai, Maharashtra); Mary Iype (Trivandrum, Kerala); Vivek Jain (Jaipur, Rajasthan); Prashant Jauhari (Delhi); Veena Kalra (Delhi); Mahesh Kamate (Belgavi, Karnataka); Lakshminarayanan Kannan (Chennai, Tamil Nadu); Anupriya Kaur (Chandigarh); Gurpreet Kochar (Ludhiana, Punjab); Ramesh Konanki (Hyderabad, Telangana); Ajay Kumar (Patna, Bihar); PAM Kunju (Trivandrum, Kerala); Lokesh Lingappa (Hyderabad, Telengana); Priyanka Madaan (Chandigarh); Ranjith Kumar Manokaran (Chennai, Tamil Nadu); MM Mehendiratta (Delhi); Ramshekhar Menon (Trivandrum, Kerala); Devendra Mishra (Delhi); Debasis Panigrahi (Bhubneshwar, Orissa); Harsh Patel (Ahmedabad, Gujarat); Sandeep Patil (Pune, Maharashtra); Bijoy Patra (Delhi); Leema Pauline (Chennai, Tamil Nadu); KVN Raju (Bangalore, Karnataka); Arushi Gehlot Saini (Chandigarh); Lokesh Saini (Chandigarh); Naveen Sankhyan (Chandigarh); Rachna Sehgal (Delhi); Anita Sharma (Delhi); Pratibha Singhi (Gurgaon, Haryana); Vishal Sondhi (Pune, Maharasthra); Renu Suthar (Chandigarh); Sanjeev V Thomas (Trivandrum, Kerala); Manjari Tripathi (Delhi); Vrajesh Udani (Mumbai, Maharasthra); Prashant Utage (Hyderabad, Telengana); Nitish Vora (Ahmedabad, Gujarat); Sangeeta Yoganathan (Vellore, Tamil Nadu).

Neonatal Total Parenteral Nutrition: Clinical Implications From Recent NICE Guidelines

BH Prathik,[1] Abhishek Somasekhara Aradhya,[2] Tanushree Sahoo,[3] and Shiv Sajan Saini[4]

From Departments of Pediatrics, [1]Indira Gandhi Institute of Child Health, Bengaluru, Karnataka;[2]Ovum Woman and Child Speciality Hospital, Bengaluru, Karnataka;[3]Department of Neonatology, All India Institute of Medical Sciences, Bhubaneshwar, Orissa; and [4]Division of Neonatology, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh; India.

Correspondence to: Dr Shiv Sajan Saini, Assistant Professor, Division of Neonatology, Department of Pediatrics, Post Graduate Institute of Medical Education and Research,Chandigarh 160012, India. Email: sajansaini1@gmail.com

Postnatal growth failure and its impact on the long term outcomes in preterm neonates is a long-standing problem. Optimal and aggressive nutrition strategies are required to ameliorate these concerns. Total parenteral nutrition (TPN) is widely practiced in management of preterm neonates. Recently published National Institute for Health and Care Excellence (NICE) guidelines provide recommendations for best practices for parenteral nutrition in neonates. However, healthcare associated sepsis, expertise as well as infrastructure of TPN, monitoring facilities and cost remain major constraints for widespread use of TPN in resource limited settings. Current update is aimed to summarize NICE and European society for Clinical Nutrition and Metabolism (ESPEN) guidelines to inform best practice for TPN for neonatologists in India.

Keywords: *Central venous access, ESPEN guidelines, Lipids.*

Preterm neonates, mostly <1500 g birthweight and/or <32 weeks gestation, are prone to subsequent growth failure. Growth failure in preterm neonates is associated with long term malnutrition and poor neurodevelopmental outcomes [1,2]. This growth failure can be ameliorated by balancing nutrition needs with optimal total parenteral nutrition (TPN) and aggressive enteral feeding [3]. Early parenteral nutrition (≤48 hours of life) in preterm neonates leads to earlier attainment of birthweight and improved weight at discharge [4]. Therefore, TPN is currently a useful strategy to achieve optimal postnatal growth, especially when enteral nutrition is compromised because of prematurity and/or underlying illnesses. Recently, National Institute for Health and Care Excellence (NICE) guidelines [5] summarized and reported available evidence systematically using the GRADE profile. NICE guidelines have recommendations on whom and when to start TPN, constituents, monitoring, and stopping TPN. Currently, there are no available national guidelines for parenteral nutrition in neonates in our country. There are wide variations in how the TPN is initiated, hiked, and monitored depending upon individual unit practices. In this update, we have summarized NICE guidelines, and compared them with European society for Clinical Nutrition and Metabolism (ESPEN), 2018 guidelines [6], to inform best practices and standardize optimal utilization of TPN (**Table I**).

Implications for Resource Limited Settings

There are specific challenges in the direct implementation of both of these guidelines in our country. The main concerns are as follows:

TPN in term/late preterm: Most of the late preterm or term neonates are managed in public sector hospitals in Special newborn care units (SNCU). Starting TPN in these units will be a challenge due to understaffing, lack of training, and infrastructure for TPN prescription.Smaller units in the private sector also face similar challenges. Evidence shows that early initiation of TPN by seven days among critically sick term neonates is associated with an increased incidence of sepsis and decreased likelihood of earlier live discharge compared to TPN initiation after day 7 of ICU stay [7]. These adverse outcomes are likely to worsen in the absence of proper asepsis and standardized practices. However, neonates in the late TPN group experienced hypoglycemia more often. Notably early and late TPN groups had similar mortality rates. Therefore, it is challenging to recommend delayed initiation of TPN in late preterm and term neonates with the available evidence.

TPN formulation (Standardized TPN): Availability and cost is a significant concern for widespread usage. In most developed countries, TPN is prepared and dispensed by trained central pharmacists. Contrastingly, TPN is

Table I Comparison of National Institute for Health and Care Excellence (NICE) guidelines with European Society for Clinical Nutrition and Metabolism (ESPEN)Guidelines for Total Parental Nutrition in Neonates

	NICE guidelines, 2020[5]	*ESPEN guidelines, 2018 [6]*	*Remarks*
Whom to start?	Immediate perinatal period: • Gestational age ≤31 wks – Start in all • 31 wk-insufficient feeds progression in first 72 h Previously established enteral feeds which was stopped due to illness: If enteral feeds are unlikely to start in 48 h (preterm neonates) or 72 h (term neonates)	Not mentioned	NICE guidelines recommend to start TPN in all neonates ≤31 wk gestational age. However, due to higher incidence of gram-negative sepsis and sepsis related countries, mortality in developing the practice of TPN should be individualized in units depending on resources.
When to start?	Start as soon as possible (preferably within 8 h).	No mention	To be initiated within 8 h of identification of an eligible neonate.
Energy	Day 1: 40-60 kcal/kg Day 2-4: gradually↑ to reach 75-120 kcal/kg/d. >Day 4: (maintenance) 75-120 kcal/kg/d.	Day 1:45-55 kcal/kg/dVLBW: Maintenance 90-120 kcal/kg/d aiming a weight gain of at least 17-20 g/kg/d after initial weight loss.	In view of limited evidence, the wide range of proposed energy intake was an expert consensus to improve consistency of care
Glucose	First 4 days: Initiate at 6- 9 g/kg/day gradually ↑9-16 g/kg/day. After 4 days of life: 9-16 g/kg/day.	Preterm neonates: Start with 5.8-11.5 g/kg/d and gradually ↑to 11.5-14.4 g/kg/d Term neonates: Start with 3.6-7.2 g/kg/d and gradually ↑to 7.2-14.4 g/kg/d	Both the guidelines recommend similarly. There is no clarity on the target range of blood glucose in both guidelines. A reasonable target range would be 100-120 mg/dL.
Amino acids	Preterm neonates First 4 days: Initiate at 1.5-2 g/kg/d, gradually ↑ to 3-4 g/kg/d. After 4 days: Give 3-4 g/kg/d Term neonates First 4 d: Initiate at 1-2 g/kg/d gradually ↑to 2.5-3 g/kg/d After 4 days: Give 2.5-3 g/kg/d.	Preterm neonates Day 1: 1.5 g/kg/d Day 2 onwards: Target 2.5-3.5 g/kg/d Term Neonates Minimum recommended intake of 1.5g/kg/d to maximum of 3g/kg/d.	The upper limit of starting dose and maximum maintenance dose of TPN should be 2 g/kg/d and 3.5 g/kg/d, respectively. For preterm neonates, formulations providing bioavailable cysteine (50-75 mg/kg/d) and taurine (>18 mg/kg/d) amino acids should be preferred [6].
Lipids	Preterm and term neonates First 4 d: Initiate at 1- 2 g/kg/d gradually ↑to 3- 4 g/kg/d. After 4 d: Give 3- 4 g/kg/d. Parenteral nutrition related liver disease:Prefer composite lipid emulsion.	Preterm and term neonates Lipid intake should not exceed 4 g/kg/d. Continuous infusion over 24 h advised. 20% lipid emulsion preferred. Unexplained thrombocytopenia needs lipid dose reduction.	Lipid lower limit (25%) and upper limit (40%) is set for avoiding hyperglycemia and hypertriglyceridemia/fatty liver, respectively.
Electrolytes	Sodium and potassium as per standard daily requirement.	In ELBW and VLBW, electrolytes can be started from day 1 after ascertaining good urine output and also considering the potential of development of non-oliguric hyperkalemia.	Sodium and potassium should ideally be started during the phase of initial weight loss in neonates i.e., from day 2-3 onwards.
TPN volume	No recommendation	Total TPN volume based on weight and day of life	ESPEN recommendations can be used to decide fluid administration.
Calcium	Preterm and term neonates Day 1-2: 3- 4 mg/kg/d Day 2 onwards: 6-8 mg/kg/d	Preterm and term (initially): 3-8 mg/kg/d; Growing preterm: 6-14 mg/kg/d	To avoid aluminium contamination in glass vials, use calcium gluconate packed in plastic container.

continued....

Table I *contd...*

	NICE guidelines, 2020[5]	*ESPEN guidelines, 2018 [6]*	*Remarks*
Phosphate	Preterm and term neonates Day 1-2: 1 mmol/kg/d and Day 3 onwards: 2 mmol/kg/d	Preterm neonates (initially): 1-2 mmol /kg/d Growing preterm:1.6-3.5 mmol/kg/d Term: 0.7-1.3 mmol/kg/d	Despite recommendation on early phosphorus, due to concern of aluminium toxicity with currently available preparations in Indian market, its use is still limited.
Iron	Preterm and term neonates No parenteral iron in first 28 d	Short term TPN (<3wk), not to give parenteral iron	-
Other trace minerals	To start as soon as TPN is started. No specific recommendation on dose	Dose recommendations given for zinc, copper, manganese, selenium, molybdenum, chromium.	Suitable preparation combining all the trace elements in appropriate dosage proportion is often not available, most lack iodine and molybdenum.
Magnesium	To give as soon as TPN is started. No specific recommendation on dose.	Preterm neonates and term (initially): 0.2- 0.5 mg/kg/d Growing preterm: 0.5-0.7 mg/kg/d	In preterm neonates, who are exposed to maternal magnesium therapy, the intake should be adapted to postnatal blood levels. Caution should be exercised in presence of acute kidney injury.
Vitamins	Start at outset as per standard requirement in lipid emulsions	Same as NICE guidelines except doses for term and preterm neonates given separately	Separate preparations of fat soluble and water-soluble vitamins tailor-made for neonates (preferred) currently not available in India.
TPN formulation	Standardized TPN formulation is preferred over individualized formulation except in babies with complex needs	Same as NICE guidelines	Availability and cost is a major concern for using standardized TPN bags in our country.
Venous access in TPN	Central venous access is preferred. Peripheral venous access - If there is anticipated short term use (<5 days) or central access is impractical.	Provides specific recommendations for central lines (type, insertion sites, ports, lumen, dressing method) and strategies for CLABSI prevention. For short-term, allows peripheral line TPN if osmolarity<900 mOsm/L	It is better not to exceed dextrose >12.5% through the peripheral line. Skin disinfection and CLABSI prevention can follow multimodal strategy as per ESPEN guidelines.
Protection from light	Advocated protection of bags, syringes and infusion sets of both aqueous and lipid solutions.	Recommended only for lipid emulsions in preterm neonates.	Most units cover only lipid solutions. Based on European Medicines Agency and Medicines and Healthcare products, Regulatory Agency guidance, all TPN solutions need to be covered.
Use of filters	No recommendation	Recommends use of filters. Membrane pore size for Lipid emulsions: 1.2-1.5 micrometer, and for Aqueous solutions: 0.22 micrometer	ESPEN recommendations are based on RCTs of pediatric patients; however, neonatal studies have not shown a clear benefit of inline filters. Therefore, routine use of inline filters cannot be currently recommended for neonatal TPN.
Stopping TPN	Neonates <28 wk: Stop once enteral feeds 140-150 mL/kg/d is attained Neonates >28 wk and fullterm: Stop	No specific neonatal recommendation	Due to higher incidence of CLABSI and cost of TPN, in Indian scenario, it can be safely

Table continued....

Table I *contd...*

	NICE guidelines, 2020[5]	*ESPEN guidelines, 2018 [6]*	*Remarks*
	once enteral feeds 120-140 ml/kg/d is attained		stopped once neonate starts tolerating atleast 100 mL/kg/d oral feeds

TPN: Total parenteral nutrition; CLABSI: Central line associated blood stream infection; PNALD: Parenteral nutrition associated liver disease, VKBW: Very low birthweight. No recommendation in both guidelines for acetate. Recommendations for glucose, pH, serum electrolytes, triglycerides and liver function tests monitoring are similar in both guidelines.

constituted in India by mixing the individual components by physicians and staff nurses. Manual mixing of various TPN constituents carries a risk of sepsis. There is an additional risk of errors in calculation or adding the right amount of TPN constituents with manual methods.

Micronutrients: Availability of phosphate, trace elements, and multi-vitamin solution in appropriate customized doses for neonates is a concern.

Venous access: Central line is preferred for delivery of TPN for long-term use. However, in most settings, maintenance of the central line and risk of sepsis are major limiting factors. Both guidelines allow peripheral line TPN for short-term use only.

Infections: Due to overcrowding, understaffing, and lack of laminar flow, the risk of infection is higher with TPN usage. The risk of infection can be reduced by strict asepsis during preparation and Quality improvement approaches for central line-associated bloodstream infection reduction.

Monitoring: Frequent monitoring can be a challenge, which can be overcome by using a standardized monitoring chart.

Stopping TPN: Maximal benefit of aggressive parenteral nutrition is achieved by continuing it until enteral feeds intake is above >120-140 mL/kg/day. However, to reduce the risk of sepsis-associated with central lines, TPN can be stopped once enteral nutrition delivers two-third of desired energy intake (roughly 100 mL/kg/day of oral feed).

Cost: Cost of central lines, TPN constituents, and frequent monitoring is an additional cost apart from the hospital stay for sickness and prematurity of the neonates, limiting TPN use across wider settings.

Due to the challenges mentioned above in limited-resource settings, we need to apply these guidelines cautiously in our setup. Moreover, there are no specific recommendations for TPN during cooling, volume, and infection control strategies.

In conclusion, early aggressive TPN ameliorates the risk of growth failure in premature neonates by providing calories and essential nutrients. Some of the best practices as per international guidelines may be contextual and restricted to developed nations. There is an urgent need to set up national guidelines on TPN's standardized use of TPN in neonates in India to achieve its maximum benefits.

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Herbal Medicine-Induced Seizures in Children: Single-Center Experience Over 18 Months

Many common household herbal preparations may have seizurogenic ingredients. We report 15 children with seizures following exposure to such compounds: oral ingestion of liquid preparation in 13, and local application of balm and Eucalyptus oil ingestion in one each. All children, except one, had generalized seizures. This study highlights the need to address this history during evaluation of first seizure, and increase awareness of seizurogenic potential of such preparations.

Keywords: *Adverse effects, Complementary and alternative medicines, Epilepsy.*

It is common practice in Indian households to treat minor ailments with herbal preparations. They are considered natural and safe, and are easily available as over-the-counter medications. The herbal preparations have ingredients like camphor, eucalyptus oil, menthol and other aromatic compounds. All these compounds have adverse effects, with the most serious being their tendency to provoke epileptic seizure. The objective of the present study was to highlight the seizurogenic potential of these components and increase awareness among pediatricians.

This is a case record review, with cases having been evaluated between December, 2018 and June, 2019 at a tertiary care pediatric center in Southern India. All children (up to 18 years) with first afebrile (apparently unprovoked) seizure presenting to emergency room were evaluated and treated as per standard protocol [1]. The necessary investigations like blood sugar, serum electrolytes, electroencephalography (EEG) and neuroimaging were done, with extent of evaluation varying on case-to-case basis, and treating physician's discretion. Children with confirmed acute symptomatic seizures (due to fever, hypoglycemia, electrolyte disturbances, systemic infections) and those with remote symptomatic etiology were excluded. All the children in whom no cause could be identified, but had an antecedent exposure to any of the seizurogenic compounds and/or herbal preparations in any form (enteral, inhalational or local application) were included. Children with unprovoked seizures who were evaluated at other medical centers, but had come for neurological consultation later, were also included if all the inclusion criteria were met. The details of dose, route of exposure, time between exposure and seizure onset, type and duration of seizures were noted.

A total of 15 children (8 girls) met the inclusion criteria, with median (range) age of 4.8 years (6 months-14 years) – 10 were younger than 5 years (**Table I**). All children were with typical development except one child with pre-existing ischemic stroke and left hemiparesis due to mineralizing angiopathy. There was no past history or family history of febrile seizures or epilepsy in any of the subjects. All these herbal medicines were used by the caretakers for treatment of minor ailments like nose block, cold and cough in young children, and headache in older kids.

The most commonly used preparation was a liquid formulation Zinda Tilismath (Karkhana Zinda Tilismath) (13, 86.7%); menthol plus was locally applied for one child and eucalyptus oil ingestion in one child. For Zinda tilismath, drinking after dilution with water was the commonest mode of exposure (n=10), while three children had local application as well. Its ingredients include eucalyptus oil, camphor, menthol, thymol and alkanet root as mentioned in the package insert. One child was exposed to herbal balm with similar composition. The quantity of the liquid preparation used was 2-5 drops (6 of 13 children) and 0.5-2.0 mL (6 of 13 children). One child drank 5 mL of preparation.

Of 15 children, 8 were hospitalized. Two children were admitted for status epilepticus (eucalyptus oil ingestion, 5 mL of liquid formulation); one child was ventilated for 1 day for poor respiratory efforts, and one child was admitted for two days in view of prolonged post-ictal encephalopathy. Five children were admitted for unprovoked seizures for one day each. Mean duration of stay was 2.6 days. Later in the study, children were managed on an outpatient basis if there was unequivocal history of antecedent exposure to one of these compounds, and other causes of acute symptomatic seizures were ruled out. History of previous exposure to the herbal medicine was present in 10 children. The median (range) interval between exposure and onset of seizures was 49 (15-120) minutes. The median (range) seizure duration was 3 minutes (30 seconds-5 minutes). Investigations like blood sugar, serum calcium, magnesium, and serum electrolytes were done in all children to rule out other causes of acute symptomatic seizures, and were normal. EEG was done in ten children and was normal. Five children underwent neuroimaging (computerized tomographic scan, 3; magnetic resonance imaging, 2), which was normal in all. This included two children with status epilepticus and one child with focal seizures. During follow-up of 6-12 months, one child had afebrile seizure and one had febrile seizure after one month and 20 days, respectively; the rest of the children were normal.

To the best of our knowledge, this is the largest case series in children till date, highlighting the seizurogenic potential of herbal medications/compounds. The list of toxic compounds/drugs that can cause acute symptomatic seizures is exhaustive and include compounds like industrial chemicals, pesticides and natural toxins [2]. Among these, natural plant toxins are the main ingredients of many herbal medicines, and encephalo-pathy, seizures, hallucinations, coma and death have been reported [3].

Few animal studies in rats have proven the seizurogenic effects of camphor and 1,8-cineole, which is an ingredient of

Table I Characteristics of Study Subjects

No.	*Age (mo)/ sex*	*Amount ingested* [a]	*Indication*	*Seizure onset (min)*	*Seizure type*	*Seizure duration (min)*	*Hospitalization (d)*
1	24/F	1 mL	URI	90	GTCS	2	None
2	35/M	1 mL	URI	20	GTCS	2	1
3	168/M	1 mL	Headache, body pain	60	GTCS	1	1
4	31/F	2 drops+LA	URI	30	GTCS	5	None
5	6/M	2 drops+LA	URI	20	GTCS	5	None
6	45/F	4-5 drops	For general well being	90	GTCS	0.5	None
7	36/F	Topical[c]	URI	30	GTCS	2	None
8	21/F	5 drops	URI	15	GTCS	2	None
9	18/M	2 mL	URI	60	GTCS	4	2
10	66/M	2 drops	For digestion	120	Focal[b]	3	1
11	20/M	3 drops	URI	30	GTCS	5	None
12	79/M	2 mL	URI	120	GTCS	1	2
13	36/F	5 mL	Accidental ingestion	15	GTCS	30	6
14	118/F	3 drops[d]	Coryza	30	GTCS	45	4
15	73/F	2.5 mL	URI	15	GTCS	5	2

GTCS: Generalized tonic clonic seizures; LA: Local application, [a]of liquid preparation taken orally; [b]with behavioral arrest; [c]Menthol plus balm; [d]Eucalyptus oil.

eucalyptus and other essential oils. They have shown that epileptiform activity is induced by blockade of K^+ channels and upregulation of Ca^{2+} inward currents [4-6]. The toxic effects of these compounds are more pronounced in children due to immature brain. Some of them have dose-related effects and some are idiosyncratic responses. When multiple compounds are present in a preparation, the complex interplay of all ingredients can cause toxic effects [7]. In a similar study by Mathew, et al. [8] on eucalyptus oil inhalation and seizures, 10 patients (5 children) were studied [8]. The mean duration for seizure onset and type of seizures were similar to our study. However, all the patients in that study were evaluated with EEG and imaging, whereas these were done in only a few of the children in this study. This was so because during the later part of the study duration, we could limit our investigations when an unequivocal temporal relation was found with herbal compound exposure.

In previous case reports of camphor poisoning in 4 children (age range 15-36 months), the interval between exposure and seizures was 40 minutes to 2 hours, similar to our study [9,10]. Duration of seizures in this study ranged from 2 minutes to 1 hour, with all requiring admission and observation. Dose was mentioned for only one child (750 mg). In our study, the amount of preparation taken had no correlation with either onset of seizures or duration of seizures (excluding status epilepticus). This is highlighted by the oldest case (case 14) developing seizure after ingesting 3 drops of herbal substance. There were no unique clinical, biochemical, imaging or electrographic findings associated with herbal compound induced seizures in our cohort.

Seizures occurring in association with minor infections without fever, and underlying genetic predisposition for epilepsy could not be ruled out. Two children in our study had seizure recurrence within a month, and that is less likely to be due to single exposure to herbal compounds. Long-term, prospective studies should be done to answer this.

Despite the previous case reports in literature quoting seizurogenic potential of the herbal compounds, this awareness is lacking in both clinicians and parents. This was the reason five children in our study were admitted (and underwent neuroimaging) as either the history was taken later or exposure was not considered causative initially.

Ethics clearance: Institute Ethics Committee of Rainbow Children's Hospital. No. RCHBH 085/03-2019, dated 24 August, 2018.
Contributors: RB, RL, LL, RK: were involved in patients' care and wrote the initial draft. All authors reviewed the manuscript and approved the final version.
Funding: None; *Competing interest*: None stated.

RAMYA BANDI,[1] RINI LATHIYA,[2] LOKESH LINGAPPA[1] AND RAMESH KONANKI[1]*
Departments of [1]Neurology and [2]Genetics, Rainbow Children's Hospital, Banjara Hills, Hyderabad 500 034, Andhra Pradesh, India.
**rameshkonanki@gmail.com*

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Pertussis Epidemic in Lower-Grade Schoolchildren Without Preschool Vaccination Boosters

We investigated the characteristics of patients with pertussis who did not receive preschool vaccination boosters. Fifteen patients with laboratory-confirmed pertussis and 29 pertussis-negative patients were compared. All pertussis-positive patients, but only 17% of pertussis-negative patients, were elementary school age and older. There is a need to study the utility of routine preschool pertussis vaccine booster in Japan.

Keywords: *DPT, Immunization, LAMP, Seroprevalence*.

The pertussis vaccine is effective in preventing *Bordetella pertussis* infection and death, and the risk is high in young infants who do not receive the vaccine [1]. *B. pertussis* infection in siblings is considered a common route of transmission to young infants [2]. Currently, three brands of DPT-IPV (acellular pertussis, diphtheria and tetanus toxoids, and inactivated polio combined) are used in Japan. All contain pertussis toxin and filamentous hemagglutinin (6-23.5 and 23.5-51.5 µg/0.5 mL, respectively), and one contains additional pertactin and fimbriae (5 and 1 µg/0.5 mL, respectively) [3]. Children receive a total of four doses of DPT-IPV: three primary doses at the ages of 3, 4, and 5 months, and one booster dose at 18 to 23 months as a national routine vaccination. In 2018, vaccine coverage for the four doses was 95.0%, 95.7%, 96.2%, and 96.2%, respectively [4]. The preschool pertussis vaccination booster is used in some Asian countries like India, but not in Japan [5]; even though Japan has one of the highest primary pertussis vaccination rates in the world [6]. We, herein present data from an outbreak of pertussis, which occurred mainly in lower-grade school children without preschool vaccination boosters.

A retrospective chart-based study was conducted on patients who visited the Saiwai Pediatric Clinic, Tokyo, Japan, with persistent cough. Patients were examined by board-certified pediatricians for suspected pertussis and received a laboratory diagnosis between August and September, 2018. In accordance with the Pediatric Respiratory Infection Practice Guidelines in Japan [7], diagnostic tests for pertussis were defined as positive by either nasal swab loop-mediated isothermal amplification (LAMP) or anti-pertussis IgM/IgA in sera. The positive and negative predictive rates of LAMP are 100% and 97%, respectively (Loopamp Pertussis Detecting Reagents D; Eiken Chemical Corporation). The sensitivity of anti-pertussis IgM and IgA are 29-56% and 25-44%, respectively and the specificities are 93% and 99%, respectively (Novagnost *Bordetella pertussis* IgM/IgA; Siemens Healthcare Diagnostics KK). The patient background (sex, age, and vaccination history), and diagnosis method were collected.

Statistical analyses included a bar graph review and Fisher exact test of age-distribution comparisons. We used SPSS Statistics 25 (IBM Corp.) and BellCurve for Excel for Windows (Social Survey Research Information Co. Ltd.) software programs.

Of the 44 patients (age distribution: 0-21 years, median: 6 years), data of 15 patients who were diagnosed with laboratory-confirmed pertussis (age: 7-21 years, median: 8 years) and 29 patients who were pertussis-negative (age: 0-11 years, median: 5 years) were compared. All patients (n=15) who were pertussis-positive but only 17% (n=7) of patients who were pertussis-negative were elementary school age and older (P< 0.001) (**Fig. 1**). All 16 preschool children were negative. Excluding serodiagnosis cases (3 positive cases, 1 negative case), a significant difference in age distribution (P<0.001) was also observed. When a 2 × 2 table was prepared with 7 years of age as the cut-off value, the sensitivity, specificity, positive predictive rate, and negative predictive rates were 100%, 83%, 75%, and 100%, respectively.

None of the 44 patients had a history of preschool vaccination booster at around 5 years of age. Of 15 children who were positive, 14 patients had received four routine vaccinations and the booster history was uncertain in 1 patient. Of 29 children who were negative, 26 patients had received four routine vacci-

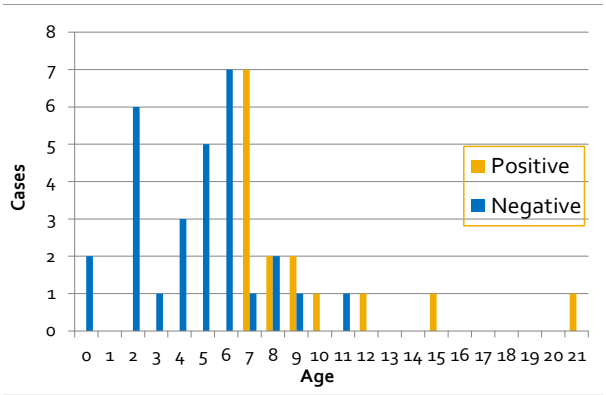

Fig. 1 Pertussis test results and age distribution.

nations, but two patients who were a few months old were vaccinated 0 and 2 times, and the booster history was uncertain in another patient.

The absence of pertussis in preschool children and the presence of pertussis in lower-grade schoolchildren suggest the need of additional preschool vaccinations. It has been reported that the prevalence of anti-pertussis toxin titer in individuals aged 4 to 7 years declines to 26-38% even among regular vaccines [8]. During our research period, the Japanese Society of Pediatrics began to recommend that preschool children aged 5 to 6 years receive a DPT vaccination, but this is on a voluntary basis [9].

This report covers a limited number of cases in a single institution, and the question remains of whether the data on sensitivity and specificity for pertussis at age 7 years or older can be generalized. However, the all-Japanese pertussis cases reported indicate that over 60% of cases are between the ages of 6 and 15 years, peaking at the age of 7 years [10], which is consistent with the age distribution reported herein.

We experienced a pertussis epidemic in elementary school-age children, all of whom had been immunized with at least three doses of primary DPT-IPV immunization. We believe that popularizing the preschool pertussis vaccination is important in order to eliminate the infection source for young infants. Consideration should be given to routine preschool pertussis vaccination boosters in Japan if larger community-based studies confirm our findings.

Ethics approval: Keio University School of Medicine Ethical Committee, Tokyo, Japan; No. 20190205, dated December 26, 2019.

Contributors: TK, MS, AM, TT: designed the study; TK, MS, AM: collected and analyzed data: TK, MS, AM, TT: wrote the manuscript; AM,TT: critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding: None; *Competing interests*: None stated.

TAKAHISA KIMIYA,[1,2*] MASAYOSHI SHINJOH,[1] AKIKO MIYATA,[2] AND TAKAO TAKAHASHI[1]

[1]*Department of Pediatrics, Keio University School of Medicine, Shinjuku-ku, Tokyo;* [2]*Saiwai Pediatric Clinic, Tachikawa-shi, Tokyo; Japan.*

**kimiya0920@hotmail.com*

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Impact of Coronavirus Disease 2019 Pandemic and Lockdown on Mental Health Symptoms in Children

Pediatric symptom checklist (PSC)-youth self-report short version was administered telephonically to children between 11-15 years to study the impact on mental health. Out of 423 children, 130 (30.7%) had psychosocial problems, of which 107 (25.2%) had anxiety or depressive symptoms. The common reasons were fear of acquiring COVID-19 infection (60%), not able to attend school (56%), and not able to meet friends (80%).

Keywords: *Psychosocial wellness, COVID-19.*

Published online: November 29, 2020;
PII:S097475591600256

During the coronavirus disease (COVID-19) pandemic-induced nationwide lockdown, children were staying indoor (home confinement) and limited online teaching was provided by some schools. The impact on children may not be only because of the virus but also due to psychological effects created by exposure to verified/unverified information through various sources. Our primary objective was to study the effects of pandemic and lockdown (home confinement) on mental health symptoms in children aged 11 to 15 years.

The study period was from 15, April, 2020 to 15 May, 2020 in Pune, India. We included children aged between 11-15 years in whom medium of instruction in schools was English. Children receiving neuropsychiatric medicines/treatment were excluded from the study. Telephonic interview of children was conducted after obtaining prior informed verbal consent from one of the parents. Approval was taken from institutional ethics committee.

Children were identified from our hospital records. Friends/ relatives and other contacts of researchers were contacted to identify more children in that age group who would be willing to participate. The information about the survey was put on personal Facebook pages of investigators and interested people were asked to contact a dedicated telephone number. Children who participated in the survey were also asked to suggest contacts that would be willing to participate.

Pediatric symptom checklist (PSC) – youth, self-report shorter version consisting of 17 questions was used [1,2]. This is a validated method for screening for psychosocial problems of school-aged children. A cut-off more than 15 was considered abnormal. Subscale scores were also calculated for anxiety or depressive problems, and a subscale score of 5 or more was considered significant. In addition to PSC, 13 questions exploring adaptation to lockdown and post-lockdown expectations were also administered. The complete questionnaire was administered to the children by three researchers in a uniform and standardized format.

We calculated that with a confidence level of 95% and acceptable margin of error 5%, we would need a sample size of 384 respondents. Assuming a 10% drop out rate, a sample size of 422 was chosen. We used SPSS version 23 (IBM Inc,) for statistical analyses. Linear regression analysis was used to determine effect of various parameters on mental health. P value of less than 0.05 was considered significant.

Overall, we telephoned 486 children, of which 36 phone calls were not answered despite repeated attempts. Twenty-seven parents declined participation. Finally, 423 (87%) children [mean (SD) age, 12.3 (1.6) year; 54.4% boys] completed the questionnaire and were included in the study. Of these 70% belonged to nuclear families, 25% had no siblings and 10.8% had one/both parents in healthcare profession. Mothers of 34% and 18% were employed full-time or part-time, respectively. The source of information on the pandemic was from news (51.3%), parents (27.4%), both of these in 6% and friends in 7.5%.

Of these, 130 (30.7%) children had psychosocial problems, of which 107 (25.2%) had anxiety or depressive symptoms, the common reasons being fear of acquiring COVID-19 infection (60%), not able to attend school (56%), and not able to meet friends (80%). Of others, 23 (5.4%) were feeling hopeless, 107 (25.2%) seemed to be having less fun, and 99 (23.4%) were feeling sad or unhappy. Around a quarter (24.3%) were worrying a lot and 12.5% were 'down on oneself.'

Of the remaining, 246 (58%) children were happy to spend more time with family, 140 (33%) did not feel any anything unusual, while 32 children (7.6%) children were annoyed by the constant presence of parents.

The topic of discussion with friends was COVID-19 pandemic in 43 (10%) children and 103 children (23.2%) kept a daily count of patients suffering and dying from COVID-19. All children responded that they had not anticipated this

Table I Coping With the Pandemic and Long Term Outlook

Responses	*No. (%)*
Measures taken to reduce anxiety[a]	
Music	88 (21)
Talking to friends	73 (17.3)
Talking to parents	51 (12)
Hobbies	123 (29)
Physical exercise	35 (8.3)
What are you missing most?[b]	
Freedom to move out	140 (33)
School	79 (18.7)
Friends	133 (31.5)
Sports	48 (11.4)
What is the first thing you do once the lockdown is over?[c]	
Meet friends	279 (66)
Stay at home	66 (15.6)

[a]Reading and playing games on mobile phone in 4.7% each, and sleeping more in 3%; [b]shopping (3%) and movies in theater (2.4%); [c]Go shopping (6.6%), and organize a party or go to watch movie in 5.9% each.

happening, and 267 (63%) children felt that this lockdown will change their habits, mind set or outlook towards other people.

Binary regression analysis showed that duration of lockdown, family size, siblings, working status of parents, healthcare status of parents, source of information of pandemic etc did not have any significant effect on mental health (anxiety or depression). However, increased use of social media was associated with higher risk of anxiety or depressive symptoms [OR (95% CI) 1.83 (1.21 to 3.96); *P*=0.001]

We found that anxiety or depressive symptoms were seen in nearly 25% of all surveyed children as a result of lockdown. We started the survey after completing 4 weeks of lockdown and finished by 8 weeks after which the lockdown restrictions were relaxed. Completing the study within lockdown time ensured that children were able to answer all questions with complete clarity and lack of memory lapses. We did not find any relation between duration of lockdown and impact on mental health symptoms. Nearly half of this lockdown period coincided with the regular summer break for most children. So, it is possible that the impact is less due to this overlap.

Interestingly, we found that higher usage of social media platforms was associated with anxiety or depressive symptoms. However, it can also be argued that children with mental health issues were more likely to access social media rather than use of social media being the cause of mental health issues. We restricted to children age 11 years or more of age since the cognitive function and social skills are better developed in this age group [4], and proxy-reporting is avoided [3].

The data is self-reported and hence subject to reporting bias. Also, the children may have been influenced by other family members though they were requested to not seek help while answering questions. This is not a truly representative sample since the children interviewed are from private English-medium schools, which typically represents upper-middle socioeconomic strata. None of the interviewed children had COVID-positive patients in the family. We do not know if this effect on mental health is a temporary phenomenon but these children will need to be followed up for long term effects. Majority of the children were optimistic about long term outlook, leading us to believe that adverse impact on mental health may be short-lived.

The study results are important to healthcare providers, parents as well as policy makers. Policy makers should devise ways to minimize these effects while implementing a lockdown (home confinement) on children. Parents and health providers should recognize these problems early and treat if necessary.

Contributors: SS: designed the questionnaire, data interpretation and analysis. Critical appraisal of the manuscript was done by him; AK: conceptualized this study, designed the questionnaire and interviewed the children, assisted in the data interpretation and analysis, and drafted the manuscript. RS: gave inputs on the questionnaire, interviewed the children, did the data entry and drafted the manuscript. SM: helped in interviewing the children, data entry, and in drafting of the manuscript. All authors approved the final manuscript.

Ethics clearance: Surya Hospital Scientific research and ethical review committee on 1 April, 2020.

Funding: None; *Competing interests*: None stated.

SACHIN SHAH,[1] AMITA KAUL,[1*] RIMA SHAH[2] AND SANKEERTH MADDIPOTI[1]

Surya Mother and Child Superspecialty Hospital, Pune 411 057, Maharashtra, India.

**amitakaul@hotmail.com*

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PLA2G6-Associated Dystonia Parkinsonism

Phospholipase-associated Neurodegeneration (PLAN) with *PLA2G6* mutation comprises a continuum of three phenotypes with overlapping clinical and radiological features. The spectrum comprises typical Infantile neuroaxonal dystrophy (INAD) also known as Seitelberger disease, atypical neuroaxonal dystrophy (ANAD) and more recently described entity *PLA2G6*-associated dystonia parkinsonism (PLAN-DP). We, herein, report an adolescent with PLAN-DP.

A 14-year-old boy, product of a non-consanguineous marriage and with a normal birth and developmental history, presented with difficulty in walking from last one year. Parents noticed dragging of the left leg while walking with short steps. This was followed by stiffness of both the legs and arms with frequent falls on left side while walking along with dystonic posturing of left leg. Patient developed generalized slowness with decreased arm swing, unable to close fist and poor interest in surroundings. Patient was unable to sit and stand after one year of onset of illness along with poor speech in form of decreased phonation and articulation. There were no psychiatric or behavioral changes. There were no other affected family members with a similar illness.

On examination, patient was conscious and oriented but lacking emotional expression on the face. Generalized bradykinesia was present involving trunk and all four limbs. Motor examination revealed cogwheel rigidity with exaggerated deep tendon reflexes and positive Babinski sign. Sensory, cranial nerve and cerebellar examination were normal. Kayser-Fleischer ring was not detected, and fundus evaluation was normal. Patient developed urgency and incontinence of urine during his course of illness. On the basis of clinical diagnosis of neurodegeneration with extra pyramidal symptoms a differential diagnosis of Wilson disease, dopa-responsive dystonia (Segawa disease), pantothenate kinase-associated neurodegeneration (PKAN), hypoparathyroidism and mitochondrial disorder were considered and evaluated for.

Brains magnetic resonance imaging MRI showed T2 hyper intense shadow in the insular cortex and some part of temporal lobe but no evidence of T2-weighted hypo-intensities in the basal ganglion and substantial nigra. There was no evidence of cerebellar atrophy or brainstem involvement. All laboratory tests including serum biochemistry, liver and thyroid function test, serum ceruloplasmin, and 24-hour urinary copper excretion were within normal limits. Direct gene sequencing revealed a homozygous missense variation in exon 16 of the *PLA2G6* gene (chr22:g.38508565C>T; Depth: 315x) which resulted in the amino acid substitution of Glutamine for Arginine at a codon 741(p.Arg741Gln; ENT00000332509.3). The mutation was previously described as pathogenic (rs121908686) and is present in ExAC database with very low frequency (0.0002277). Patient was put on levodopa which resulted in dramatic improvement in motor symptoms and speech. He is under follow-up and sustaining good response to drugs.

Paisan-Ruiz, et al. [4] described 23 patients of PLAN-DP from 16 pedigrees [3,4], with youngest age of onset of 4 years and the oldest 37 years. Dystonia and parkinsonism were seen uniformly but neuropsychiatric and cognitive decline were seen invariably as initial presentation in adult-onset disease. Autonomic dysfunction, specifically urinary symptoms have been observed frequently as in this case and may be an important clue in diagnosis. Kapoor, et al. [5] in a review discussed the genetic analysis of *PLA2G6* in 22 Indian families with phospholipase-2 associated neurodegeneration. This mutation was found in 12/22 (54.55%) families with INAD and ANAD which again suggest variable phenotypic expression of this disorder. Majority of families presented with INAD/ANAD and only one family presented with PLAN-DP, but was negative for this mutation.

In our patient, MRI showed no evidence of hypointensity in globus pallidus and substansia nigra; although, PLAN has been consistently reported to have neurodegeneration with brain iron accumulation. Iron accumulation was found in only eight patients (33%) in a previous review of 23 patients, which is less than what is reported in INAD (40-50%). The process of iron accumulation; however, is not well described.

The protein product of *PLA2G6*, phospholipase–A2 group VI (iPLA2-IVA) is an enzyme involved in the metabolism of glycerophospholipids and it plays an important role in inner mitochondrial membrane homeostasis [8].

In conclusion, PLAN-DP is characterized by remarkably heterogeneity in presentation and at present no specific clinical criteria are there to pinpoint the diagnosis but the early onset dystonia parkinsonism with psychiatric symptoms, speech deterioration, cognitive changes, autonomic dysfunction, iron deposition in MRI and response to levodopa is suggestive towards this differential diagnosis and these children should be evaluated for *PLA2G6* mutation.

Deepak Sachan,* Amit Yadav and Dinesh Yadav
Department of Pediatrics, PGIMER,
Atal Bihari Vajpayee Institute of Medical Sciences
and Dr Ram Manohar Lohia Hospital, New Delhi, India.
**deepaksachan26@yahoo.com*

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Takotsubo Cardiomyopathy in Pediatric Scrub Typhus

Takotsubo Cardiomyopathy or stress cardiomyopathy is a heart failure syndrome characterized by transient left ventricular dysfunction with typical regional wall motion abnormalities [1]. The wall motion abnormalities are not confined to the vascular distribution of a single epicardial coronary artery; hence, non-ischemic mechanisms are considered responsible. Initially described in adult women with emotional stress as 'broken-heart syndrome', it was subsequently recognized in both males and females. Takotsubo cardiomyopathy has been reported rarely in children. We describe a case of Takotsubo cardiomyopathy associated with sepsis in a child.

A 10-year-old boy presented with complaints of high-grade fever since four days and fast breathing and poor oral intake since one day. On examination, he had tachycardia, hypotension, respiratory distress, generalized edema and hepatomegaly. High-flow oxygen, intravenous fluids and inotropes were started (noradrenaline followed by dobutamine). Laboratory investi-gations revealed a C-reactive protein of 101 mg/L. As clinical and laboratory features were suggestive of severe sepsis, intravenous antibiotics were started. Since hypotension persisted, 2D echocardiogram was done, which showed mid-ventricular regional wall motion abnormality (**Fig. 1a**), with normal contractility of cardiac apex (**Fig**. **1b**) and mild mitral regurgitation. ECG showed mild ST elevation in lead V2. Troponin level was mildly elevated (16.4 ng/L), and B-type natriuretic peptide (BNP) markedly elevated (15725 pg/mL). In view of a diagnosis of Takotsubo cardiomyopathy, noradrenaline was tapered and diuretic drugs were prescribed. A repeat echocardiogram after three days showed normalization of left ventricular function and resolution of mitral regurgitation. Repeat ECG showed T wave inversion in V2. Work-up for persistence of fever spikes and thrombocytopenia revealed negative dengue serology, and positive result for OX K antigen on Weil Felix test The child showed improvement on oral Doxycycline and was discharged without any cardiac medications by ninth day of hospitalization.

Takotsubo cardiomyopathy is a reversible heart failure syndrome. It derives its name from the shape of the left ventricle in the typical apical-ballooning form, which resembles a Japanese octopus-trap. Four common morphological variants have been described [1]. In younger patients, a high proportion of non-apical anatomical variants are seen [2]. Our case was of the mid-ventricular type, with hypokinesia of the mid-ventricle and sparing of the apex.

Distinguishing Takotsubo syndrome from acute infective myocarditis can be challenging. However, involvement in Takotsubo cardiomyopathy shows typical regional pattern whereas in myocarditis it tends to be diffuse, and it shows a low or moderate troponin rise while there is frequently a significant rise in troponin in myocarditis [1]. The differential diagnosis includes sepsis-induced cardiomyopathy, but in the latter too, there is global involvement and enlargement of the ventricle, as opposed to regional affection in the former [3].

Regional wall motion abnormality of Takotsubo cardio-myopathy requires differentiation from acute coronary syndrome, a less common entity in children. Characteristically laboratory evaluation shows an extremely elevated BNP and mild troponin elevation. In contrast, in coronary ischemia, the degree of BNP elevation is typically lesser than in Takotsubo cardiomyopathy, troponin is significantly elevated and ECG and echocardiographic wall motion abnormalities are confined to the vascular distribution of epicardial coronary arteries [4]. ECG in Takotsubo cardiomyopathy may show non-specific ST changes, with later development of T wave inversion, as seen in our case, or even QTc prolongation [1]. Cardiac magnetic resonance during the acute phase may help differentiate Takotsubo cardiomyopathy from both, myocarditis as well as acute myocardial infarction [2].

Sepsis has been widely described in adults as a cause for Takotsubo cardiomyopathy, with a causative organism identifiable in culture in up to 50% of admissions [5]. Our search of English language scientific literature did not reveal any report of this disorder in pediatric sepsis following scrub typhus infection. There is a possibility that scrub typhus as a cause is

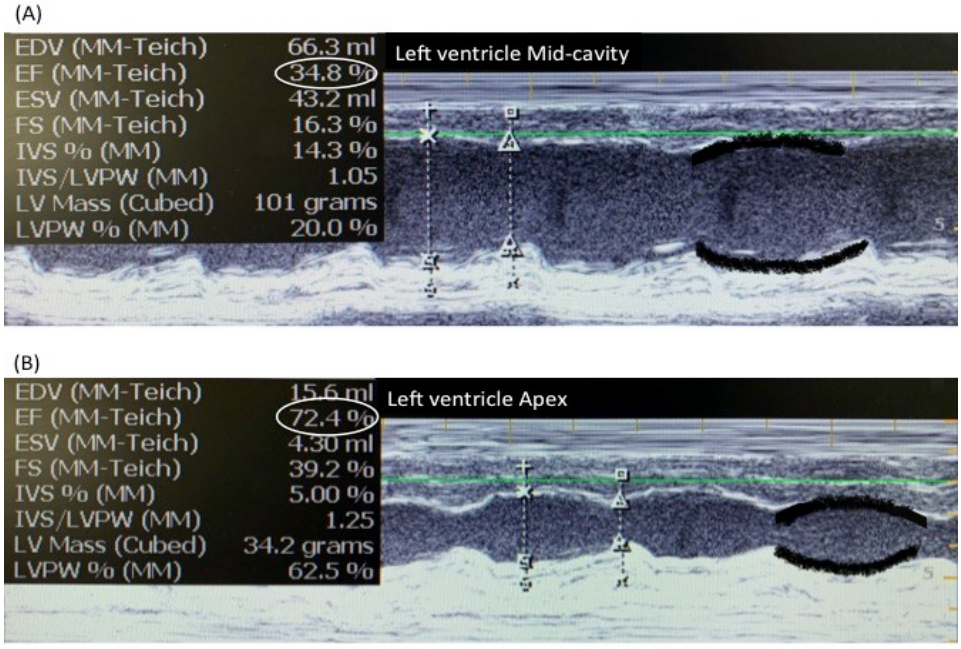

Fig. 1 M-mode Echocardiogram of Left ventricle (LV). (a)Poor contractility of LVMid-cavity with Ejection fraction (EF) of 34%. The black lines marked along anterior and posterior LV walls show poor excursion with time, (b) Normal contractility of LV Apex with EF: 72%. The black lines highlight excellent approximation during systole.

either unrecognized or under-reported.

Management of this disorder is unique in that catecholamines are incriminated in the pathophysiology and hence, must be avoided. Beta-blockers and ACE inhibitors may be used. Mechanical support such as extracorporeal membrane oxygenation may be required. For inotropic support, Levosimendan is considered safe, and has been reported to be effective specifically in sepsis-associated Takotsubo cardiomyopathy [6].

The long-term prognosis is favorable, but it is now recognized that upto 50% can have acute complications with a mortality rate of 4-5 % [1].

To conclude, Takotsubo cardiomyopathy may be identified by the typical echocardiographic appearance and laboratory features, and entails specific management considerations. Recognition of the entity is of importance because of the unique management approach that it entails

SWETA MOHANTY[1]*, KN HARSHA[2] AND NIKHIL KALALE[2]
From Departments of [1]Pediatric Cardiology and [2]Pediatrics, Aster RV Hospital, Bengluru, Karnataka, India.
**doctorsweta@yahoo.com*

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Wolcott-Rallison Syndrome Affecting Three Consecutive Conceptions of a Consanguineous Couple

Permanent neonatal diabetes mellitus (NDM) is a debilitating condition. In couples with consanguineous marriage, and especially with multiple children being affected, a strong possibility of genetic causes should be kept and evaluated appropiately. Wolcott-Rallison syndrome is one such syndrome, now being more commonly diagnosed in Indian families. A couple presented to the fetal medicine unit for genetic counselling at a gestational age of 9 weeks, because of two previous babies being affected with early onset type 1 diabetes mellitus. There was a 3rd degree consanguinity. The elder child was 6 year-8 month-old girl, with hyperglycemia detected at 1 month of age. She was evaluated by the pediatrician. She had history of multiple episodes of seizures, unconsciousness and developmental delay in all fields, with a motor age of 2 years and social and language age of 4 years. Parents were not compliant with either regular insulin administration or home blood glucose monitoring. On examination, she was stunted (height 86 cm, <3rd centile), underweight (weight 11.4 kg, <3rd centile) and had microcephaly (head circumference 43 cm, <3rd centile). The child had a chubby look, round facies, delayed dentition, dental caries and short stubby fingers. There was firm hepatomegaly with liver span of 12 cm. We evaluated for hypothyroidism, celiac disease, polyendocrinopathies and genetic syndromes causing type 1 diabetes mellitus. There were no clinical features suggestive of exocrine pancreatic insufficiency. The younger sibling was a female child who was diagnosed as type 1 diabetes mellitus at 1 month of life and succumbed the following month. Medical records were unavailable. A detailed three-generation pedigree did not reveal any other family member with similar manifestations.

The skeletal survey revealed a bone age >4 years, with small carpals, hypo-mineralized metacarpals, and notching of anterior vertebrae, suggestive of skeletal dysplasia (**Fig. 1**). The laboratory evaluation did not reveal any abnormalities in hemoglobin, leucocyte counts, thyroid function tests and liver enzymes. Blood urea nitrogen was 15.3 mmol/L, creatinine was 61.9 µmol/L, and glycosylated hemoglobin was 12.7%. A genetic panel for causes of PNDM and maturity-onset diabetes of the young (MODY) was done. It revealed a homozygous non-sense variation in exon 17 of the *EIF2AK3* gene (chr2:g. 88857412G>A), consistent with Wolcott-Rallison syndrome. Subsequently, we carried out sanger variant analysis for the same gene in the fetus by chorionic villus sampling at 14 weeks of gestation. It also revealed homozygosity for chr2:g. 88857412G>A and c.3193C>T. The couple were advised termination of pregnancy and were counseled regarding recurrence risk and need for antenatal diagnosis. The importance of home blood glucose monitoring and insulin administration was explained for the older child and management plan with concerned specialist was arranged.

Neonatal diabetes mellitus is a rare form of type 1 diabetes mellitus, with onset in first 6 months of life and an incidence of 1 in 90,000 to 1,60,000 live births [1]. Most NDMs are monogenic, and can be either transient or permanent. The most common mutations causing NDM worldwide are related to defects in potassium channel subunit genes, namely *KCNJ11* and *ABCC8* [2]. Similarly, in India, most published literature shows that the commonest mutations are related to potassium channel mutations [3]. In the setting of parental consanguinity, most common causes related to an autosomal recessive inheritance. These include mutations in *EIF2AK3, GCK, GLIS3, RFX6, IER31P1* and *MNX1* genes. Except GCK1, the remaining mentioned mutations result in syndromic forms of type 1 diabetes mellitus, with extra-pancreatic involvement [1,4]. Thus, it becomes important to get focused evaluation for autosomal recessive conditions in such a scenario. Wolcott-Rallison syndrome is being recognized as an important cause of syndromic permanent NDM in Indian subcontinent [5,6]. This syndrome has high mortality and several associated morbidities including skeletal dysplasia, episodic liver failure, renal dysfunction, exocrine pancreas insufficiency and developmental delay. The frequency of extra-pancreatic manifestations increases with increasing age, with initial appearance of skeletal abnormalities, followed by liver and renal dysfunction. In the index child, we could note developmental delay and skeletal dysplasia.

Evaluation for monogenic causes should be done in all cases of permanent NDM. When associated with consanguinity and extra-pancreatic manifestations, syndromic neonatal diabetes mellitus with autosomal recessive inheritence is most likely. Timely genetic diagnosis and prenatal confirmation can avert birth of an affected progeny.

RAJENDRA PRASAD ANNE,[1*] MADHAVI VASIKARLA[2] AND TEJO PRATAP OLETI[1]

Department of [1]Neonatology and [2]Genetics, Fernandez Foundation, Hyderabad, Andhra Pradesh, India.

**rajendra.omc@gmail.com*

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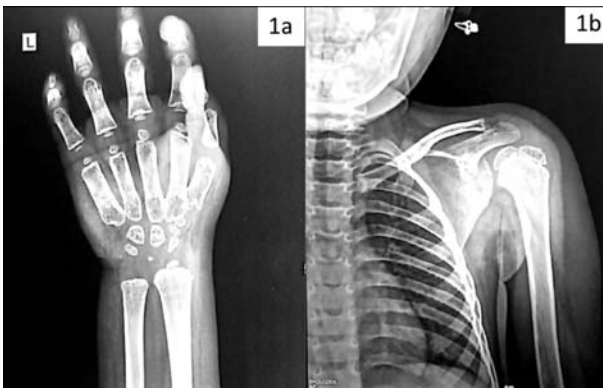

Fig. 1 (a) *X*-ray wrist anteroposterior view of the index child, and (b) *X*-ray showing thoracic spine, ribs and humerus.

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Glossopharyngeal and Vagus Nerve Palsy in a Child With Scrub Typhus Meningitis

Scrub Typhus is an acute febrile illness caused by *Orientia tsutsugamushi,* an obligate intracellular Gram negative bacterium. The disease is endemic in Southeast Asia and Pacific Islands, and is prevalent in the Shivalik ranges from Kashmir to Assam, the Eastern and Western Ghats and the Vindhyachal and Satpura ranges in Central India [1]. The usual clinical features include fever, myalgia, headache, an eschar, regional or generalized lymphadenopathy and hepatosplenomegaly [1].

A five-year-old boy, from North 24 Parganas district of West Bengal, was referred with high grade fever for eleven days and severe headache and myalgia. On examination, he was haemodynamically stable and had generalized lymphadenopathy and hepatosplenomegaly. Other system examinations were normal. He was given supportive management with antipyretics.

A few hours after admission, he developed nasal intonation of voice with nasal regurgitation of food. Deviation of the uvula to the left and weakness of right palatal muscles was noted on examination, signifying palsy of right sided glossopharyngeal nerve and pharyngeal branch of vagus nerve. The possibility of involvement of other vagal branches was ruled out in the absence of dysphonia. Other cranial nerves and rest of the neurological examination were normal.

Complete blood counts showed a high (90%) neutrophilic differential leukocyte count. Acute inflammatory markers were raised but liver and renal function tests were normal. Work-up for etiology of fever was positive for scrub typhus IgM antibody (ELISA) which showed a five-fold rise subsequently. Cerebrospinal fluid revealed mononuclear pleocytosis with elevated protein but negative cultures. MRI brain was normal. He was started on oral azithromycin prescribed at 10 mg/kg once a day for 7 days. Child was afebrile within 30 hrs of the first dose. Physiotherapy of pharyngeal muscles was demonstrated and he was discharged with the advice to continue the same. There was no residual nerve palsy on follow-up after 4 weeks.

Glossopharyngeal and vagus nerve palsy have been associated with Varicella Zoster, Enterovirus and other pathogens [2]. However, palsy of these nerves due to *O. tsutsugamushi* has not been described earlier in the paediatric age group.

[1]The disease process is initiated by the bite of the mite. The pathogen multiplies at the bite site, forming an eschar, followed by proliferation of the organism in the endothelial cells of small vessels with perivascular infiltration of lymphocytes causing focal or disseminated vasculitis. The eschar is considered pathognomic but may be found in 7% to 80% of the patients [3]. Central nervous system involvement commonly manifests with altered sensorium due to aseptic meningitis or acute encephalomyelitis. Occasionally, seizures, intracerebral haemorrhage, cerebellitis, and rarely acute transverse myelitis, neuroleptic malignant syndrome, Gullain Barre syndrome or nerve palsy may be noted [4].

Cranial nerve involvement in scrub typhus may result from direct invasion of central nervous system by the bacteria leading to acute vasculitis or secondary immune reaction leading to vasculitis of vasa vasorum of nerve. There have been four earlier reported cases of abducens nerve palsy in scrub typhus, causing diplopia [3-5]. Multiple cranial nerve involvement, viz. 3rd, 7th, 9th, 10th and 12th have been earlier described in a case of scrub typhus meningitis and cerebellitis [6]. There were no residual deficits in any of the above cases.

The index case developed glossopharyngeal and vagus nerve (pharyngeal branch) palsy at the summit of symptoms. Although doxycycline is the recommended drug for treatment, he was treated with azithromycin, as use of doxycycline below 8 years of age is controversial. In an endemic country like India, scrub typhus should be kept as a differential in fever for more than 7 days with neurological deficits. Timely diagnosis and intervention can have complete resolution of neurological deficits.

POULAMI DAS,* SAYAN BANERJEE AND ABHISHEK ROY
Department of Paediatrics, RG Kar Medical College and Hospital, Kolkata, West Bengal, India
**drpoulamidas@gmail.com*

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Tuberculosis in Catastrophic Antiphospholipid Antibody Syndrome

Antiphospholipid syndrome (APS) describes patients with antibodies targeting phospholipid molecules causing recurrent arteriovenous thromboses, fetal losses, thrombocytopenia along with antiphospholipid antibodies viz. lupus anticoagulant and the anticardiolipin antibodies [1]. It can be either primary, or secondary that is triggered by infections or malignancies [2]. Catastrophic APS (CAPS), also known as Asherson syndrome, is a rare accelerated variant characterized by the rapid appearance/progression of more than three organ thromboses, with microangiopathy leading to multiorgan failure. We describe a child with pulmonary tuberculosis triggering CAPS.

A 14-year-old girl presented with increasing pyrexia and cough for 3 weeks. Mild left upper/middle zone crepitations were present with no respiratory distress. Investigations on admission revealed anemia (hemoglobin 8.5 g/dL), leucocytosis (leucocyte count 13×10^9/L, polymorphs 85%), thrombocytopenia (platelet count 45×10^9/L), with mildly elevated C reactive protein (10 mg/dL) and erythrocyte sedimentation rate (ESR 40 mm/h). Blood cultures were sterile. With an initial chest roentgenogram revealing pneumonitis, she was commenced on antibiotics (amoxicillin and clavulanic acid) with no response. Worsening in the productive cough with persistent fever, despite 7 days of antibiotics, prompted a computed tomography (CT) scan, which revealed a left upper consolidation with cavitatory changes and necrotic mediastinal lymphadenopathy. Sputum tested positive for *Mycobacterium tuberculosis* and anti-tubercular therapy (ATT) was commenced.

While on ATT, she developed severe bifrontal headache, vomiting and worsening respiratory distress. Magnetic resonance imaging of brain was performed, which was suggestive of thrombosis of superior sagittal venous sinus, right transverse sinus and sigmoid sinus with thrombus extending to proximal internal jugular vein. Repeat investigations revealed anemia, falling leucocyte counts (5.8×10^9/L), thrombocytopenia (platelet count 60×10^9/L), increasing CRP (107mg/dL), high ESR (120 mm/h) and transaminitis. Activated partial thromboplastin time (aPTT) was prolonged. Thrombophilia work-up was suggestive of antiphospholipid antibody (APLA) positivity [Lupus anticoagulant positive; Prolonged Russel viper venom time (RVVT), 78.5 (control- 48.3) seconds; anti-cardiolipin (ACL) IgG, 15 U/mL (normal range 0-12.5 GPL U/mL); Beta 2 glycoprotein 1 IgG, 30 U/mL (control 12 U/mL)]. Protein C, Protein S, anti-thrombin levels were unremarkable. Hyperfibrinogenemia (450 mg/dL), hypocomplementemia (C3, 80.8mg/dL and C4 9.2 mg/dL), positive direct coombs test, elevated serum lactate dehydrogenase (600 U/L), high serum ferritin (800 ng/mL) and significant proteinuria (spot urine protein creatinine ratio 1.2) were other positive findings. Peripheral smear ruled out schistocytes. Antinuclear antibody (ANA), Rheumatoid factor and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. A CT angiogram revealed bilateral segmental pulmonary thromboembolism, ground glass changes and diffuse alveolar hemorrhage (DAH) with multiple splenic infarcts. With imaging and laboratory evidence of progressive multiorgan dysfunction, a diagnosis of CAPS triggered by pulmonary tuberculosis was made.

Child was started on parenteral methyl prednisolone followed by oral steroids and anticoagulation with low molecular weight heparin, while continuing ATT. Fever and cough resolved over the next 2 and 4 weeks, respectively. Steroids were tapered over 3 months. Repeat APLA work-up after 12 weeks confirmed APLA positivity. Anticoagulation was continued for 6 months. APLA tested negative at 6 months ruling out primary APS and establishing tuberculosis as the etiology. Repeat neuroimaging at 6 months showed significant resolution of the thrombus.

CAPS is a rare life-threatening autoimmune disease defined by definite criteria [3]. The diagnostic urgency of CAPS lies in a canonical onset of multiorgan thromboses/dysfunction, thrombotic microangiopathies (TMAs), systemic inflammatory response syndrome (SIRS) mimicking septicemia and a high mortality rate. Skin infections (18%) and human immunodeficiency virus infection (17%) are the most common associated infections [4]. ACL antibodies have been reported in a proportion of tuberculosis patients compared to normal controls [5]. Pneumonitis in the lower respiratory tract and systemic inflammation causes endothelial activation along with a reduction in the anti-coagulant mechanisms, impaired fibrinolysis with resultant hypercoagulopathy and pulmonary and systemic thrombin generation [6]. Besides, molecular mimicry between *M. tuberculosis* and β-2GPI molecule has also been proposed for the development of CAPS. In the index child, presence of such rapidly progressive deterioration with microangiopathy and thromboses (with APLA positivity) in the

setting of proven tuberculosis suggested CAPS. Clinical improvement only after steroids, along with complete disappearance of APLA by 6 months confirmed CAPS with tuberculosis as the etiology.

Persistent tubercular infection with a rapid clinical deterioration (multiorgan dysfunction) should raise the possibility of inflammatory complications like hemophagocytosis or CAPS. CAPS being a potentially life-threatening condition, a high index of suspicion, early diagnosis and aggressive treatment with steroids, anticoagulation and occasionally plasmapheresis is needed for a favorable clinical outcome.

Acknowledgements: Dr Parmanand Andankar, consultant pediatric intensivist and Dr Ratna Sharma, consultant pediatric hematologist for valuable assistance in management.

FARHEEN QURESHI,[1] VIJAY VISWANATHAN[1*] AND SUDHIR SANE[2]

From [1]Pediatric Rheumatology Clinic and [2]Department of Pediatrics, Jupiter Hospital, Thane, Maharashtra, India.

**dr_vjay77@yahoo.co.in*

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Repeated Chelation in Lead Encephalopathy

Lead is an abundantly distributed heavy metal in our environment which in higher concentrations is hazardous to the body [1]. Nervous system remains the most severely affected, effect being more pronounced on growing children [2]. Common sources are lead based paint, lead contaminated air, soil, dust, drinking water through lead soldered pipes, lead coated vessels used for cooking, traditional medications and certain cosmetics [1]. Absorbtion of lead varies depending on the chemical form and the mode of exposure (ingestion > inhalation >transdermal). The half life of lead in blood and soft tissues is 35 days as compared to bones being 5-20 years. Bone stores release lead to the blood which may add up to a toxicologically significant amount [3]. We report a boy with lead encephalopathy, who required repeated chelation therapy.

A 7-year-old boy, presented with refractory status epilepticus. He was the first born child of a non-consanguineous marriage from Nilgiris, Tamilnadu, with unremarkable neonatal period. He was developmentally and neurologically normal with no behavioural problems and immunized upto date as per national immunization schedule. There was no family history of seizures. The child was on traditional medicines for about a year for vitiligo over lips and face. He developed unilateral headache 10 days prior to the onset of seizures along with intermittent abdominal pain and vomiting for which symptomatic treatment was given. One such episode of vomiting was followed by right sided focal seizures. The child was given parental anticonvulsants. However, due to worsening of sensorium and uncontrolled seizures, he was put on mechanical ventilation and started on multiple anticonvulsants. Child was gradually stabilized and extubated.

Laboratory analysis showed leucocytosis with polymorphic preponderance and microcytic hypochromic anemia. Serum Iron was low - 21 mcg/dL [Normal 50-120 mcg/dL] though serum ferritin and total iron binding capacity were within normal range. Liver functions, renal functions and coagulation profile were normal. Cerebrospinal fluid analysis showed mild leucocytosis, with minimally elevated proteins. Cerebrospinal fluid Gene *X* pert for tuberculosis was negative. Neuro-imaging was normal. Heavy metal screening of blood showed high lead levels of 80.31 mcg/dL (acceptable upto 5 mcg/dL). Skeletal survey showed lead lines over lower end of femur (**Fig. 1**). Parents were screened and their blood lead levels (BLL) were within normal limits.

He underwent lead chelation therapy with Dimercaptosuccinic acid 30 mg/kg/day for 5 days followed by 20 mg/kg/day for 14 days. Other effective agents including Dimercaprol and Edetate disodium calcium (CaNa2EDTA) could not be procured at that time. Supplementation with Iron, vitamin D, zinc, vitamin C was done. He was stabilized, anticonvulsants were gradually weaned off. BLL dropped to 38.08 mcg/dL. On review after 2 months, BLL showed a rise to 56.38 mcg/dL. Child, however remained asymptomatic. Repeat chelation therapy was given and BLL dropped further to 32.9 mcg/dL only to rise to 62.9 mcg/dL in 2 months. He has undergone four doses of periodic chelation at the time of writing this report. He

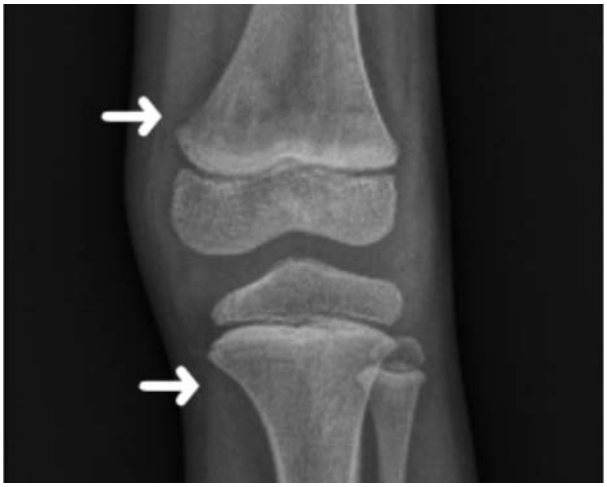

Fig. 1 *X*-ray left knee of the index patient showing lead lines (arrows) over lower end of femur and upper end of tibia.

has been stable except for a few bouts of anger outbursts for which he is on follow up with child psychiatrist. He is on close follow-up and may require further chelation.

Lead is not known to serve any significant biological function and deposition does not spare any organ in the body [1]. It has high affinity for the skeleton and chronic exposure often sequesters large proportion in the bones followed by the kidneys [4]. After a period of initial exposure lead is redistributed to the soft tissues. If cessation of exposure occurs at this juncture, there is a decrease in the blood lead levels post the initial rise [5]. Bone, being a dynamic tissue, undergoes remodelling throughout life which is regulated by a wide range of hormones and local availability factors. Prolonged exposure also results in slow release of lead from the bone stores over a protracted period of time [4]. Children are at high risk of lead poisoning as they are in a state of constant growth and development. Moreover, the growing bones in children undergo perpetual remodelling which allows lead to be regularly re-introduced into the blood stream [6]. Chelation therapy brings down the blood lead levels acutely only to rebound within weeks to months after treatment. Often, repeated courses of chelation are required [5].

This case report emphasizes the need for long term follow-up with periodic monitoring of lead levels in children with chronic lead poisoning to assess the need for repeated chelation therapy. Blood lead concentration may rise to toxic levels even after removal of exposure due to constant re-distribution in a growing child.

SAIDALIKUTTY FOUZEAMOL,* SHEIK SHAHANA PARVIN AND RAMALINGAM RAMAKRISHNAN TIRUPPUR CHINNAPPAN
Department of Pediatrics,
G Kuppuswamy Naidu Memorial Hospital,
Coimbatore, Tamil Nadu, India.
**s.fouzea@gmail.com*

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Autoimmune Hypophysitis in Systemic Lupus Erythematosus

Autoimmune hypophysitis (AH) is a rare autoimmune disease that occurs when the pituitary gland is infiltrated with lymphocytes and plasma cells, leading to impaired hormonal secretion. Rare cases of association of systemic lupus erythematosus (SLE) with AH have been reported in literature but mainly in adult population. AH commonly involves anterior pituitary; labelled as lymphocytic adenohypophysitis (LAH) but it can also involve posterior pituitary which is called lymphocytic infundibulo-neurohypophysitis (LINH) [1-4]. Herein, we report a rare case of lupus in a male child who presented with features of central hypothyroidism and diabetes insipidus that was diagnosed as SLE-associated AH. He was treated with pulse methylpre-dnisolone and cyclophosphamide with hormone replacement.

A 14-year-old male child, fourth issue of a non-consanguineous marriage was admitted with history of fever, weight loss, pallor and generalized weakness since one month. There was no history of rash, bleeding manifestations, abdominal distension, night sweats, oral ulcers, icterus, headaches, visual disturbances or joint swelling. He had received multiple oral antibiotics with no improvement. In the past, he had suffered a stroke at ten years of age with MRI brain showing acute lacunar infarct in right corona radiata. Birth history was uneventful and he was immunized as per schedule.

Anthropometric parameters and vitals, including blood pressure, were normal. Clinical examination revealed malar rash, oral ulcers, severe pallor with moderate hepato-splenomegaly. Laboratory investigations revealed anemia (Hb, 6.4 g/dL), direct Coombs test (DCT) positive, normal white blood cell (WBC) counts (WBC, 7.9×10^9/L, Neutrophils 49%, Lymphocyctes 51%), thrombocytopenia (Platelet count, 30,000/cmm), raised ESR (81 mm at end of one hour), prolonged activated partial thromboplastin time (APTT) [Test, 54 sec (26.9-36.3)], high spot urine protein creatinine ratio (0.9, normal <0.2) with normal liver enzymes, serum electrolytes and *X*-Ray chest. Immunological investigations showed strongly positive anti-nuclear antibody (ANA titres 1:2560, speckled pattern), low serum complement C3 (C3-60 mg/dL; normal range 82-173 mg/dL) and C4 (C4 11.2 mg/dL; normal range: 13-46 mg/dL), positive anti-cardiolipin IgM antibody, beta-2 glycoprotein IgM antibody and lupus anti-coagulant. Anti-double stranded DNA antibody and anti-Smith (anti-Sm) antibody were negative. Ophthalmology examination showed retinal hemorrhages. Thyroid function test revealed central hypothyroidism [low free T3 (<1 pg/mL), low free T4 (0.46 ng/dL), and low TSH (<0.01uIU/mL)], with positive anti-thyroid peroxidase (anti-TPO) antibodies. During the hospital stay, child started developing delirium and agitation along with polyuria. Serum osmolality was high (320 mOsm/kg). Magnetic resonance imaging (MRI) showed absence of posterior pituitary bright spot in T1-weighted imaging consistent with diabetes insipidus. Serum cortisol, prolactin, and sex hormone levels were within normal limit. Parents did not consent for renal biopsy. Although desirable, IgG4-related disease (IgG4-RD) workup could not be done due to financial constraints. A diagnosis of SLE with multiple organ involvement with AH was made. He was initiated on intravenous pulse methylprednisolone and cyclophosphamide followed by oral steroids, monthly cyclophosphamide, hydroxychloroquine, warfarin, thyroid replacement and oral desmopressin, with a close follow up.

In our patient, SLE was diagnosed based on constitutional symptoms, malar rash, oral ulcers, thrombocytopenia with auto-immune hemolytic anemia (Evans syndrome), low WBC counts, high ESR, ANA positivity, low complement levels, positive antiphospholipid antibody, and high urine protein creatinine ratio. AH is a rare disease, mainly affecting females though in our case it was a male. It has incidence reported to be 1 in 9 million [5] but the actual number may be more, particularly as IgG4-RD and involvement of the hypophysis by systemic pathologies has increasingly been recognised [6]. AH can be primary (idiopathic) or secondary to sella and parasella lesions, systemic diseases, or drugs (mainly immune checkpoint inhibitors). The predominant feature of LINH is central diabetes insipidus which was present in our patient. The diagnosis of AH was made when our patient showed features of central hypothyroidism and diabetes insipidus with loss of normal posterior pituitary bright spot on T1-weighted MRI. The gold standard of diagnosis is pituitary biopsy which reveals massive infiltration of lymphocytes and plasma cells in the pituitary gland but is usually denied by patients due to its invasive nature. Our patient is similar to the case reported by Jing, et al. [4] in which a 15 year lupus child revealed low levels of sex hormones, thyroid hormones and serum cortisol with MRI of pituitary region demonstrating an enlargement of the pituitary stalk. She was diagnosed as LINH associated with SLE and responded well to glucocorticoids and cyclophosphamide [4]. We treated our patient with steroids, cyclophosphamide, hydroxy-chloroquine, hormone replacement and warfarin with significant clinical improvement in constitutional symptoms, normalization of acute phase reactants, complement levels, thyroid function and urine proteinuria at 3 months of follow up. Warfarin was added to treatment protocol considering positive antiphospholipid antibody and history of prior lacunar infarct. To the best of our knowledge this is the first case reported from India with features of AH in a case of juvenile SLE.

Our case demonstrates association of SLE and AH in children. In the presence of central hypothyroidism and diabetes insipidus in a lupus patient, endocrine hormonal evaluation and an MRI of pituitary gland is warranted to rule out AH.

SUNIL KAPUR,[1] JITENDRA OSWAL,[1]* RAHUL JAHAGIRDAR[2] AND VIJAY VISWANATHAN[1]

[1]Pediatric Rheumatology and [2]Endocrinology, Department of Pediatrics, Bharati Vidyapeeth University Medical College Hospital and Research Centre, Pune, Maharashtra, India.

**dmd.bharatihospital@gmail.com*

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Neonatal Thyrotoxicosis Co-existing With Early Onset Sepsis

Neonatal thyrotoxicosis is a rare disorder, and still rarer is its co-occurrence with early onset neonatal sepsis. Thyroid dysfunction, both hypothyroidism and hyperthyroidism, can alter a range of immune functions including chemotaxis, phagocytosis, production of reactive oxygen species, and cytokine production [1].

A 31-week-old appropriate for gestational age, baby girl weighing 1420 g was born to gravida 2 mother by precipitate labor. Mother was an unbooked case and presented to our hospital in labor with meconium stained amniotic fluid. Apgar scores were 7 and 8 at 1 and 5 minute, respectively. On admission baby had severe respiratory distress with Silverman Anderson score of 8. She was noted to have tachycardia with a heart rate of 198/per minute. Due to non-availability of ventilator, she was manually ventilated for 6 hours. We kept the differential diagnosis of early onset sepsis, respiratory distress syndrome and meconium aspiration syndrome. She received injectable ampicillin and gentamicin and provided supportive care. On investigation, her total leucocyte count was 3675×10^9/L, platelets 8900×10^9/L and procalcitonin levels 7.28 µg/L (normal, less than 0.5 µg/L). Chest *X*-ray showed cardiomegaly and bilateral clear lung fields. Blood culture grew *Enterococcus faecalis* sensitive to ampicillin and gentamicin.

After 6 hours of age baby showed improvement and was shifted to continuous positive airway pressure (CPAP). However, she was noted to have persistent tachycardia, with heart rates ranging from 180-210 per minute without any evidence of poor tissue perfusion. Electrocardiogram showed sinus tachycardia. Echocardiography demonstrated structurally normal heart. Detailed examination of baby revealed a swelling over anterior aspect of neck. The eyes of the baby were prominent. Baby appeared irritable and hyperalert. Mother gave history of neck swelling for 3 months and tremors prior to delivery. She had exophthalmos and tachycardia. Thyroid profile of baby on day 3 of life in venous blood showed triiodothyronine (T3) levels of 315.4 ng/dL, thyroxine (T4) levels of 19.5 µg/dL and thyroid stimulating hormone (TSH) levels of <0.01 mU/mL. Mother's thyroid profile showed a free T3 value of 10.2 pmol/L, free T4 value of 80.4 pmol/L and TSH value of <0.01 mU/mL. Ultrasound of neck of the baby showed bulky thyroid gland with altered echotexture, suggestive of thyroiditis. TSH receptor antibody levels in baby were 37.75 IU/L (normal, less than 1.75 IU/L).The final diagnosis was early onset sepsis with neonatal thyrotoxicosis.

We started oral propranolol 2 mg/kg/day in three divided doses along with methimazole 0.5 mg/kg/day in three divided doses from day 3. Tachycardia settled after 72 hours of treatment following which propranolol was tapered. Thyroid function tests were repeated after 7 days of starting methimazole which showed no significant improvement, hence dose of methimazole was increased. On follow-up at 6 weeks and 3 months of age, baby showed normal growth and development. Thyroid functions normalized by 18 weeks of age. Methimazole dose was tapered and stopped. Baby tolerated methimazole well and did not show any adverse drug reaction.

In the present case, neonatal thyrotoxicosis coexisted with early onset sepsis which made diagnosis challenging. Although, free T4 could not be done in the postnatal period in the index case, rest of the investigations and clinical examination findings of the mother and baby were suggestive of neonatal thyrotoxicosis. Thyroid hormones are known to act as modulators of immune response [1] and it is possible that thyrotoxicosis predisposed the baby to early onset sepsis. The clue to diagnosis of thyrotoxicosis was persistent tachycardia in the absence of any known cause, such as tachyarrhythmia or shock.

Previous studies on pregnant women with thyrotoxicosis showed that women treated earlier in pregnancy were more likely to be euthyroid at delivery and had better pregnancy outcomes [2]. Uncontrolled thyrotoxicosis in pregnancy is associated with abortion, prematurity, low birthweight, and stillbirth [2]. Polak, et al. [3] reported clinical manifestations on 10 neonates with congenital thyrotoxicosis. Nine of them were due to autoimmune causes. Tachycardia was the commonest sign followed by goiter and hyperexcitability. Our patient responded well to treatment. Tachycardia settled first, followed by hyperexcitability. Neck swelling gradually reduced in size on follow-up but eye signs persisted longer. Thyroid function returned to normal by 4.5 months of age. The present case shows the rare occurrence of neonatal sepsis with congenital thyrotoxicosis, and highlights the importance of maternal history and examination in making correct neonatal diagnosis.

RIMJHIM SONOWAL,*AKANKSHA ANJALI AND ASHOK KUMAR
From Division of Neonatology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.
**rimjhimsonowal@yahoo.in.*

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Outcome of PatientsWith Systemic Onset Juvenile Idiopathic Arthritis With Macrophage Activation Syndrome at Onset

Macrophage activation syndrome (MAS) is a well-known complication of rheumatic diseases such as systemic onset juvenile idiopathic arthritis (SJIA), Kawasaki disease and systemic lupus erythematosus (SLE) [1]. However, MAS may be a difficult diagnosis to make when it happens at the onset of the disease.

We reviewed hospital records of 149 pediatric SJIA patients (age range 0.6 years -15 years) seen by us between 2011-2016. MAS at onset was seen in six patients, defined as per 2016 Classification criteria for MAS in SJIA [2]. The data of these 6 patients was analyzed with respect to initial clinical presentation, course, treatment and outcome.

Fever in all six and lymphadenopathy in 5 children were the most common clinical findings. The median duration of fever was 30 (range 7-45) days before the onset of MAS. Arthritis, which was transient in nature was noted in 2 patients (knee, 1; wrist, 1). All the 6 patients developed frank arthritis weeks to months after MAS resolved along with characteristic quotidian fever pattern, and other features of SJIA. Evanescent rashes were noted in 3 patients. Transaminitis (range 116-837 U/L) in five patients was the most common abnormal laboratory parameter, followed by thrombocytopenia (range 15-181×10^9/L) in four patients. Three children each had cardiac manifestations (2, clinical shock; 1, pericardial effusion), nervous system manifestations (2, seizures; 1, encephalopathy), and hepatosplenomegaly. Leukopenia was seen in four children (range 2.2-6.7 × 10^9/L)

Three patients needed intensive care unit care. None of the patients showed any evidence of an underlying infection and had negative blood cultures. All six patients had markedly elevated serum ferritin levels [median (IQR) 8587.5 (1053-22000) ng/mL)]. All patients underwent bone marrow aspiration of which four showed hemophagocytosis.

All patients were treated with intravenous steroids followed by oral steroids. Cyclosporine was used in 2 patients and tacrolimus was introduced in one patient, when response to steroids was suboptimal in the form of persistent fever and presence of cytopenia. The clinical response in the form of defervescence was seen within a few days after initiation of the treatment and cytopenias recovered within a week of initiation of treatment. Cyclosporine was continued for 6 months in the first patient and for one year in the second patient, and tacrolimus was continued for two years in the one patient in whom it was used. These drugs were continued in view of uncontrolled systemic JIA features.

Mean duration of follow-up of patients was 4.1 years (range 1-10 years). Three children had a monocyclic course and went into remission with a standard treatment protocol of steroids and methotrexate. Of the remaining 3 with polycyclic course of SJIA, only one patient is in remission without drugs while the other two patients continue to be on drugs to control their disease.

Minoia, et al. [3] described that of the 362 patients with SJIA with MAS, 22% of MAS episodes were seen at the onset of SJIA [3]. Other authors reported MAS at onset to be more common in SJIA patients than SLE patients [4]. All patients in this series evolved to develop arthritis and classic picture of SJIA in due course. The treatment protocol followed by the authors was similar to previous reports.

The limitation of the study is the small size of patient cohort. MAS at onset of SJIA can be a diagnostic dilemma and it should be a differential diagnosis in any sick child with febrile illness with multiorgan dysfunction, progressive cytopenias and transaminitis in the absence of any evidence of infectious cause. Absence of arthritis at onset of illness should not be a deterrent for diagnosis of SJIA as it may appear later.

JYOTHI RAGHURAM,[1*] VINOD KUMAR GORNALE[2] AND ANAND PRAHALAD RAO[3]

[1]Columbia Asia Hospital and Pediatric Rheumatology Clinic, Indira Gandhi Institute of Child Health, Bangalore, [2]Department of Pediatrics, Indira Gandhi Institute of Child Health, Bangalore, [3] Director, Pediatric Rheumatology Clinic, Manipal Hospital & Indira Gandhi Institute of Child Health, Bangalore, Karnataka, India

[*]jyothiraghuram16@gmail.com

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Beneficial Response to Phosphate Lowering Therapy in Normophosphatemic Tumoral Calcinosis

Calcinosis cutis is a comprehensive terminology for disorders characterised by deposition of calcium salts in the cutaneous and subcutaneous tissue. Based on etiology, it can be classified into: dystrophic, metastatic, idiopathic, iatrogenic, and calciphylaxis. Dystrophic calcinosis occurs following a necrotic process unrelated to serum calcium level. Metastatic calcification results from precipitation of calcium salts due to high calcium or phosphorus levels. Calciphylaxis denotes calcification of the small and medium-sized blood vessels, of the dermis or subcutaneous tissue usually in the setting of renal failure [1]. Tumoral calcinosis refers to a severe form of calcinosis involving deeper tissues, especially around joints leading to limitation of movement.

A 14-year-old boy presented with history of hard swellings in the skin around multiple joints for past two years. Some of them ulcerated to extrude chalky white material. There was restriction of movements at knees, shoulders and elbows. He did not have history or examination findings to suggest autoimmune connective tissue disorders, pancreatic disease, chronic renal failure, malignancy, trauma, medical intervention in the affected regions. His previous records showed normal calcium and phosphorus levels, and he was not on calcium or vitamin D supplementation. There was no family history of similar condition. He had undergone excision of a large lesion from right axilla but did not receive any oral or parenteral medications for treatment of lesions before presenting to us.

There were multiple hard swellings involving the skin and subcutaneous tissue around shoulder, elbow, hip, knee joint and neck on both sides (**Fig. 1a**). Range of movement of all large joints measured using a universal goniometer showed restriction of joint movements which was maximum at right knee joint (50 degrees) and right elbow (30 degrees) for extension. Restriction of movements at the knee joints had resulted in limping. The physical examination was otherwise unremarkable.

Blood counts, renal function, liver function parameters were normal. Average serum calcium and phosphorus level(fasting sample) after multiple measurements were normal (9.4 mg/dL and 4.8mg/dL, respectively).Vitamin D insufficiency (25-hydroxy vitamin D level 12ng/mL) and secondary hyperparathyroidism (Serum PTH level 126 pg/mL) were present. Plasma levels of 1, 25- dihydroxy Vitamin D was normal. Antinuclear antibody (ANA), Anti ds-DNA, Anti neutrophil cytoplasmic antibody (ANCA), anti-centromere, anti scl-70 and U1RNP were normal. Radiographic skeletal survey showed multilobulated 'cloud-like'soft tissue calcification around joints with normal joint morphology (**Fig.1b,c**). Sonographically there were no renal and ureteric calculi or nephrocalcinosis. He had undergone excision of a lesion from the axilla before presenting to us, and the histopathology report had shown multiple cysts filled with calcified deposits lined by histiocytes consistent with tumoral calcinosis.

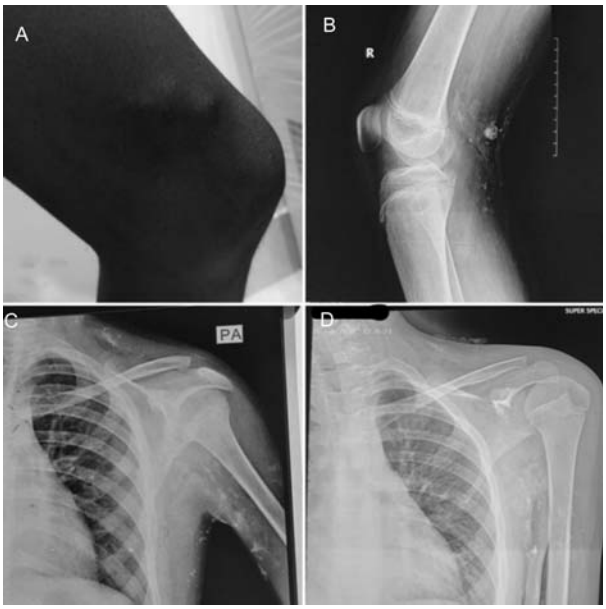

Fig. 1 (a) periarticular hard swellings at right knee, (b) *X*-ray of right knee joint showing multiple "cloud- like" periarticular calcifications, (c) *X*-Ray showing periarticular calcifications at left axilla and neck along platysma, (d) *X*-Ray of left axilla after 6 months of treatment with sevelamer and low phosphorus diet showing decrease in extent of calcification at axilla and neck.

Differential diagnoses considered were disorders which cause dystrophic calcification (like infection, inflammatory processes, cutaneous neoplasm or connective tissue diseases), metastatic calcification (like hypercalcemia or hyperphosphatemia) and secondary tumoral calcinosis due to chronic kidney disease. All these differentials were effectively excluded by evaluation. Final diagnosis of normophosphatemic idiopathic tumoural calcinosis was made.

Multidisciplinary team including endocrinologist, orthopaedician, paediatrician and physiatrist decided to start phosphate lowering medical management aiming to keep phosphorus in the low normal range, with graded physiotherapy and follow up closely after obtaining patients consent. Along with a low phosphorus diet, sevelamer at a dose of 400 mg twice daily was given orally. Surgical correction of deformity was reserved for a later scenario if medical and physical measures failed.

After 6 months of follow upon therapy, he reported improvement in joint movements and limp had disappeared which were confirmed on examination. *X*-rays showed decrease in the size of calcifications at axilla, knee and neck (**Fig. 1d**), whereas the lesion in the elbows did not increase in size. Smaller lesions have disappeared also. During the one year of follow-up, while maintaining serum phosphorus level between 3.3mg/dL and 3.5 mg/dL, he reports no new skin lesions or movement restriction nor any adverse events related to therapy.

Tumoral calcinosis is divided into hyperphosphatemic (familial), normophosphatemic and secondary variants [2]. Hyperphosphatemic form is the most common. High

phosphorus levels are due to a reduced renal clearance due to decreased action of the phosphaturic hormone fibroblast growth factor 23 (*FGF23*) which in turn may be due to mutated *FGF23* or an enzyme involved in stabilization of wild type FGF23, or α-klotho (the cofactor for *FGF23* action). Disorders like chronic renal failure with secondary hyperparathyroidism and hyper-vitaminosis D cause the secondary variety. In normophos-phatemic tumoral calcinosis, family history is usually absent, even as recent literature shows emerging evidence of familial basis occurring due to mutations in the gene encoding for the protein sterile alpha motif domain-containing-9 protein (SAMD9) [3]. Normophosphatemic version presents before second decade of life and is associated with tropical or subtropical region of living.

Traditionally, complete surgical excision of symptomatic lesions as and when they appear is the treatment of tumoral calcinosis, but recurrence is the rule. Various methods to lower serum phosphorus have been tried in hyperphosphatemic familial variety, with marked clinical and radiological resolution of lesions and includes the use of aluminium hydroxide, sevelamer, lanthanum carbonate or acetazolamide [4]. Bisphosphonates have also been tried with successful resolution of lesions in some cases [5]. Dietary phosphorus restriction to as low as 400 mg/day is required.

Unlike the hyperphosphatemic variety, the effectiveness of medical therapy in normophosphatemic variety is not established. The only report in literature on medical therapy in normophosphatemic TC is by Jubbin, et al. [6], who described resolution of pain and radiological subcutaneous calcification with alendronate. The present case is the first to report beneficial effect of phosphate lowering therapy in normophosphatemic tumoral calcinosis.

The current case report shows subjective improvement in pain, limitation of movement and gait and an objective improvement in range of movements of joints when phosphate lowering therapy was used with graded physiotherapy in normophosphatemic tumoral calcinosis. Further consideration to phosphate lowering therapy is warranted in children with normophosphatemic tumoral calcinosis.

SARAYU SOUMYA,[1] NANDINI PRASAD,[2] PUTHIYAVEETTIL KHADAR JABBAR,[1] SAJID HUSSAIN,[3] CHELLAMMA JAYAKUMARI[4] AND ABILASH NAIR[1]*

From Departments of [1]Endocrinology and Metabolism, [3]Orthopaedics, [4]Internal Medicine, Government Medical College; Thiruvananthapuram; [2]Pediatrics, Health Services Department, Government of Kerala, Kerala, India.

*-*abhimck@gmail.com*

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Successful Convalescent Plasma Therapy in a Child With Severe Coronavirus Disease

Most pediatric coronavirus disease (COVID-19) patients are asymptomatic or have mild to moderate disease and recover within two weeks [1,2]. In children, severe acute respiratory distress syndrome (ARDS) can occur, which may progress to toxic shock syndrome. In some affected children clinical features of Kawasaki disease may be observed [3]. Therapeutics like antiviral drugs and/or immune modulators available for COVID-19 children have weak recommendations [4]. COVID convalescent plasma (CCP) has been used successfully in the recent global outbreak for the treatment of adult patients with COVID-19 [5,6]. We report paediatric patient who received CCP as a therapeutic option for treatment of severe COVID-19.

A severely undernourished 13-year-old girl with fever, cough, sore throat for three days was admitted with severe respiratory distress and restlessness. On admission, she was febrile, with tachycardia (146/min), hypotension (90/58 mm Hg) and respiratory rate of 20/min. The oxygen saturation was 88% on room air. Nasopharyngeal swab reverse transcriptase – polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2, and a diagnosis of severe COVID-19 was made. Child was tried with non-invasive ventilation, which was subsequently escalated to pressure control mode of mechanical ventilation. In view of hypotension, cytokine storm was thought of as a possibility and appropriate fluid resuscitation was done. Arterial invasive blood pressure monitoring was done, along with use of inotropic agents like noradrenaline. Bedside echocardiography suggested ejection fraction of 26%. Child was

shifted to a COVID-designated intensive care unit and started on remdesivir, enoxaparin and antibiotics. Investigations on day of admission revealed deranged hematological, biochemical and inflammatory markers. *X*-ray chest showed non-homogenous opacities of pneumonitic changes in the mid and lower zone of both lung fields with right-sided pleural effusion. On day 2 of admission, the child deteriorated and had worsening septic shock with arrhythmia (prolonged QTc) and subsequently adrenaline was added. Mechanical ventilation was continued in view of ARDS with highest plateau pressure around 28.

With incresing severity of symptoms on day 2, we planned to transfuse CCP 200 mL per day for consecutive two days as per the hospital COVID-19 management protocol. Both CCP doses contained antibodies against SARS-CoV-2 IgG at a titre of 1:640 (S/Co = 5.1). Due to a decreasing hemoglobin of 7.3 g/dL with high FiO_2 of 80% requirement on day 3, we transfused one unit (250 mL) leuko-depleted packed red blood cells (PRBC) each on day 3 and day 4. Between day 4 and 6, we were able to taper-off the inotropes. The child responded to the CCP therapy and from day 5 improvement of clinical features and laboratory values were noted. She was weaned off from mechanical ventilation to room air by day 7, alongwith improvement in hematological, biochemical and inflammatory markers. Remdesivir was continued for 10 days in view of critical COVID-19. Repeat echocardiography suggested normal cardiac function. Child was discharged on day 10 on tapering oral prednisolone for 14 days. Child is doing well with no squelae and currently on no medication except nutritional rehabilitation.

Presenting with classic symptoms of COVID-19, our patient deteriorated rapidly and developed septicemia and progressed to septic shock despite initiating standard therapy. Deranged haematological, biochemical and inflammatory markers with changing *X*-ray findings in the child were likely to be associated with increased severity or worse outcomes of COVID-19. Such association in adults has also been demonstrated by previous authors [7]. The treatment of severe COVID-19 in children is close monitoring and supportive care. Antiviral or adjunctive therapy is a suggestion for selected patients in clinical trials [4]. Figlerowicz, et al. [5] from Poland reported a 6-year-old girl with severe COVID-19, in whom SARS-CoV-2 was successfully eliminated after convalescent plasma transfusion. As our primary goal was to retard the disease process, improve the clinical features, and save the child, we considered transfusion of CCP in recommended doses, which not only improved the clinical features and laboratory findings, but also helped complete recovery of the child within 10 days of admission in the hospital.

We conclude that complete information on clinical manifestations of COVID-19 in children and appropriate management are still evolving. Thus, individualization of COVID-19 treatment must be considered, depending on clinical features, laboratory findings and severity. CCP transfusion in children has the potential to slow down the COVID-19 disease process and improve clinical manifestations of rapidly.

PII: S097475591600259; Published online: December 01, 2020

SUDIPTA SEKHAR DAS,* KAUSTABH CHAUDHURI AND RATHINDRA NATH BISWAS

Department of Transfusion Medicine, Apollo Gleneagles Hospitals, Kolkata 700 054, India.
**sudipta.sgpgi@yahoo.co.in*

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Sleep Coaching for Sleep Inversion in Smith-Magenis Syndrome

An 18-month-old girl with genetically confirmed Smith-Magenis syndrome (SMS) presented to the pediatric sleep clinic with excessive behavioral problems and a poor sleep pattern. She would start feeling drowsy between 5-6 PM, followed by multiple awakenings lasting 5-8 minutes, requiring being bottle fed or rocked. She would wake up at 2 AM and remain active and playful thereafter. She was hyperactive and restless throughout the day, associated with temper tantrums and head banging. A 24-hour polysomnography showed decrease in total sleep time (6 hours), delayed sleep latency (22 min), delayed REM latency (132 min) and multiple night awakenings. There were no features of obstructive sleep apnea.

Sleep coaching was initiated by setting a regular sleep routine at night. A time gap of one hour between feeding or play and sleep was maintained. All sleep associations in the form of rocking and feeding as well as co-sleeping were stopped with graduated extinction. Her night time sleep was delayed by 15 minutes each day, till she was able to sleep by 9 PM. The bed room was darkened and all access to multimedia screens was removed. Within one month, she was able to sleep by 9 PM and wake up at 6:30 AM, with no night awakenings. Her behavioral symptoms and tantrums during the day resolved. She was maintaining this schedule at the 6-month follow-up.

SMS is characterized by infantile hypotonia, expressive speech delay, mental retardation, short stature, scoliosis, characteristic craniofacial features and self-injurious behavior [1]. Sleep issues in children with SMS commonly include early sleep onset, frequent nocturnal awakenings, early morning arousal and daytime sleepiness [2]. There is increasing evidence of an inverted melatonin rhythm in SMS with low levels of melatonin at night, and significantly high levels during the day [3]. Behavioral problems increase in children when the levels peak and sleep attacks are noted when levels drop. Administering melatonin; however, only enables a patient to sleep earlier and does not affect the early morning awakening or behavioral changes. Sleep coaching has shown to produce reliable and durable changes in infant sleep patterns [4]. This report demonstrates that sleep issues in children with SMS can be managed with sleep coaching alone.

KR Bharath Kumar Reddy
From Department of Paediatric Pulmonology and Sleep, Shishuka Children's Hospital, Bangalore, Karnataka, India.
drbharathreddykr@gmail.com

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Repetitive Eye Poking in an Infant – A Diagnostic Conundrum

Poor vision in a growing child can affect all domains of development [1]. Early diagnosis of poor vision in infants is extremely challenging as they are unable to express sensory loss or cooperate for clinical and equipment-based testing [2]. We report one such infant who presented with repetitive eye poking.

A 1-year-old female child born out of a second degree consanguineous marriage presented with complaints of not picking up objects, looking downwards without making eye contact, and with repetitive eye poking since three months of life. There was no history of head or ocular injury and no family history of visual impairment. The infant was born at term following an uneventful antenatal period. Infant's growth and development were appropriate for age. Infant had photophobia, bilateral nystagmus and sluggish pupillary reflex but was able to fix and follow light at a distance of 30 cm. Slit lamp examination revealed normal anterior segment and no evidence of pigmentary retinopathy on fundus examination. Differential diagnosis considered at this point were optic nerve hypoplasia, Leber's congenital amaurosis (LCA), high refractory errors, early onset rod-cone dystrophy, achromatopsia and cortical visual impairment. Both scotopic and photopic electroretinogram (ERG) were unrecordable. Brain MRI did not show any abnormality. In view of poor vision since birth, nystagmus, normal development, normal fundus, normal brain imaging and flat ERG, a provisional diagnosis of LCA was made. Clinical exome sequencing showed a homozygous missence variation in exon 9 of *GUCY2D* gene

(chr17:g.7915502G>A; Depth 60x) that results in the amino acid substitution of glutamic acid for glycine at codon 597(p.Gly597Glu; ENST00000254854.4) in the tyrosine kinase domain of the GUCY2D protein, confirming diagnosis of LCA type 1. Child is currently under visual rehabilitation therapy and follow-up. Genetic counselling during next pregnancy identified the same defect in the fetus, leading to medical termination.

LCA, an autosomal recessive disorder, is a rare cause of congenital blindness with a prevalence of 2-3 per million, occurring due to degeneration of retinal photoreceptor cells [1]. FDA approved gene therapy (voretigene neparvovecrzyl) is available for those with *RPE65* mutation [4]. Infants present with progressive poor vision since birth, nystagmus, photophobia, hyperopia, keratoconus and a classic behavioral pattern, Franceschetti oculo-digital sign, which involves repetitive poking, pressing, and rubbing of eyes with hand. These oculo-digital mannerisms mechanically stimulate dysfunctional retinal photoreceptors by production of phosphene, but can lead to atrophy of orbital fat and enopthalmos [4]. Though characteristic of LCA, oculo-digital sign can also be a nonspecific marker of poor vision in infants.

Acknowledgement: Dr Pratyusha Ganne, Assistant Professor of Opthalmology, AIIMS, Mangalagiri, for assistance in managing this case and drafting this manuscript.

SARTHAK DAS AND THIRUNAVUKKARASU ARUN BABU*
Department of Pediatrics,
All India Institute of Medical Sciences (AIIMS), Mangalagiri,
Andhra Pradesh, India.
**babuarun@yahoo.com*

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Acalypha indica-Induced Hemolysis and Methemoglobinemia in a Child With G6PD Deficiency

Acalypha indica (*kuppaimeni*) leaf extract is an herbal remedy, widely used locally for treatment of minor ailments. A 5-years-old boy presented to the emergency room with acute onset of passage of red colored urine and yellowish discoloration of eyes for a day. He was given ~50 mL of *kuppaimeni* leaves concoction for an upper respiratory infection 6-8 hours before the onset of symptoms. There was no significant past history or family history. Child was pale and icteric at admission, SpO2 in room air was 80%, which did not improve with supplementary oxygen. Sensorium was normal, and examination of other systems were normal.

Laboratory workup showed anemia (hemoglobin, 4.5g/dL), reticulocytosis (10%), hyperbilirubinemia (indirect bilirubin, 7.1 mg/dL), high aspartate transaminase (277 U/L), normal alanine transaminase (33 U/L), high lactate dehydrogenase (7253 U/L) and hemoglobinuria suggesting acute intravascular hemolysis. Serum creatinine was normal. Peripheral smear showed blister and bite cells with polychromasia. Direct Coomb test was negative. Glucose-6-Phosphate-Dehydrogenase assay showed low level of 133 IU per million RBC (normal value, 202–522 IU). Co-oximetry was done, which showed elevated methemoglobin (10.5%).

He was managed with high flow oxygen, packed red cell transfusion, hyper-hydration and diuresis. Methylene blue for treatment of methemoglobinemia was considered but deferred in view of low G6PD levels. Child started improving on next day, and was discharged home on the fourth day. On follow-up, repeat G6PD level was low (100 IU per million RBC), confirming G6PD deficiency.

Hemolysis after use of *A. indica* has been reported previously [1]. In a systematic review, it has been categorized as a possible cause of hemolysis [2]. There are reports of symptomatic methemoglobinemia accompanying hemolytic crisis in G6PD-deficient individuals [3]. G6PD deficiency results in diminished production of NADPH through pentose phosphate pathway. NADPH deficiency leads to deficient glutathione production which is useful to protect hemoglobin from oxidative damage. This finally culminates in methemoglobinemia during oxidative stress induced G6PD deficiency hemolytic crisis [3].

We report this case to increase awareness regarding *A. indica*-induced hemolysis, in association with methemoglobinemia in G6PD deficiency.

BHRAJISHNA PALLAPOTHU* AND JANANI SANKAR
From Department of Pediatrics,
Kanchi Kamakoti CHILDS Trust Hospital & CHILDS Trust Medical Research Foundation, Nungambakkam, Chennai, India.
**bhrajishna@gmail.com*

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Acute Flaccid Myelitis: Are We Vigilant Enough?

With the eradication of poliomyelitis from most countries, acute flaccid myelitis (AFM) due to non-polio enteroviruses and other viruses is an emerging disease. Besides the vaccine-associated paralytic polio, AFM outbreaks due to other viruses are also a hazard. AFM comprises of patients with acute flaccid paralysis (AFP), characteristically asymmetric limb weakness, with MRI suggestive of a spinal cord lesion in grey matter and spanning one or more vertebral segments [1]. Over the last decade, multiple outbreaks have been reported from countries such as USA, European countries, and Japan [1]. Two outbreaks have already been reported from India [2,3]. However, the pathogen testing was limited and inconclusive in both the cohorts. Even with ongoing AFP surveillance, AFM has not been frequently reported from India. Similar to Australia, we believe that there is misdiagnosis and under-recognition of AFM. During the initial disease course, AFM is frequently misdiagnosed as transverse myelitis due to an often extensive involvement of the spinal cord, not classically limited to the grey matter of the spinal cord [5]. Hence, there is a need for creating awareness regarding this evolving entity.

With many viruses involved such as EVD68, EVA71, etc. and poor yield of pathogen testing, it is often difficult to establish causality for AFM [1-3]. Therefore, it is time that patients with AFP should also be tested for other viruses beyond the poliovirus. This can later help in strengthening the AFP surveillance system. Survey studies for non-polio AFM throughout the country may be an initial step in this aspect, in the absence of active ongoing surveillance. However, the surveys need to be more robust to capture the epidemiological aspects of both AFM and associated respiratory/gastrointestinal illnesses. The key epidemiological parameters should include the whereabouts of patients (for source identification), age group, details of neuroimaging, and virological studies, contact tracing, etc. for patients in both the groups. Besides, AFM clusters and outbreaks need to be investigated meticulously to avoid an epidemic staring at us.

PRIYANKA MADAAN AND LOKESH SAINI*
Pediatric Neurology Division, Department of Pediatrics, Advanced Pediatric Centre, PGIMER, Chandigarh, India.
**drlokeshsaini@gmail.com*

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Acute Flaccid Paralysis in a Child: It Is Not Guillain-Barré Syndrome Always!

A 6-year-old-girl presented with complaints of difficulty in walking for 5 days. Initially, the child started limping on the left side, followed by unable to bear weight; within two days, the right lower limb also got involved and she became non-ambulatory. She also complained of dull aching pain in lower limbs, especially in the upper thigh, more on the left side. There was no history of proceeding febrile illness, trauma or intra-muscular injection. She was completely immunized as per the national immunization schedule. She had tenderness in the left flank, lower back and bilateral thigh, keeping the hips in a semi-flexed position, not allowing any passive movement or formal tone examination. Even knee jerks could not be elicited bilaterally. In the left hip joint power was 2/5 and 3/5 power in the right knee, left hip and knee joint. A clinical possibility of acute flaccid paralysis (AFP) was kept, with a differential diagnosis of Guillain-Barré syndrome (GBS), viral myositis, polymyositis, transverse myelitis, paralytic polio myelitis, Perthes disease, septic arthritis of the hip joint and pseudoparalysis due to unnoticed trauma, or with pelvis/femur fracture. On investigations, *X*-ray of the hips, nerve conduction study and serum creatine phosphokinase were normal. Ultra-sonogram revealed a heterogeneous collection in left iliopsoas muscle, extending to the pelvis and inguinal region. Pus was drained by percutaneous pigtail catheter and she responded favorably to intravenous vancomycin and she was able to walk after three days.

Although predominant causes of painful, hyporeflexic weakness of bilateral lower limbs are GBS and viral myositis, often pseudoparalysis due to trauma, scurvy or referred pain from the loin, lower back or hip joint may mimic GBS, thereby causing diagnostic confusion [1]. The classic triad of psoas abscess (fever, flank pain, and limitation of hip joint movement) can be found only in 30% of patients [2].

The atypical presentation with bilateral painful gait instability in absence of fever, trauma or intramuscular injection in our case clinically resembled GBS or pathology localized to lumbosacral plexus or spinal cord. However, instead of performing costly and tedious investigations like MRI and nerve conduction study, simple ultrasonography may clinch the correct diagnosis easily. Pseudoparalysis in children under 15 may be caused due to various etiologies like skeletal trauma, lymphadenitis or muscle aches from a viral illness, transient synovitis, septic arthritis, osteomyelitis, pyomyositis, fasciitis, cellulitis, rheumatological diseases such as juvenile idiopathic arthritis, acute rheumatic fever and malignancies like sarcoma and leukemia [3,4]. Hence, atypical presentation of iliopsoas abscess requires a high index of suspicion on part of pediatricians, to establish a timely diagnosis.

PRATEEK KUMAR PANDA AND INDAR KUMAR SHARAWAT*
Pediatric Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, India.
**sherawatdrindar@gmail.com.*

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What is the Determinant of 2019 Novel Coronavirus Prognosis in Children?

We read the article by Li, et al. [1] with interest and would like to offer some observations about the study based on the current literature.

In the pathogenesis of a standard viral infection, the pathogen's contact with the mucosa is initially followed by an innate immunity response (macrophage, antigen presenting and natural killer cell). Subsequently, adaptive immunity comes into play and is responsible for the elimination of infected cells, activation of the antibody response, and production of memory T-cells. T-cells are the primary decisive element in adaptive immunity capability. For this reason, the adaptive immune response mediated by the thymus is a process that regulates the immune response responsible for preventing invasive damage from a virus. Therefore, the thymus is the most influential organ in the transmission of viral disease [2].

The thymus generally decreases in function and anatomically shrinks with age. This function and size loss becomes specially prominent after the age of 50 [3]. Thymic involution and the gradual decrease in T-cell count and ability with age are together termed as immunosenescence [4]. The primary reason for morbidity and mortality in COVID-19 cases is due to lung manifestation. The primary reason for a frequently severe clinical presentation in patients of ages 50 and up is thought to be due to a deficient, irregular and uncontrollable antiviral response as a result of thymus involution and immunosenescence. Important factors in achieving an adequate immune response are an increase in thymus activity and T-cell action along with immune system coordination.

When examining the critical COVID-19 cases in the literature, the male gender seems to be more common; this is speculated to be due to greater tobacco use and ACE-2 receptor expression. The literature also shows that thymic involution is more apparent in males compared to females. This difference in thymic involution indicates that males face a greater extent of immunosenescence. We believe this mechanism might be responsible for clinical worsening in males [5].

We believe that thymus regression and lung immunosenescence are the main deciding factors of lung involvement depth in adult COVID-19 patients. But, we do not know thymus activity in children cases with severe COVID-19. We feel that there is a need to examine the patients for thymus size, and look for association between thymus size and the severity of lung involvement.

PII:S097475591600257; Published online: November 29, 2000.

SADIK YURTTUTAN
Neonatal Intensive Care Unit, KSU University SUA Hospital, Kahramanmara, Turkey.
sdkyurttutan@gmail.com

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Requesting National Guidelines for Screen Time in Indian Children from IAP

We read with great interest the research article by Meena, et al. [1] on screen time in children by 15-18 months of age. We wish to share our survey findings of 109 well children (12-36 months) at three hospitals in Bangalore between September, 2016 to April, 2017. We found that the mean (SD) screen time exposure was 120 (96.2) minutes (range 0-540 min) in this age group, similar to the study by Meena, et al. [1]. Television (69%), mobile phones (66%), tablet (27.5%) and laptop (22%) were the most common electronic media used in our study. We found rhymes (89%) commercial advertisements (62%), educational videos (36%), and cartoons (20%) constituted majority of the activities during screen time. Importantly, 73% of the parents used screen time to help the child in eating, 51% for entertain-ment, and 34.8% as a distraction to give the caregiver some free time. Contrary to their findings, we found that only 7% of the parents thought screen time was good for the child. We found that 26% of these children had delay in speech for their respective ages. An association with speech delay and screen time has also been reported earlier [2,3].

We agree with the authors that it is the need of the hour to not only provide Indian guidelines for screen time in toddlers to parents but also to make them aware of possible adverse effects it may cause in their toddler's speech development. We are eagerly waiting for guidelines of Indian Academy of Pediatrics on screen time for children to address this important issue, and to communicate these to parents in addition to practitioners.

Ethics clearance: Institutional Ethics Committee, Kids Clinic India Pvt Ltd; No. ECR/791/ Inst/ KA/ 2015/RR-18, dated August 20, 2016.

MEGHNA MANOCHA* AND MEENA VENKATRAMAN
Cloudnine Hospital Old Airport Road,
Bangalore, Karnataka, India.
**drmeghna@cloudninecare.com*

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The Need for Geographic Location Specific Optical Density Cut-offs for IgM ELISA Serology to Diagnose Scrub Typhus in Children

We read with interest the article on detection of immunoglobulin M and immunoglobulin G antibodies against *Orientia tsutsugamushi* for scrub typhus (ST) diagnosis by Gupte, et al. [1]. This study was done to estimate the regional cut-off of optical density (OD) values of serum IgM antibodies by ELISA for the diagnosis of ST. Authors had successfully determined regional cut off of OD value for IgM antibodies, which will be utilized in diagnosing ST in that area. This study has shed light into one of the most obvious pitfalls in diagnosing ST by serology (IgM ELISA) i.e., using an inaccurate, arbitrary OD value cut off for diagnosis. This has serious implications that are applicable beyond the study population.

We would like to raise two pertinent points based on the study conclusions. Most studies conducted in pediatric ST using serology by IgM ELISA used 0.5 OD as an arbitrary cut off in accordance with the definition of 'probable case' by the IAP guidelines on rickettsial diseases in children [2]. Since OD of 0.5 is much lower than most of the cut offs reported from Southeast Asia, where ST is endemic in many parts, all these studies with OD cut off of 0.5 might have actually over diagnosed ST and hence the results have to be cautiously interpreted [3-5]. Since the OD cut off is going to be influenced by geographical location and degree of endemicity, it is imperative to use location specific OD cut off to diagnose ST [4]. Conducting epidemiological studies to identify the OD cut

off in the normal population would be challenging and not feasible. The Government run laboratories in the district and state headquarters can pitch in and publish district- or state-wise OD cut off based on the previous samples tested, which can be regularly updated with time.

Timely diagnosis is crucial in reducing morbidity and mortality of ST in children, and since ST PCR is not freely available everywhere, earliest laboratory confirmation is often done by serology by IgM ELSIA after 5-7 days of fever onset [2]. While IgM ELISA serology testing to diagnose ST is affordable, easy-to-use, with reasonable diagnostic accuracy for screening and diagnostic purposes, regional cut-offs should be identified and maintained by regional health authorities and should be validated from time to time in order to prevent misdiagnosis.

THIRUNAVUKKARASU ARUN BABU[1]* AND DINESH KUMAR NARAYANASAMY[2]
From Departments of Pediatrics,
[1]AIIMS, Mangalagiri, Andhra Pradesh; and
[2]JIPMER, Karaikal, Puducherry; India.
**babuarun@yahoo.com*

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AUTHORS' REPLY

We thank the authors for their comments about our article [1]. In exercises of determining the cutoff for diagnostic tests, it is inevitable that some amount of misclassification would always happen. We always try to minimize this risk but there is no way to eliminate it altogether. It is thus possible that the published studies, by using the cut-off of OD values of >0.5, would have over-estimated the proportion of *Orientia tsutsugamushi* infection among probable scrub typhus patients. We also feel that conducting well-planned epidemiological studies to estimate regional cut-offs in scrub typhus endemic area would be challenging without involving credible laboratories. Such studies would need sera from sufficient number of patients with detailed granular data on clinical details from a given region. The feasibility of involving district/state public health laboratories and using previous samples, as suggested by the authors, would therefore need a careful consideration before such studies are initiated.

MANOJ MURHEKAR* AND MOHAN GUPTE
ICMR–National Institute of Epidemiology,
Chennai, Tamil Nadu, India.
**mmurhekar@nieicmr.org.in*

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Variation in Tribe-Specific Mortality Indicators of Child Health in India: Emphasizing Tribe-Specific Action Plan

Under-five mortality exhibits uneven distribution, incurring heavy toll among tribal population compared to non-tribal population in India. This necessitates the persistent need for research on tribe-specific indicators of child mortality and life expectancy in India. In this context, Verma, et al. [1] provided tribe-specific estimates of infant mortality rate (IMR), under-five mortality rate (U5MR) and expectation of life at birth (LEB) for 123 tribes in India using Census 2011 data. As is evident from the study, majority of selected tribes depicted higher IMR and U5MR than the national average and the total scheduled tribe (ST) population. The study not only highlighted immense difference in these estimates among tribal and non-tribal population, but also the differences in the estimates among tribes residing in different states and even within the same state.

The above findings are critical with respect to availability of maternal and child health care services and the sporadic success of related government flagship programs in achieving universal health coverage in tribal areas. Although the study acknowledges the need to develop programs to reduce the gap in child mortality and life expectancy within tribal population and between tribal and non-tribal populations, but it left scope for many unaddressed questions. It is important to explore the factors underpinning such huge gap in the indicators of child mortality and life expectancy among tribal and non-tribal populations in India.

Socio-cultural, economic and environmental factors varying across states and social groups play a critical role in uneven distribution of child mortality and life expectancy between tribal and non-tribal populations and even within tribal

population. Although various government programs and policies have been implemented to curb infant and childhood mortality and improve the maternal and child health (MCH) status, but these do not exhibit uniform improvement across all sections of society [2]. The investigators of the present study used Census 2011 data, which is about a decade old, and may not characterize currently prevailing conditions in tribal communities. In addition, the authors have also highlighted the limitations of the indirect method used to estimate IMR, U5MR and LEB.

Nevertheless, the present research has an added value in the absence of any other tribe-specific data source and estimates. The study opens the door for further research to explore disparities among tribal groups in health-seeking behavior so as to address differences in child mortality and life expectancy. Cultural acknowledgement, economic improvement and political empowerment are utmost crucial to address these disparities [3]. The inherent diverse nature of tribal population in India necessitates tribe-specific data. It is important to involve tribal people in the development of the tribe-specific data so as to ensure that indigenous values, beliefs, and notions related to health and wellbeing are captured effectively in the data system [4]. There is a need for ensuring 'pro-culture' tribe-specific action plans to address the disparities in child mortality rates and life expectancy among tribal communities.

VIJIT DEEPANI AND DAMODAR SAHU*
ICMR-National Institute of Medical Statistics, New Delhi, India.
**sahuicmr@gmail.com*

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CLIPPINGS

Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic (*Circulation. 2020;142:429-36)*

This is one of the first studies describing MIS-C, a Kawasaki-like illness occurring after exposure to SARS-CoV-2. The study included 35 children admitted for cardiogenic shock, left ventricular dysfunction, and severe inflammatory state in 14 centres in France and Switzerland.

Median age at admission was 10 years and median duration between the first clinical symptoms and symptoms of heart failure was 6 days. None of the patients met criteria for typical Kawasaki disease. About 80% were admitted directly to the intensive care unit due to cardiogenic shock. Two-thirds required invasive mechanical ventilation while one-fourth required use of veno-arterial extracorporeal membrane oxygenation. Echocardiography at admission revealed depressed left ventricular systolic function in all, with normal left ventricular dimensions in 29 of 35 patients. Dilatation of the coronary arteries was found in 17% with coronary aneurysms in none. All patients received intravenous immunoglobulin, with adjunctive steroid therapy used in one-third. Complete recovery of left ventricular function was observed in 71% of patients 2 days (median) after admission. Median ICU stay was 7 days and no patient died.

The authors postulated that the rapid resolution of systolic dysfunction, together with mild to moderate troponin elevation, suggests that the mechanism of acute heart failure in children is myocardial stunning or edema, rather than inflammatory myocardial damage as in adults.

JAY RELAN
jr2321990@gmail.com

COVID-19 vaccines- A closer look

The Oxford vaccine (ChAdOx1 nCoV-19 vaccine) trial interim data were recently published in the Lancet. This randomized controlled trial was conducted in the UK, Brazil and South Africa. Both safety and efficacy were tested. The control was the meningococcal vaccine. The primary outcome were rates of symptomatic COVID 19 infection. This is a replication-deficient chimpanzee adenovirus vector containing the SARS CoV2 spike protein gene.

The 11,636 participants received 2 doses roughly 1-2 months apart. A small subsection (around 3000) inadvertently received a lower dose of the first vaccine. The majority of participants were between 18-55 years and only 12% were above 55 years of age. The efficacy was around 62% in the vaccinated group and 90% in the group which received the lower dose initial vaccine. The reason for this is still unclear. There was one case of transverse myelitis in the vaccine group and one case of hemolytic anemia in the control group. Two more cases of transverse myelitis in the vaccine group were considered to be unrelated to the vaccine. One because of an underlying multiple sclerosis and one because it occurred 68 days after the vaccine.

A subset of participants were also monitored using weekly nasal swabs for asymptomatic infections. It appears the low dose subgroup is 60% effective in preventing asymptomatic infections. This data was not evaluated in the Moderna and Pfizer vaccine. Prevention of asymptomatic infections is an important consideration for policy makers.

The vaccine will be marketed by Astra Zeneca at a relatively low cost of $2-4/ dose. In contrast the Moderna vaccine will cost $37, the Pfizer vaccine $20 and the Sputnik vaccine $10 per dose. The Oxford vaccine has an added advantage. It requires only routine cold chain refrigeration unlike the ultra low freezers (<70º C) which the mRNA vaccines (Moderna and Pfizer) require.

In summary, though the Moderna and Pfizer vaccine have a superior efficacy of over 90% in preventing symptomatic COVID19 infections, the practicalities like cost and ease of storage may bias governments towards the Oxford vaccine.In India, the Serum Institute is manufacturing the Oxford vaccine as Covishield and another vaccine Novavax which has SARS CoV2 spike proteins packaged as nanoparticles. Bharat Biotech and ICMR are producing an indigenous inactivated virus vaccine "Covaxin". Dr Reddy's is partnering the Russian vaccine Sputnik V with an efficacy of 92%.
(*Lancet December 2020*)

COVID-19 risk in planes and other mass transport

It appears that therisk of SARS-CoV-2 transmission during air travel are not as high as imagined. In commercial jets, inflow of air occurs from the roof downwards to the floor on the aisle side, from where it is then swept out below the seats. Air changes occur about 20-30 times per hour. Half of the air inflow is from outside and 50% is recirculated through HEPA filters which are highly effective in clearing out viruses. There is very little flow between rows. A US Department of Defence modelling using mannequins found that a person would need 54 hours of exposure to contract an infectious dose of the virus in a plane. Suggestions for passengers include wearing a mask at all times, adjusting the sir nozzle full blast towards ones face, sanitising hands regularly and avoiding touching ones face.

Suggestions for bus travel include taking a window seat and keeping the window open, using a mask and limiting travel to short bus rides. In taxis, keeping the windows open, limiting rides to under 15 minutes, avoiding conversation as far as possible beside masking are the best strategies.
(*Scientific American 19 November 2020*)

The mRNA vaccine

Scientists have long been tinkering with the idea of an mRNA vaccine. This is because they can be rapidly and cheaply manufactured compared to traditional inactivated viral vaccines. The Pfizer and Moderna COVID 19 vaccines are the first to reach such an advanced state of approval. In the Pfizer vaccine, the mRNA coding for the spike protein is enclosed in a lipid nano particle formulation. After entry into cells the mRNA is used by cellular machinery to code for the spike protein. It is expressed on the cell membrane and sparks the immune response.

Safety and efficacy results of the Phase III trial studying the Pfizer vaccine have also been recently published in the NEJM. This RCT was conducted on 43,448 participants above 16 years of age. It's efficacy in protecting against symptomatic COVID 19 infection was 95%. Fatigue and headache occurred in about half of the participants and fever in around 15%. Axillary lymphadenopathy was reported in 0.3%. Younger participants had more adverse effects than older participants. Britain has approved the Pfizer vaccine for emergency use in the UK, but added a caveat after 2 NHS workers developed anaphylactoid reactions after the vaccine. People with prior history of allergic reactions are to avoid its use.
(*N Engl J Med 10 December 2020*)

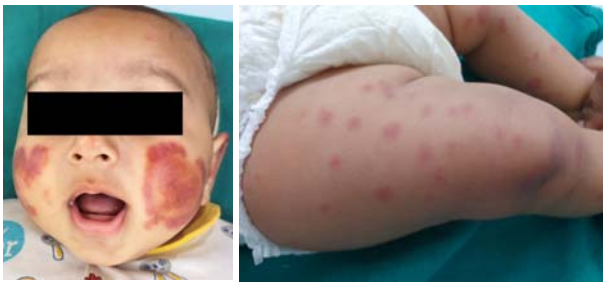
Gouri Rao Passi
gouripassi@gmail.com

IMAGE

Childhood Rashes: A Pediatrician's Dilemma

An 8-month-old male infant was brought with complaints of extensive reddish-purple cutaneous lesions over face (**Fig. 1a**), ears and lower limbs (**Fig. 1b**) of three days duration. There was a history of low grade fever and coryza 48-72 hours prior to the appearance of skin lesions. The baby was active, playful and feeding well. The lesions resolved spontaneously over the next two weeks, without any active intervention.

Acute hemorrhagic edema of infancy (AHEI), also called Finkelstein disease or Seidlmayer disease, is a benign and rare cutaneous leukocytoclastic small-vessel vasculitis, characterized by palpable purpura and peripheral acral edema, seen in children aged 4 to 24 months of age. The lesions are non-pruritic, targetoid or annular purpuric plaques or ecchymosis, symmetrically distributed over face, auricles, and extremities with sparing of the trunk and mucosal membranes. Systemic and visceral involvement usually does not occur and the child remains non-toxic. It may be triggered by infection, drugs or immunization. The cutaneous lesions generally disappear spontaneously over 10-14 days and no specific treatment is needed. AHEI closely mimics Henoch-Schönlein purpura (HSP), which is more common in older children aged 3-6 years. Unlike AHEI, children with HSP commonly have visceral involvement, may have thrombocytopenia, and present with hematuria, acute kidney injury or arthralgia. Other differentials include erythema multiforme, erythema infectiosum, idiopathic thrombocytopenia, meningococcemia, Kawasaki disease, COVID-19, urticaria multiforme, Gianotti-Crosti syndrome, and child abuse. Since clinical presentation of AHEI is often acute and dramatic, the condition must be promptly diagnosed to avoid unnecessary investigations or hospitalization, and to reassure parents.

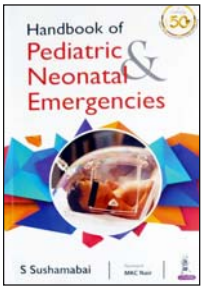


(*a*) (*b*)

Fig. 1 (a). Symmetrical purpuric plaques on both cheeks and (b) targetoid purpuric lesions on both lower legs in a child with acute hemorrhagic edema of infancy.

Pooja Dewan[1]* and Archana Singal[2]
Departments of [1]Pediatrics and [2]Dermatology, University College of Medical Sciences, Delhi, India.
**poojadewan@hotmail.com*

BOOK REVIEW



Handbook of Pediatric and Neonatal Emergencies

S Sushamabai
Jaypee Brothers Medical Publishers (P) Ltd.
Pages: 594

With guidelines for having a department of emergency medicine as mandatory in all medical colleges, pediatric emergency medicine as a specialty also needs strengthening. This handbook is a right step to fulfil the need of young learners and practitioners.

The book has 16 sections, carefully segregated with a system-wise approach. Chapters on common procedures, drug formulary and clinical scoring systems provide extra zest to the book. The chapters are appropriately complemented with relevant pictures and easy comprehensible flow diagrams, making it a ready reckoner. The first section on setting up of a PICU is very useful; supplementing another chapter on designing a pediatric emergency room in future editions will be really helpful in current scenario. Incorporating child abuse, trauma, surgical emergencies, gynecologic emergencies and point of care ultrasound in ER will further add to this beautifully produced book. The book is recommended for all the young pediatricians and neonatologists.

Dr Prerna Batra
Professor, Department of Pediatrics
UCMS and GTB Hospital, Delhi.
drprernabatra@yahoo.com

Printed and published by Dr Devendra Mishra on behalf of Indian Academy of Pediatrics and printed at Cambridge Press, Kashmere Gate, Delhi-110006 and published at 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049. Editor: Dr Devendra Mishra

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Iron Deficiency Anaemia