E-copy

Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

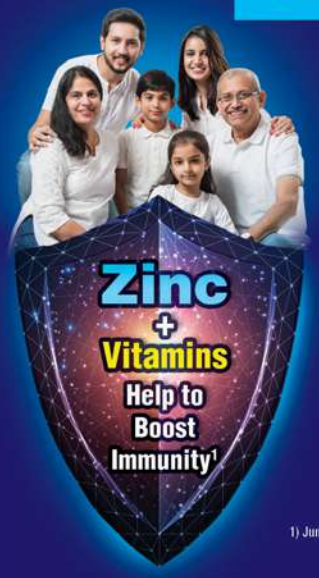
VOLUME 60
NUMBER 10
October 2023

www.indianpediatrics.net
ISSN0019-6061 (Print) | ISSN0974-7559 (Online)

Supplement

Zincovit®

Tablets / Syrup / Drops



The **Trusted** No.1 **Brand**

(Awacs, for March 2023)

1) Junejo S, Lateef M, Eme PE. Life and Science. 2020; 1(suppl): 120-123.

The Tasty Treat... Meant...
for kids in Pyrexia...

P-100® Drops
Paracetamol 100 mg/ml

P-120® Suspension
Paracetamol 120 mg/5ml

P-250® Susp/ Tabs
Paracetamol 250 mg

P-500® Susp/ Tabs
Paracetamol 500 mg

P-250® MF Suspension
Mefenamic Acid 100 mg & Paracetamol 250 mg/5ml

Offers Micronized Paracetamol

apex laboratories private limited SIDCO Garment Complex, III Floor, Guindy, Chennai - 600 032. INDIA
www.apexlab.com | Ph.No: 044-4222 5000

Indian Pediatrics

October 2023 Volume 60 Number 10

CONTENTS

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with monthly circulation of print/e-copies to over 34,000 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.

Address for ordinary letters: **The Editor-in-Chief, Indian Pediatrics, P. Box No. 3889, New Delhi-110 049, India.**
Address for registered/speed post letters: **Dr. Devendra Mishra, Editor-in-Chief, Indian Pediatrics, 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049, India. Tel: (011) 46052593**
E-mail: *jiap@iapindia.org*; Website: *www.indianpediatrics.net*; LinkedIn: *indianpediatrics*
Facebook: *www.facebook.com/Indianpediatrics;* Twitter: *@EditorIndPed;* Instagram: *@indianpediatrics*

Rising Concern of Childhood Obesity in India

UPENDRA KINJAWADEKAR
President, Indian Academy of Pediatrics, 2023
upen228@gmail.com

The prevalence of overweight/obesity amongst children under five years of age has increased almost two-fold in the urban parts of the country. Overweight was defined as weight for height being more than 2 SD above the median of the reference population. By this definition, about 4.2% of urban Indian children under the age of 5 were overweight, as of 2020. Although figures for overweight adolescents are not captured in this survey, independent studies show that the prevalence of overweight among adolescents rose from 9.8% in 2006 to 11.7% in 2009 [1]. Although, the numbers do not seem very troubling right now, they are indicative of a greater challenge looming in the horizon. India is predicted to have more than 27 million obese children, representing one in 10 children globally, by 2030. Further, it ranks 99th on the list of 183 countries in terms of preparedness to deal with the obesity epidemic.

Although unfortunate, the rise of this overweight/obesity in India is hardly shocking. It can be understood as the consequence of a complex interplay of a variety of factors. First, there is a small percentage of childhood obesity that is inherited. Parental obesity (both maternal and paternal) or hyperglycemia can result in a predis-position to increased deposition of fat in the child [1]. However, genetics may account for only about 5% of all cases of childhood obesity. Like most non communicable diseases, the socio-economic and environmental factors have a larger role to play, the most important being the dietary intake during childhood. With the advent of globalization, children are exposed to more high-fat, high-sugar, and high-salt (HFSS) foods than we ever were. These often are marketed and advertised as healthy, accessible alternatives to traditional meals. Further, the narrative around 'eating out' is also rapidly shifting. What was once considered an occasional luxury is rapidly becoming a weekly norm. Food delivery apps and a plethora of dining options have made HFSS food available at the click of a button. Children's idea of leisure time with friends by and large involves a calorie-dense meal. A drastic behavioral change is seen in children as they enter higher secondary school – increasing academic pressures result in a depletion of time allocated to physical activity, especially in adolescents. We have all witnessed how the evening hullabaloo of children running around has increasingly come to be replaced with a silent group of teenagers huddled together around a device. Every additional hour of TV-time per day increases the prevalence of obesity in children by 2% [2]! Binge eating or increased snacking to relieve stress, anxiety or loneliness is also now evidenced by a body of neuro-science that shows that the chronic consumption of energy-dense foods brings about changes in the brain's reward pathways (pleasure center in the brain), leading to a loss of control over food intake, portion control, impulsive eating – all despite often knowing the health consequences. Higher socio-economic status is another risk factor. This is also not very surprising. Childhood obesity was under-stood to be predominant in the developed west, and associated with affluence. Adopting western lifestyle – and their consumption patterns – as a sign of class mobility is a common Indian aspiration, one that has risen conco-mitantly with the rise of the Indian middle class.

Obesity in childhood is highly likely to continue well into adolescence and adulthood. Overweight/obese children become susceptible to a plethora of lifestyle and non-communicable diseases, including pediatric meta-bolic syndrome, diabetes, dyslipidemia, hypertension, cardiovascular disease, non-alcoholic fatty liver disease as well as other endocrine, orthopedic and psychosocial disorders [3]. The United States is now seriously trying to contain the obesity epidemic, but is constrained by entrenched mindsets and strong lobbyists from the food and beverage industries. The time is now for India to learn by observation, and prevent a major public health crisis in the near future.

The WHO suggests a three-pronged strategy: curbing the genetic incidence of childhood obesity by improving parental nutrition, tackling obesogenic environmental factors, and treating overweight/obesity in childhood to prevent its continuation into adulthood. Early detection of gestational diabetes and hypertension, counseling on adequate nutritional intake and exercise are other important measures suggested. We already know the importance of

early initiation of exclusive breastfeeding, and complementary feeding after six months to ensure ideal nutritional status of the baby. Responsive parenting while feeding allows infants to decide portion control while eating. This simple intervention is powerful in preventing overeating. The second strategy, one of curbing obesogenic environmental factors, needs an innovative approach. Stringent policy measures could include ensuring junk food outlets are not too close to school premises. However, individual messaging may be more feasible and practical. Celebrities need to be made aware of their moral responsibility in not advertising HFSS products such as packaged beverages, and in fact, advocating for the opposite. Replacing HFSS with home-made snacks, monitoring and limiting eating-out are other initiatives that parents have to take to protect their children's health. Schools need to be proactive in reaching out to parents of students who show signs of overweight/obesity, and counseling them on the consequences. IAP's school outreach program *Sankalp: Sampoorna Swasthya* (*www.iapsss.org*) is also contributing to this effort of spreading awareness amongst parents, teachers and students. I appeal to our members to visit iapsss.org; get more information about this wonderfully designed interactive program and start conducting it in as many schools as they can.

India is at the precipice of a nutrition paradox. While on one hand, the incidence of wasting, stunting, and underweight is still very high (more than 30% on all parameters), we are also seeing the warning signs of an imminent crisis of childhood obesity. Other countries have launched innovative efforts to curb this rising phenomenon: Brazil prohibits advertisements which are intended to influence children or adolescents to consume HFSS foods. Ireland has strictly banned using celebrities, icons and personalities to promote food products which target children. Norway censors' food advertisements on channels for children under 18, advertising for approved food categories during prime-time television. We too need to act upon this danger before it becomes an uncom-fortable, prevalent reality in our country. Pediatricians should talk about about healthy and balanced diet during each visit irrespective of the reason for which an infant or child is brought. Plotting the growth parameters is another simply way of picking overweight which can progress to obesity in no time if we don't address it.

The Indian Academy of Pediatrics will soon publish the pediatric obesity guidelines and will also hold a first of its kind pediatric obesity conclave to make our members more aware and committed for the prevention of childhood obesity.

REFERENCES

1. Gupta DK, Shah P, Misra A, et al. Secular trends in prevalence of overweight and obesity from 2006 to 2009 in urban asian Indian adolescents aged 14-17 years. PLoS One. 2011;6:e17221.
2. Report of the Commission on ending childhood obesity. World Health Organization, Geneva. 2016.
3. Anderson PM, Butcher KE. Childhood obesity: Trends and potential causes. Future Child. 2006;16:19-45.
4. Sashindran KV, Dudeja P. Obesity in school children in India. *In*: Anugwom EE, Awofeso N, editors. Public Health in Developing Countries. IntechOpen, 2020.

INVITED COMMENTARY

Unity in Diversity – Uniting Youth and Transgender Health

NITIN KAPOOR,[1]* SANJAY KALRA[2]
[1]*Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu.*
[2]*Department of Endocrinology, Bharti Hospital, Karnal, Haryana.*
**nitin.kapoor@cmcvellore.ac.in*

Unity in diversity is the national motto of not only India [1], but at least four other nations/ organizations as well: the European Union, Indonesia, Papua New Guinea, and South Africa. Unity in diversity is the foundation of modern health care, which understands the value of multi-disciplinary and multi-professional teamwork.

Unity in diversity also extends across the diverse phases of the life cycle, as pediatricians work in close collaboration with colleagues from other specialties to provide transitional care through adolescence and young adulthood. Pediatrics, in fact, provides a platform or foundation for optimizing health throughout an individual's lifespan [2].

The definition of pediatrics has broadened over the last five decades, as has its scope and spectrum. One of the ways in which this manifests is the wide spectrum of activities and actions that constitute pediatric practice. While preventive and promotive care was earlier considered synonymous with only vaccination and sanitation, lifestyle modification [3], mental and emotional health, gender identification and expression, and sexual health are now considered an integral part of the diverse facets of pediatric care.

The Adolescent Health Academy Statement

In their statement on transgender care [4], the Adolescent Health Academy (AHA) celebrates this diversity[4]. Pediatricians care for all children, irrespective of their neurodiversity. At times; however, conventional training does not give adequate exposure to the needs and requirements of transgender and gender diverse children. The AHA statement on transgender care works to towards encourage acceptance of all children and fosters inclusivity in all pediatric care setups.

Language matters: The statement clarifies the various terminologies and definitions used in transgender care, making them easy to understand. It must be noted that the word 'transgender' is an adjective, and not a noun. Inadvertently; however, the word has been used as a common noun in few places in the text. It is important for neonatologists and pediatricians to be able to distinguish between intersex conditions (also known as differences in sexual development DSD). Extra emphasis may be in added in future iterations, to explain these two distinct conditions, and guide health care providers in appropriate counseling and care.

Pragmatic practice: The publication describes social and legal issues in great detail, and alludes to the challenges faced by transgender children. It is important to advocate for the rights of transgender and gender diverse children and adolescents. Best practices on how to "create a nurturing environment" and "initiate early gender-affirmative care by family and society" should be discussed, to create a practical and pragmatic blueprint for pediatricians. Suggestions on how to handle bullying at school, navigate social encounters, maintain self-esteem, and improve coping skills are required [5].

Transgender care can be represented as a pyramid, in which lifestyle modification and psychological support, counseling and treatment should be integrated and offered at all health care levels, including the primary level [6]. This means that all pediatricians should be equipped to offer psychological and social support to transgender children and adolescents. Not only that, they should be able to offer necessary support to the family of transgender children and adolescents as well. They should also be able to provide medical and metabolic support, or refer to the appropriate professional expert if needed.

Gender Affirmation

Gender-affirmative therapy includes both medical and surgical interventions. These should be planned only after the age of consent i.e., 18 years. The statement describes these in detail, but pays less importance to puberty postponement, or suppression of puberty. Though these interventions have been embroiled in needless controversy, they are 'potentially life-saving,' and are essential drugs for transgender children and adolescents. Puberty postponement allows the child time to understand their body, and minimizes gender dysphoria.

The window period that is created ensures that the child or adolescent is sure of their gender identity, and bridges the gap between diagnosis of a transgender identity and provision of gender-affirmative interventions [7].

AHA clearly speaks against conversion therapy, calling it out as "harmful and unlawful." It proposes screening for gender identity in clinics, and encourages pediatricians to screen for transgender health issues.

The Pediatrician's Responsibility

The most important take home message from the statement is the call for pediatricians to think beyond mere medical care. The pediatrician should shoulder the responsibility of learning about transgender and gender diverse health, educating the society, advocating for children's rights, and acting as a part of a multi-disciplinary team, and take support from concerned experts as and when needed.

The Indian Professional Association for Transgender Health (IPATH) [8] provides a platform for medical professionals to engage in academic and research activities related to transgender health. Together with IPATH and Indian Academy of Pediatrics, AHA can work to encourage discussion, and optimize delivery of health care for transgender children and adolescents.

The statement on transgender care [4] is an important step towards achieving an inclusive society for all gender diverse children and adolescents. This statement should be viewed as the beginning of a beautiful journey, as a dynamo for continued dialogue and discussion, so as to build better health for all.

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

REFERENCES

1. Mastana SS. Unity in diversity: an overview of the genomic anthropology of India. Ann Hum Biol. 2014;41:287-99.
2. Schidlow DV, Fiel SB. Life beyond pediatrics. Transition of chronically ill adolescents from pediatric to adult health care systems. Med Clin North Am. 1990;74:1113-20.
3. Clarke EA. What is preventive medicine?Can Fam Physician. 1974;20:65-8.
4. Pemde HK, Bansal U, Bhattacharya P, et al. Adolescent Health Academy Statement on the Care of Transgender Children, Adolescents, and Youth.Indian Pediatr. 2023: S097475591600534. Epub ahead of print.
5. Majumdar A, Sanyal D, Sukumar S, Kalra S. Transgender endocrinology. Indian J EndocrinolMetab. 2020;24:126-27.
6. Kalra S, Sharma S, Sanyal D, et al. The pyramid of transgender health therapeutics. Indian JClinPract. 2023;34:30-31.
7. Sharma S, Kumar A, Kalra S. Transgender health issues: children of a lesser god. Indian J ClinPract. 2022;33:8-9.
8. Association for Transgender Health in India. Accessed Aug 24, 2023. Available from: *https://athi.meriinfo.com/ipath.aspx*

PERSPECTIVE

Advancing the Field of Fetal Neurology: A Call for Global Collaborations

SONIKA AGARWAL, CHARU VENKATESAN, TOMO TARUI, DAWN GANO

Division of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Correspondence to: Sonika Agarwal, Division of Neurology and Pediatrics, Children's Hospital of Philadelphia, 3401, Civic Center Blvd, Philadelphia, PA, 19104, USA. agarwals2@chop.edu

Fetal Neurology continues to grow as a distinct subspecialty informed by evolving precision diagnosis with advancements in prenatal neuroimaging, genetic and infectious testing. While there are inherent limitations and challenges in prenatal diagnostic testing and prognostic counseling, the interdisciplinary approach allows comprehensive guidance for perinatal and postnatal management of neurological disorders detected early in development. The current practice of fetal neurology is heterogenous and variable across centers. In low- and middle-income countries (LMICs), fetal neurology practice is under the umbrella of neonatal and perinatal medicine. Since infrastructure and capacity for prenatal diagnostic and prognostic counseling may be variable, the practice approach may have to be modified regionally based on resources, education, and setting. There is a need for collaborative development of educational opportunities, training, guidelines, and research exploring short- and long-term outcome of prenatally identified neurological conditions. Interdisciplinary collaborations and global professional networks are crucial to advance this unique subspecialty.

Keywords: *Collaborative network, Counseling, Fetal MRI, Perinatal neurology.*

The last two decades have seen a remarkable evolution in prenatal testing. With advancements in diagnostic neuroimaging and genetic testing enhancing diagnostic accuracy for prenatally detected central nervous system (CNS) disorders, fetal neurology has emerged as a distinct subspecialty [1-4]. Fetal neurologic consultations benefit from a unique interdisciplinary approach involving pediatric neurologists, maternal fetal medicine specialists, geneticists, neonatologists, pediatric surgeons and at times, perinatal nurse coordinators or social workers, palliative care specialists and other subspecialists, to interpret prenatal testing information, manage maternal medical conditions, and comprehensively provide prognostic counseling to guide pregnancy care and postnatal follow-up of children born with neurological disorders. There are inherent challenges and uncertainties in prenatal counseling for brain abnormalities due to continued development of the brain through pregnancy, limitations of prenatal imaging and genomic testing, as well as heterogeneity of the literature with limited long-term outcome studies [4].

Globally, pediatric neurologists and obstetricians are increasingly providing fetal neurology consultations. In low- and middle- income countries (LMICs), fetal neurology practice is under the umbrella of neonatal and perinatal medicine. Specialists from neonatology, pediatrics, obstetrics, maternal fetal medicine, genetics and neurology may also guide the prognostic counseling discussions. Management of children born with prenatal neurological disorders is supported by multiple pediatric medical and surgical specialties. Fetal care centers are becoming more prevalent around the world to offer comprehensive care for high risk pregnancies, including diagnostic testing, prognostic counseling and management. With rapid advancements in the field, there are challenges with access to testing, care, and standardization of practice. We, herein, focus on key perspectives related to fetal neurology practice and how it integrates with care for prenatally diagnosed neurological disorders globally.

CURRENT LANDSCAPE

The global incidence of congenital anomalies varies from 3-7% of all newborns [5-7]. CNS anomalies, such as neural tube defects, posterior fossa anomalies, disorders of forebrain development, and disorders of cortical migration, are the most common congenital anomalies and the leading cause of morbidity, mortality and fetal loss [5-7]. Many authors have discussed experiences about the process of fetal neurologic consultations that include utilizing fetal neuroimaging with ultrasound (US) and fetal magnetic resonance imaging (MRI), fetal genetic testing (karyotype, chromosomal microarray, gene panels, whole exome or genome sequencing), evaluation for congenital infections, and multidisciplinary collaborative discussions to aid the prognostic counseling [3,8,9]. Globally, US remains the first line for fetal imaging and radiologists and obstetricians undergo specific training to develop expertise in focused imaging to screen and diagnose various systemic anomalies.

A survey study of fetal care centers from the United

States, in 2014, highlighted variability among centers, beyond what could be attributed to the novelty of the field [10]. The study found significant heterogeneity in practice, and that families may have non-uniform experiences, indicating the lack of consensus about best practices in fetal care. The study provided directions for future research to understand the variability among these unique multidisciplinary centers [10]. Almost a decade later, we are still lacking consensus and guidelines in the field. A recent publication specifically looking at the practice of fetal neurology in the United States showed significant variability related to frequency of consultations, gestational age and modality for neuroimaging, genetic testing and counseling, multidisciplinary team approach, trainee education and subspecialty training of the consultants [11]. This fetal neurology practice survey was the first study looking at details of the practice landscape from a single high resource country, and provided guidance to broaden educational opportunities during pediatric neurology and subspecialty training. The study identified gaps in the field such as limited practice guidelines and highlighted the role of multi-center fetal neurologic registries and natural history/outcome studies for better informed prognostic counseling and management of these pregnancies [11]. Given the heterogeneity in fetal neurological care across the United States alone, there is an immense need for interdisciplinary multicentered research and disseminatable practice tools that can enhance patient care in resource-rich and resource-limited countries.

ROLE OF REGION-BASED CASE

Sonography remains the mainstay modality to visualize the brain in utero. Globally, radiologists and obstetricians are especially trained for focused neuroimaging during the perinatal period. Fetal MRI is relatively newer and expertise in interpretation by trained radiologists is paramount. Several studies have shown the superior resolution of fetal brain MRI compared to ultrasound, particularly for evaluating cortical development. In a recent review on challenges in prenatal neurologic diagnosis and counselling [4], the authors discussed a series of cases focused on challenges in interpretation of fetal MRI due to continued development and maturation of the brain in pregnancy, and highlighted the limitations of prenatal testing. In a systematic review (13 articles, *n*=710 fetuses undergoing both US and fetal MRI) looking at the value of fetal MRI following US suspicion of a CNS anomaly [12], the overall concordance rate was 65.4% between US and MRI results, additional information was obtained with fetal MRI in 22.1% and led to a change in clinical management in 30% cases. Major abnormalities in this study (*n*=405) included ventriculomegaly (44.7%) and midline anomalies (33.8%) [12]. In the survey of fetal neurology programs in the United States, the top five diagnoses for fetal neurologic consultations included: agenesis of corpus callosum, ventriculomegaly, cerebellar/posterior fossa malformations, absent septum pellucidum, and abnormalities of cerebral morphology (lissencephaly, schizencephaly, polymicrogyria) [11].

In a 10-year retrospective study from a tertiary medical center in Malaysia (*n*=365), less than 50% of the fetuses with prenatally diagnosed CNS anomalies resulted in live birth, 36% passed away in the first 2 years and about 63% of the survivors had neurodevelopmental disability [13]. Overall, the most common CNS anomalies diagnosed on prenatal US were ventriculomegaly (23.4%) and neural tube defects (20%) [13]. Fetal brain MRI was obtained in only a small proportion in this study (6 out of 365 pregnant women) after a diagnosis of CNS anomaly on the pregnancy US [13], emphasizing the importance of better understanding the acceptability of fetal brain MRI across diverse practice settings and populations.

Another study from a tertiary care center in India that evaluated the role of MRI (*n*=23) in fetal anomalies showed CNS anomalies remained the top diagnoses [14]. Mohan, et al. [14] reported that interpretation of fetal MRI at 20 weeks was challenging due to motion and small size, US remained the primary diagnostic tool at 18-20 weeks of gestation and the majority of the referrals for fetal MRI were later in the second and third trimester of pregnancy. Among CNS anomalies, there were six cases of agenesis of corpus callosum, two cases of ventriculomegaly, two cases of encephalocele, and one case each of Chiari malformation, Dandy-Walker malformation, unilateral cerebellar hypoplasia, vermian hypoplasia, and Blake pouch cyst [14]. Spinal anomalies detected were diastematomyelia, absent sacrum, myelomeningocele, and sacrococcygeal teratoma [14]. A retrospective observational study from a tertiary care center in India assessed the potential of first trimester US in detection of congenital malformations [15]. Out of 4080 pregnant women undergoing US, 312 (7.6%) had structural malformations. Out of 139 women diagnosed with fetal structural anomalies after 20 weeks gestation, 47 (33.8%) could have been diagnosed before 12 weeks and 92 (66.1%) had fetal anomalies that could have been diagnosed between 12-20 weeks. This study highlighted the immense gap in early diagnosis and potential for intervention for congenital malformations [15].

Common diagnoses and underlying etiologies, gestational age at referral, parental choice and options for termination or continuation of pregnancy likely vary across regions. The diagnostic information based on neuroimaging, infectious and genetic testing needs to be individualized based on specific conditions prevalent in that area. Variability in maternal health among regions could contribute to

the differential diagnosis of fetal neurological conditions. The treatment and outcomes for a particular diagnosis for each region or country are also dependent on the supportive care and resource infrastructure, including access to early intervention therapies. Fetal neurology consultations should carefully consider the regional outcomes for a particular disorder, along with parental/family perspectives through interdisciplinary discussion. However, not every patient or center will have access to a multidisciplinary team of specialists including maternal fetal medicine, pediatric neurology, fetal surgeons, genetics, genetic counselor, nurse coordinator, and other subspecialists. At times, such consultations are being done by a single specialist with limited access to comprehensive diagnostic testing. The prognostic counseling and management may have to be based in the realm of such limitations, such as use of US only where access to fetal MRI is limited.

NATURAL HISTORY REGISTRIES AND OUTCOME STUDIES

Neuroimaging by US or fetal MRI provides discrete temporally defined snapshots that are integrated with other testing to approach the diagnostic and prognostic counselling with prospective parents. Brain maturation and development continue through the pregnancy and there is a range of neurodevelopmental outcomes reported for various prenatally diagnosed neurologic conditions, limiting our ability to predict the exact outcome for a particular fetus. Also, medical or obstetric complications and placental abnormalities may further impact growth, worsen brain injury and development, and modify the final neurodevelopmental trajectory.

While there are no national registries focused on fetal neurological disorders in the United States, the EUROCAT study is a multi-national multi-center network of registries with regional population-based census data. The 29 population-based EUROCAT registries surveyed 1.7 million births per annum (29% of all European births) and reported a prevalence of congenital cerebral anomalies of 9.8 (95% CI 8.5-11.2) per 10,000 births. The reported 4927 cases were subcategorized to holoprosencephaly, arhinencephaly, septo-optic dysplasia, megalencephaly, other reduction deformities of brain, congenital malformation of corpus callosum, other specified congenital malformations of brain, congenital cerebral cysts, and congenital malformation of brain unspecified. The study provided a robust overview of fetal neurological conditions in the European population. However, considering the heterogeneity of the conditions and variable clinical prognosis, further diagnostic and natural history data from diverse geographies would be of value to improve fetal neurological care [16]. Parallel studies done in different countries and regions could identify the etiopathogenesis of common early origin neurological disorders for that particular geography and facilitate more individualized counselling and management for such pregnancies. Moreover, such studies may reveal important insights about environmental, infectious and genetic contributions to early origin neurological disorders that vary globally.

Outcome studies analyze developmental tests and scales to predict neurodevelopmental outcome; however, this may not always translate into functional, vocational and societal success. There are limited data on actual functional outcomes, integration into the educational or functional setting and societal and community inclusion. A recent phenomenological study from Australia looked at adults with disorders of the corpus callosum and identified systemic and knowledge gaps in their society through first-hand experiences and perspectives [17]. Participants of this study felt excluded from key life domains, struggled with identity as adults, and described barriers to educational and employment opportunities and integration into society. This study gives direction to researchers for a spectrum of fetal neurological disorders where understanding and knowledge through lived experiences and participatory research could provide a powerful tool to inform best practice guidelines. Scientists should consider lived experiences of adults with such diagnoses that could guide support through educational and vocational years for more effective integration into the community and foster program building.

PARENTAL PSYCHOSOCIAL STRESSORS

Fetal neurology consultations for prospective parents facing a neurological anomaly in the developing fetus are associated with profound stress and a range of emotions [9, 18,19]. Perinatal mental health issues and traumatic stress among expectant parents have been studied. Psychosocial teams to facilitate mental health screening and interventions for parental support and coping through the challenging course of pregnancy are recommended [18,19]. As clinicians in a multidisciplinary setting discuss diagnostic and prognostic information and lay out the best- and worst-case scenarios for any infant, there is uncertainty in prediction of neurodevelopmental outcomes due to continued development of the fetal brain, inherent limitations of neuroimaging and laboratory testing, and lack of predictability of progression or associated complications in the pregnancy [4]. About half the parents with children admitted to the neonatal intensive care experience clinically significant anxiety, trauma and depression, which may negatively influence parent-child bonding and neurodevelopment [20]. Perceptions of prenatally diagnosed neurological disorders and postnatal management may also vary among regions based on medical and social resources and cultural perceptions to such disorders. Development of easily

disseminatable tools and identifying inter-regional variations in parental psychosocial stressors are important to guide development of support programs for parents. Assessing measurement invariance of the ten-item Perceived Stress Scale (PSS-10) across eight low- and middle-income countries and across birth parity indicated the utility in assessing maternal stress across a broad range of culturally diverse settings, yet recommended taking caution when comparing mean stress levels across regions [21]. Globally, regardless of the region, parental mental health and psychosocial support for families of infants with neurological disorders are crucial to enhance parental partnership with medical teams for successful postnatal rehabilitation and care, which impacts outcome trajectory across the lifespan.

COLLABORATION AND CAPACITY-BUILDING

Fetal neurology has a unique interface with multiple disciplines, and care provided in this period impacts the burden of neurological disease throughout the lifecycle. In the post-pandemic era, the role of virtual networks for medical education has evolved. Multidisciplinary team meetings, perinatal clinical and educational rounds and audits are increasingly being used to enhance practice, training and outcomes. Enhancing collaborations across institutions engaging in fetal neurology practice through virtual education series could be a way to develop expertise and capacity-building globally. The establishment of a global professional network is imperative to enhance partnerships for curriculum development for current trainees and practicing health care professionals, as well as for standardization of imaging techniques and protocols, and development of guidelines in the field. In parallel, collaborative global research in fetal neurology is needed to determine the etiologies and outcomes of various CNS anomalies and disorders in the prenatal period to tailor the prognostic discussion and management based on the region where care is being offered.

CONCLUSIONS

According to World Health Organization (WHO) worldwide data, 2,40,000 neonates and 1,70,000 children between ages 1 month and 5 years die annually due to congenital disorders [22]. Nine of ten children born with a serious congenital disorder are in LMICs, and the associated long-term disability takes a significant toll on individuals, families and societal health and health care systems [22]. As neonatal and under-5 mortality rates decline, congenital disorders are responsible for a larger proportion of morbidity and mortality in this age group. Sustainable development goals from the United Nations and the World Health Organization highlight the need to prioritize women and children given the burden of morbidity and mortality during pregnancy and the peripartum period [8,22-24]. WHO Member States collaborated to develop a response for the resolution on birth defects at the Sixty-third World Health Assembly (2010), with a focus on developing and strengthening surveillance systems; developing expertise and building capacity for the prevention of congenital disorders and care of children affected; raising awareness on the importance of newborn screening programs and their role in identifying infants born with congenital disorders; supporting families who have children with congenital disorders and associated disabilities; and strengthening research on major birth defects and promoting international cooperation in combatting them [22]. Fetal-neonatal neurology aligns with the goals of such initiatives. For child neurologists and other related subspecialties focusing on fetal-neonatal neurology practice and program development, it is imperative to take note of the global momentum and apply these concepts given the linkage between maternal health and brain health in the fetal and neonatal periods, as well as the long-term impact on pediatric health [8]. As fetal neurology advances, global collaborations can facilitate the development of practice and guidelines, education and training in the field and also large-scale natural history studies in this new and evolving subspecialty.

Box I Important Considerations in Fetal Neurology Practice

- Interdisciplinary team approach with individualized practice based on resources/infrastructure.
- Training for neuroimaging techniques and diagnostic fetal radiology is important.
- Collaborations for multicenter natural history and outcomes studies can pave the way for more informed prognostic counseling.
- Patient and family perspectives and lived experiences of adults with congenital neurological disorders to be incorporated in research studies.
- Parental mental health screening and psychosocial support is important.
- Role of a global interprofessional network for advancing clinical practice, education and research in fetal neurology is imperative.

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

REFERENCES

1. Arroyo MS, Hopkin RJ, Nagaraj UD, et al. Fetal brain MRI findings and neonatal outcome of common diagnosis at a tertiary care center. J Perinatol. 2019;39:1072-7.
2. Gumayan RLF, Klamer B, Ream M. Institutional evaluation of fetal neurology consults and postnatal outcomes: a 10-year retrospective cohort review. Neurol Clin Pract. 2023;13: e200100.
3. Griffiths PD, Bradburn M, Campbell MJ, et al., MERIDIAN Collaborative Group. Use of MRI in the diagnosis of fetal

brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. Lancet. 2017;389:538-46.
4. Agarwal S, Tarui T, Patel V, Turner A, Nagaraj U, Venkatesan C. Prenatal neurological diagnosis: challenges in neuro-imaging, prognostic counseling, and prediction of neurodevelopmental outcomes. Pediatr Neurol. 2023;142:60-7.
5. Mashuda F, Zuechner A, Chalya PL, Kidenya BR, Manyama M. Pattern and factors associated with congenital anomalies among young infants admitted at Bugando medical centre, Mwanza, Tanzania. BMC Res Notes. 2014;7:195.
6. Saiyad SS, Jadav HR. Study of congenital malformations in central nervous system and gastrointestinal tract. Natl J Med Res. 2012;2:121-3.
7. Jehangir W, Ali F, Jahangir T, Masood MS. Prevalence of gross congenital malformations at birth in the neonates in a tertiary care hospital. Annals of Punjab Medical College 2009; 3:47-50.
8. Agarwal S, Scher MS. Fetal-neonatal neurology program development: Continuum of care during the first 1000 days. J Perinatol. 2022;42:165-68.
9. Hart AR, Vollmer B, Howe D, et al. Antenatal counselling for prospective parents whose fetus has a neurological anomaly: part 1, experiences and recommendations for service design. Dev Med Child Neurol. 2022;64:14-22.
10. Kett JC, Woodrum DE, Diekema DS. A survey of fetal care centers in the United States. J Neonatal Perinatal Med. 2014;7: 131-5.
11. Tarui T, Venkatesan C, Gano D, et al., Fetal neurology practice survey: current practice and the future directions. Pediatr Neurol. 2023;145:74-9.
12. Rossi AC, Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. Ultrasound Obstet Gynecol. 2014;44:388e-93e.
13. Tan AG, Sethi N, Sulaiman S. Evaluation of prenatal central nervous system anomalies: obstetric management, fetal outcomes and chromosome abnormalities. BMC Pregnancy Child-birth. 2022;22:210.
14. Mohan A, Rangasami R, Chandrasekharan A, Suresh I, Suresh S, Andrew C. Role of MRI in the diagnosis of fetal anomalies at 18-20 weeks gestational age. Journal of South Asian Federation of Obstetrics and Gynecology. 2019;11: 292-6.
15. Kashyap N, Pradhan M, Singh N, Yadab S. Early detection of fetal malformation, a long distance yet to cover! Present status and potential of first trimester ultrasonography in detection of fetal congenital malformation in a developing country: experience at a tertiary care center in India, J Pregnancy. 2015; 2015:623059.
16. European Commission. Prevalence charts and tables. [Internet] June, 2023. Accessed August 15, 2023. Available from: *https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en*
17. Maxfield, M, Cooper MS, Kavanagh A, Devine A, Gill Atkinson L. On the outside looking in: a phenomenological study of the lived experience of Australian adults with a disorder of the corpus callosum. Orphanet J Rare Dis. 2021;16:512.
18. Dempsey AG, Chavis L, Willis T, Zuk J, Cole JCM. Addressing perinatal mental health risk within a fetal care center. J Clin Psychol Med Settings. 2021;28:125-36.
19. Rent S, Lemmon ME, Ellestad S, Bidegain M. The role of perinatal palliative care in fetal neurology. Am J Perinatol. 2021;10.1055/a-1682-2798. Epub ahead of print.
20. Grunberg VA, Geller PA, Hoffman C, Njoroge W, Ahmed A, Patterson CA. Parental mental health screening in the NICU: a psychosocial team initiative. J Perinatol. 2022;42:401-9.
21. Katus, L, Foley S, Murray AL, et al. Perceived stress during the prenatal period: assessing measurement invariance of the Perceived Stress Scale (PSS-10) across cultures and birth parity. Arch Womens Ment Health. 2022;25:633-40.
22. World Health Organization. Congenital disorders. [Internet] June, 2023. Accessed August 15, 2023. Available from: *https://www.who.int/news-room/fact-sheets/detail/birth-defects*
23. World Health Organization (WHO). Reaching the every newborn national 2020 milestones: country progress, plans, and moving forward. WHO; 2017.
24. Moller AB, Patten JH, Hanson C, et al. Monitoring maternal and newborn health outcomes globally: a brief history of key events and initiatives. Tropical Med Int Health. 2019;24: 1342-68.

PERSPECTIVE

Pediatric Trauma Training in India- Need of the Hour

NEHA THAKUR ,[1] PRASHANT MAHAJAN,[2] SAMIR MISRA,[3] JABEEN FAYYAZ[4]

[1]*Department of Paediatrics, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow 226010, Uttar Pradesh, India.*

[2]*Chief, Section of Pediatric Emergency Medicine, CS Mott Children's Hospital University of Michigan Ann Arbor, Michigan, United States of America.*

[3]*Department of Trauma Surgery, King George Medical University, Lucknow, Uttar Pradesh, India.*

[4]*University of Toronto PEM Staff Physician, The Hospital for Sick Children, Toronto, Canada.*

Correspondence to: Dr Neha Thakur, Associate Professor, Department of Paediatrics, Dr Ram Manohar Lohia Institute of Medical Sciences Lucknow 226010, Uttar Pradesh. nehaimsbhu@gmail.com

Pediatric trauma is preventable yet every year the number of road accident victims continues to rise. India is facing another epidemic in the form of pediatric trauma. Children less than 14 years account for 11% of accident-related deaths in India. Road traffic injury have multipronged effects on child's mental and physical development. Injury during developing phase can have both long-term and short-term consequences. Currently, India has only 5 Level 1 trauma centers where trauma care providers have mostly undergone training in Adult Trauma Life Support. It is well established that the outcome of pediatric trauma victims is largely dependent on the management received in the golden hour. Yet no standardized pediatric trauma training programme exists in India, and there is a need to address this gap.

Keywords: *Emergency medicine, Golden hour, Injury, Road traffic accident*.

Published online: May 19, 2023; **PII:** S097475591600545

Trauma is the leading cause of mortality and morbidity in children worldwide [1]. More than 31 kids lose their life in road accidents per day [2]. Under-19 children are most susceptible to fatal and non-fatal injuries occurring due to road accidents, thus posing a big responsibility for society, lawmakers and non-government organizations (NGOs) alike. Worldwide, nearly, 220,000 children and adolescents lose their life due to road traffic injuries. As per World Health Organization, Global status report on road safety, 2018 [2]. India ranks first world-wide in road traffic accidents (RTA) deaths in children aged 0-14 years, accounting for 11% of the accident-related deaths and 17.6% of the world's disability adjusted life years (DALYs).

RTA have multipronged effect on children. Other than loss of life it can lead to long term morbidities and persistent effects of injury. There are multiple determining factors for deciding the outcome of pediatric trauma. The most important ones being mechanism of injury, use of protective gear by children, type of injuries sustained, age of the child, time to initiate resuscitation, quality of care provided, and the competence of the care provider [2]. Government agencies and various NGOs have been making efforts to educate the public on road safety measures. The National Road Safety Policy was released in March, 2010 [3]. The policy emphasized on the need of having a national database on trauma, better road infrastructure, safer vehicles and driver, road safety education and training, and enforcement of laws [3]. However, the deaths rate continues to rise, particularly in children. A recent study compared the independent prognosticators of pediatric trauma mortality between India and the United States [4]. In this study, data was collected from the apex trauma centers from various regions of India for a period of three years. Data was entered in Towards Improved Trauma Care Outcomes (TITCO) data base and compared with National Trauma Data Bank (NTDB) in USA. The researchers found that risk adjusted odds of pediatric trauma related mortality is 22 times higher in India as compared to US. The odds of mortality were highest in children with lower injury scores and physiologic severity. The researchers suggested that prevention, trauma training, development of protocols and early imaging would improve the outcome of pediatric trauma victims in India [4].

Pattern of Pediatric Trauma in India

Head injury has emerged as the most common mechanism of injury from studies on pediatric trauma in both rural and urban India [5,6]. In children, besides accidental trauma, a proportion of emergency department (ED) visits may be due to non-accidental trauma or child abuse [6,7]. Studies from northern India show accidental injury as the most common cause of pediatric trauma [5,8,9] as compared to those from southern India showing non-accidental trauma due to domestic violence as a major cause [6,10]. Published

literature shows that the outcome of children with non-accidental trauma is worse as compared to accidental trauma [7].

Trauma Training Program

Until now, no standardized pediatric trauma training program exist in India. Advanced Trauma Life Support (ATLS) training is an internationally recognized standardized training of adult trauma. It was started in 1978 and has covered all the continents of the world, being called as a global resuscitation program for trauma management [11]. In April, 2022, a multicentre cluster randomized trial was started for comparing the effect of trauma life support training programs on patient and provider outcomes under the aegis of Trauma life support training Effectiveness Research Network (TERN) [12]. The focus of TERN is now to look at pediatric trauma training and outcomes. Internationally there are few countries who have developed their own trauma training programs like Canada developed TRIK (Trauma Resuscitation in Kids) course [13]. The TRIK course is a two-day simulation-based training particularly tailored for health care providers who manage pediatric trauma patients, emphasizing on the roles of team leader and team members. USA developed a multidisciplinary pediatric trauma training using high-fidelity trauma stimulation [14]. They found better patient outcomes with reduced human errors. Few centers started online pediatric trauma training programs e.g., the Acute Assessment and Management of Pediatric Trauma by Harborview Medical Centre, which is a 7-module course designed for care providers of pediatric trauma [15]. Unlike ATLS, the courses mentioned above were not standardized and did not receive global recognition. None of the low- or middle-income countries have developed any trauma training programs.

Even in India, there is no standardized trauma training program. Though ATLS training does provides the basics of understanding trauma resuscitation, children are not little adults hence when managing pediatric victims, we need to understand their physiology and anatomy while designing trauma resuscitation programs for them. It is important to adapt standardized trauma evaluation approaches such as ATLS to children. In addition, the approach should also adapt to the local community needs, for example if falls are more common in India, then the trauma system training should be geared towards recognition of all trauma but have a particular vigilance/training towards falls and their anticipated injuries and evaluation of the same. Currently, India has ATLS protocol in place for adult trauma but not for pediatric trauma. Nationwide ATLS training is conducted in all major trauma centers. However, no module for pediatric trauma management has been developed in India.

Pediatric and Neonatal Resuscitation Programs available in India

Standardized formal resuscitation training programs are in place for improving survival of newborn infants and children (**Table I**) [16-20]. These training programs are based on knowledge and skill. The neonatal resuscitation programs focus on neonatal resuscitation [16]. Navjaat Shishu Suraksha Karyakaram (NSSK) essential care and resuscitation training programs under India Newborn Action Plan [17] and New-born Stabilization Unit Training Program under the Ministry of Health and Family Welfare [18] are designed to reduce neonatal mortality in India. Indian Academy of Pediatrics (IAP) also provides Basic Life Support (BLS) and advanced life support courses (ALS) [19]. American Heart Association has also authorized certain centers in India to conduct BLS, Advanced Cardiac Life Support (ACLS) and Pediatric Advanced Life Support (PALS) courses [20]. Apart from these standardized courses, numerous other training programs are carried out at regional levels. These training programs cannot replace formal trauma training programs. We need separate courses tailored for managing pediatric trauma as seen in other developed nations.

Table I Standardised Training Programmes in Paediatrics and Neonatology in India

Name	*Age group*	*Organization*
Neonatal Resuscitation Programmes (NRP)	Newborns	IAP-NNF-NRP-FGM) [16]
Basic Newborn Care and Resuscitation Programme (BNCRP)	Newborns	IAP-NNF-NRP-FGM) [16]
Newborn Stabilization Unit Training Programme	Newborns	Ministry of Health and Family Welfare [18]
Navjaat Shishu Suraksha Karyakaram (NSSK) essential care and resuscitation training programmes	Newborns	Government of India. India Newborn Action Plan [17]
Basic Life Support (BLS)	Pediatric	IAP [19]
Pediatric Advanced Life Support Courses (PALS)	Pediatric	IAP and AHA [20]

IAP: Indian Academy of Pediatrics; NNF: National Neonatology Forum; FGM: First Golden Minute Project; AHA: American Heart Association.

Need of Pediatric Trauma Training

The need of pediatric trauma resuscitation training has been studied in multiple countries. Whitehead, et al. [21] concluded that residents working in the pediatric ED perform signi-ficantly better with hands-on opportunities. In addition to hands-on training course, designers incorporated online videos in online education modules in order to investigate its impact on resident confidence and comfort with pediatric trauma resuscitation. Similarly, in USA, Burke, et al. [22] conducted a qualitative assessment of simulation-based training for pediatric trauma resuscitation. They proposed the need of development of future simulation-based training programs to improve teamwork, confidence, and communication between trauma team members [22]. In Saudi Arabia, a boot camp intensive simulation-based training was conducted to study the improvement of the basic knowledge, confidence, and performance in the management of pediatric trauma cases by the ED residents who had undergone training. The results of the study were promising [23].

In order to study the need of a separate training for pediatric trauma victims, we conducted a nationwide survey on the need of separate pediatric trauma training. A structured pretested questionnaire was circulated among the trauma care providers across India in the last quarter of 2022. Participants were asked on the trauma training programs they had undergone, the need of separate pediatric trauma training, their confidence on management of pediatric trauma victims, and whether ATLS training has made a difference in managing pediatric trauma victims. Out of the 800 participants approached, 642 (80%) participated in the study; 93.5% of these were doctors, and rest were nurses and paramedical staff. Study participants were working in Level 1 and 2 trauma centers across India. The need for a separate pediatric trauma training course was felt by 86% participants. Results of this unpublished national survey emphasized the need that India should have its own pediatric trauma training program. This program should promote the use of evidence-based practice in the early identification of life-threatening events and timely management of pediatric trauma patients, improve outcomes for patients, healthcare providers, and health care organizations. This program would be catering to the demographic patterns of injury and should have a standardized approach like the ATLS. It is high time that India develops its own pediatric trauma and resuscitation program. We are in the process of a developing pediatric trauma resuscitation educational intervention module funded by the Indian Council of Medical Research. It would focus on developing clinical skills appropriate for managing pediatric trauma patients.

CONCLUSION

Development of a pediatric trauma training program in India would promote the use of evidence-based practice in early identification of life-threatening events and timely management of pediatric trauma patients. It will improve outcomes for patients, health care providers, and health care organizations. Additionally, the development of a protocol for national pediatric trauma data registry is also needed. This trauma registry would enable to get a complete picture of demography, pattern of injury and outcome of pediatric road injury victims in India.

Contributors: NT, PM, SM and JF: conceptualized and designed the study, drafted the initial manuscript, 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.
Funding; ICMR (5/4-5/3/14/Trauma/2022/NCD-1);
Competing interests: None stated.

REFERENCES

1. WHO fact sheets 2022 -Road Traffic injuries. Accessed January 25, 2023. Available from: *https://www.who.int/news-room/fact-sheets/detail/road-traffic-injuries*
2. World Health Organization. Global status report on road safety 2018: Accessed January 25, 2023. Available from: *WHO/NMH/NVI/18.20). World Health Organization. 2018*
3. National Road safety Policy. Government of India. Accessed January 25, 2023. Available from: *https://morth.nic.in/national-road-safety-policy-1*
4. Amato S, Culbreath K, Dunne E, et al. Pediatric trauma mortality in India and the United States: A comparison and risk-adjusted analysis. J Pediatr Surg. 2023;58:99-105.
5. Rattan A, Joshi MK, Mishra B, et al. Profile of injuries in children: report from a level i trauma center. Indian Pediatr. 2021;58:553-5.
6. Prabhakar AKP, Vincent D, George AS, et al. Pattern and outcome of unintentional pediatric trauma in the emergency department of a tertiary care hospital in South India. J Med Sci 2018;38:269-74.
7. Estroff JM, Foglia RP, Fuchs JR. A comparison of accidental and nonaccidental trauma: it is worse than you think. J Emerg Med. 2015;48:274-9.
8. Thakur NR, Jaiswal V, Singh A, et al. Epidemiology and pattern of injury of pediatric trauma patients in level l trauma centre of Northern India. Trauma. 2023 Aug (online).
9. Kundal VK, Debnath PR, Sen A. Epidemiology of pediatric trauma and its pattern in urban India: A tertiary care hospital-based experience. J Indian Assoc Pediatr Surg. 2017;22:33-7.
10. Prakash Raju KNJ, Jagdish S, Kumar GK, et al. Profile of pediatric trauma among the patients attending emergency department in a tertiary care hospital in South India. J Emerg Trauma Shock. 2020;13:62-67.
11. Carmont MR. The advanced trauma life support course: A history of its development and review of related literature. Postgraduate Medical Journal. 2005;81:87-91.
12. Gerdin Wärnberg M, Berg J, Bhandarkar P, et.al. Trauma life support training Effectiveness Research Network (TERN) collaborators. A pilot multicentre cluster randomised trial to compare the effect of trauma life support training programmes on patient and provider outcomes. BMJ Open. 2022;12:e057504.

13. TRIK Course. Accessed 11 Dec 2021. Accessed from: *https://www.royalcollege.ca/rcsite/ppi/courses/trauma-resuscitation-in-kids-trik-e*
14. Falcone J, Daugherty M, Schweer L, et al. Multidisciplinary pediatric trauma team training using high-fidelity trauma simulation. J Pediatr Surg. 2008;43:1065-71.
15. Harborview Medical Center. Acute Assessment and Management of Pediatric Trauma. Accessed Dec 11, 2021. Accessed from: *https://depts.washington.edu/pedtraum/*
16. Indian Academy of Paediatrics National Neonatology Forum First Golden Minute Project. Accessed May 1, 2023. Available from: *http://www.iapnrpfgm.org/cms/*
17. Ministry of Health and Family Welfare, Government of India. Navjat Shishu Suraksha Karyakram 2022 [online]. Accessed May, 2023. Available from: *https://nhm.gov.in/index1.php?lang=1&level=1&sublinkid =1427 &lid=781*
18. Ministry of Health and Family Welfare, Government of India. Newborn Stabilisation Unit Training Accessed May 1, 2023. Available from: *https://nhm.gov.in/images/pdf/ programmes/child-health/guidelines/NBSU/NBSU.pdf*
19. Indian Academy of Paediatrics (IAP ALS and BLS courses) Accessed May 1, 2023. Available from: *http://www.iapalsbls.com*
20. Indian Academy of Paediatrics BLS,ACLS, PALS training centres in India Accessed May 1, 2023. Available from: *https://www.emergencymedicine.in/current/articles.php?article_id=16*
21. Whitehead A, Phillips B, Haut L. Assessment of need for trauma education for pediatric residents in the emergency department, and creation of a video module in response. Accessed March 2023. Available from: https*://hdl.handle.net/1805/24812*
22. Burke RV, Demeter NE, Goodhue CJ, et al. Qualitative assessment of simulation-based training for pediatric trauma resuscitation. Surgery. 2017;161:1357-66.
23. Khobrani A, Patel NH, George RL, et al. Pediatric trauma boot camp: A simulation curriculum and pilot study. Emerg Med Int. 2018;2018:7982315.

RESEARCH PAPER

Customization of WHO Under-five Growth Standards for an Appropriate Quantification of Public Health Burden of Growth Faltering in India

SANTU GHOSH,[1] RAJESH MAJUMDER,[2] HARSHPAL SINGH SACHDEV,[3] ANURA V KURPAD,[4] TINKU THOMAS[1]
[1]*Department of Biostatistics, St John's Medical College, Bengaluru, Karnataka.*
[2]*Division of Epidemiology, Biostatistics and Population Health, St John's Research Institute, Bengaluru, Karnataka.*
[3]*Department of Pediatrics, Sitaram Bhartia Institute of Science and Research, New Delhi.*
[4]*Department of Physiology, St John's Medical College, Bengaluru, Karnataka.*
Correspondence to: Dr Tinku Thomas, Department of Biostatistics, St John's Medical College, Bengaluru 560 034, Karnataka.
tinku.sarah@sjri.res.in
Received: Feb 4, 2023; Initial review: Mar 22, 2023; Accepted: May 27, 2023.

Objective: To examine the accuracy of World Health Organization (WHO) growth standard in under-5 year Indian children, and identify a method to contextualize the WHO standard for India.

Participants: Data of Healthy children, defined by WHO selection criteria, extracted from nationally representative Indian surveys (National Family Health Surveys, NFHS-3, NFHS-4, NFHS-5 and Comprehensive National Nutrition Survey, CNNS).

Design: Height for age *z* score (HAZ) and weight for age *z* score (WAZ) and weight for height *z* score (WHZ) distributions in healthy sample were compared against the standard normal. If deviant, age-specific correction factors for *z* scores were estimated by hierarchical linear mixed effects mean and variance polynomial models. A new term, excess mean risk of growth faltering (EMRGF), was introduced to describe growth faltering.

Main outcome: Measure of deviation of HAZ, WAZ and WHZ from standard normal distribution. Correction of WHO growth standards for India leading to accurate prevalence of stunting, underweight and wasting in Indian children using NFHS-5 data.

Results: Data on 10,384 healthy under-5 year children were extracted, of which 5377 were boys. Across surveys and metrics, the mean *z* scores were significantly lower than zero (-0.52 to -0.79). HAZ and WHZ variability (1.16, 1.07) were significantly higher than 1. Derived age-specific corrections reduced the NFHS-5 prevalence of growth faltering by 50%. The national EMRGF (after applying the age-specific correction) for height for age was 15.5% (95%CI:15.3-15.8), and weight for age was 15.0% (95%CI:14.8-15.3), respectively, in NFHS-5.

Conclusion: The WHO growth standards need contextual customization for accurate estimation of the burden of growth faltering in under-5 year children in India. When corrected, the burden of growth faltering is lower, by half or more, in all the three indices.

Keywords: *Evaluation, Height for age, Weight for age, Weight for height*.

Published online: June 21, 2023; **PII**: S097475591600556

There is a high national prevalence of undernutrition among Indian under-5 year children, as reported in the latest National Family Health Survey (NFHS-5, 2019-21) [1] with 35.5% of children being stunted, 32.1% underweight and 19.3% wasted. Another national survey of Indian children, the Comprehensive National Nutrition Survey (CNNS, 2016-18) [2], reported similar findings. This is a negligible decline from 38.4% stunting, 35.7% underweight and 21% wasting reported in NFHS-4 (2014-15) [3], and the older NFHS-3 survey (2004-05) [4]. This raises questions about the impact of national feeding programs for young children [5], but one reason could be the contextual accuracy of growth standards.

WHO growth standards [6] are used to diagnose undernutrition globally in under-5 year children. These standards are based on community study populations in six countries (Brazil, Ghana, India, Oman, Norway and USA), with growth-favourable socioeconomic conditions, along with all healthy practices of child nurture [6]. The 2.5th percentile of the distribution of height or weight for age *z* score (HAZ, WAZ) and weight for height (WHZ) in these healthy children, or -2 *z* score, was taken as the cut-off to diagnose either stunting, underweight or wasting for any child population globally.

The accuracy of this universal WHO growth standard has been questioned, since employing similar selection criteria, High Income Countries (HICs) generally have higher while the Low and Middle Income Countries (LMICs) have lower references derived from local populations [7]. Further, some populations have a higher than anticipated variability of HAZ and WAZ at a given age, which could result from measurement errors and inflate the growth faltering prevalence. A comparison of the dispersion of HAZ or WAZ in carefully selected (using criteria similar

to World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) healthy children in the local population surveys (NFHS) with that in the original WHO survey sample showed an excess dispersion (by 39%) for HAZ [8]. Deviations in the HAZ and WAZ distributions could lead to a deviation in the WHZ distribution as well.

Growth failure prevalence estimates are an essential component of Sustainable Development Goals that are used to rank nations and nudge governments to undertake actions to improve child growth. We aimed to create a robust India-specific correction for the WHO *z* score for height and weight to obtain accurate estimates of growth faltering, based on an evaluation of their distributions in healthy children in Indian national surveys. Further, a probability-based approach to define growth faltering as an alternative to the *z* score cut-off-based approach was explored.

METHODS

We utilized multiple national survey data sets, from each of which subsets of 'healthy' children were extracted, similar to those used in the WHO-MGRS survey [6].

The CNNS (2016-18) was the first national nutrition survey of Indian children and adolescents [2]. Briefly, this survey collected data from preschool children (aged 0-4 years), school-age children (aged 5-9 years), and adolescents (aged 10-19 years) in all the 30 geographical states of India, using a multistage, stratified, probability proportional to size (PPS) survey design that covered rural and urban households. Anthropometric data of 31,058 under-5 children were accessed.

The NFHS surveys were large-scale, multi-round surveys conducted in a representative sample of households throughout India, using multistage random sampling with probability proportional to size, with an almost uniform sampling scheme [1,3,4]. Data on under-5 children from three surveys, NFHS-5 (2019-21), NFHS-4 (2015-16) and NFHS-3 (2005-06) were accessed for this study [1,3,4]. The NFHS-5 surveyed 2,32,920 children, while the NFHS-4 surveyed 2,59,627 children and the NFHS-3 surveyed 1,24,385 children, for anthropometric measurements along with sociodemographic information.

Healthy children (analytical sample): The 'healthy child' selection criteria that were used for the Indian sample of the WHO-MGRS study 2006 [6] have been listed earlier [8]. We applied these 'healthy child' selection criteria: *i*) Residence in an urban locality; *ii*) Highest two quintiles of wealth index; *iii*) Graduate and above maternal education status; *iv*) Non-smoking mother; *v*) Exclusively breastfed for the first 4 months; *vi*) Partial breastfeeding continued for 12 months; and *vii*) No infection, including any fever and diarrhea, in the two weeks prior to the survey, to all four surveys (NFHS 3-5 and CNNS), to select a healthy 'analytical sample' for this study. A total of 13,204 children were identified, of which 1,821, 4,531 and 4,918 were from NFHS-3, 4 and 5, respectively, while 1,934 were identified from the CNNS (**Web Fig. 1**). Nearly 85% of the sampled healthy children belonged to the uppermost wealth quintile and 70% to uppermost wealth decile. The means and spread of *z* scores derived from the WHO-MGRS standards [6], were compared across surveys. To avoid excess variability due to unobserved factors, children outside the lower and upper 5% of the *z* scores were removed for subsequent analyses.

Derivation of corrected z score *for Indian children*: First, the mean HAZ, WAZ and WHZ were compared between the different surveys (NFHS-3, NFHS-4, NFHS-5 and CNNS) by a one-way ANOVA and the Tukey-HSD post hoc test. Between-survey variation was estimated by a linear random effects model, and by Intra Class Correlation (ICC). The estimated mean *z* scores with 95% CI were also compared against a zero value. Since consistently lower *z* scores were observed across surveys within the analytical sample, a correction method was introduced, exploring age-dependency of the correction factors. We estimated correction factors for each month of age, to ensure that *z* scores would always be unit normal in a healthy population. Then, the modified *z* scores for a child would be

$$Z_{India} = \frac{Z_{WHO} - \hat{\mu}\,(t)}{\hat{\sigma}\,(t)}$$

Where, Z_{WHO} is the *z* score of an Indian child computed using the WHO standard, and Z_{India} is the corrected *z* score for that Indian child. $\hat{\mu}\,(t)$ & $\hat{\sigma}\,(t)$ were estimated from the fixed effects components of hierarchical linear mixed effects mean and variance polynomial model on age, that removed between-survey variability from both mean and variance of *z* score of the healthy sample data extracted from the NFHS and CNNS surveys [9]. The order of polynomial was selected based on *P* value<0.05 and the least Akaike Information Criteria (AIC). The equations for $\hat{\mu}\,(t)$ & $\hat{\sigma}\,(t)$ was as follows,

$$\mu\,(t) = \Psi_p\,(t) \;\&\; \log\,\{\hat{\sigma}^2(t)\} = \Psi_p\,(t)$$

where, $\Psi_p\,(t) = \Sigma_{i=0}^{p}\ \hat{\beta}_i\, t^i \;\&\; \Psi_q\,(t) = \Sigma_{i=0}^{p}\ \hat{\gamma}_i\, t^i$ (p^{th} and q^{th} order polynomial, respectively which would be specifically identified for HAZ, WAZ and WHZ); $\hat{\beta}_i$ & $\hat{\gamma}_i$ are the estimated fixed effects regression coefficients for mean and dispersion model, respectively.

Risk of growth faltering: While stunting, underweight and wasting are diagnosed by a cut-off *Z*-score of <-2 for the HAZ, WAZ and WHZ, all children within the neighborhood of this cut-off are of concern. Second, when the prevalence of stunting, underweight and wasting are based on cut-offs, they

are sensitive to the *z* score dispersion [10], which can be inflated by measurement error.

To overcome these problems, we propose a new measure of undernutrition called 'Risk of Growth Faltering' (RGF). This is defined as follows.

$$RGF\,(\mathrm{x}) = \mathrm{Prob}\,(Z > z\,(\mathrm{x})) = 1 - \Phi\,(z\,(\mathrm{x}))$$

where Φ(.) is the cumulative distribution of a standard normal distribution and x is any anthropometric measurement of a child with a given age or given height in the case of WHZ, $z(\mathrm{x})$ is the *z* scores for x and *Z* is a standard normal variate. When the measured value of anthropometry in a population overlaps that of the healthy standard population of children, the RGF would be 0.5 (risk of 50%) (**Web Fig. 2A)**. Excess growth faltering should only be considered when the risk is greater than 50%.

A population measure that can be considered as the equivalent of 'prevalence' of stunting, underweight or wasting, is the excess mean risk of growth faltering (EMRGF), which is defined as

$$EMRGF\,(\%) = \left[\frac{1}{n}\sum_{i=0}^{p} RGF\,(x_i) - 0.5\right] \times 100$$

where x_i the measure of any growth dimension for the i^{th} child. As it is a function of the mean, the EMRGF is less sensitive to overdispersion in the measurement. A value of EMRGF of zero (0) can be interpreted as no excess population risk, >0 can be interpreted as a population with growth faltering, and <0 can be interpreted as population with better than average growth. The values EMRGF must be between -50 to +50 and EMGRF value approaching 50 indicates severe growth faltering. The estimation of EMGRF in a simulated data from a growth-faltered population is demonstrated in **Web Fig. 2B.**

The estimates of stunting, underweight and wasting prevalence, that were obtained using the corrected *z* score (Z_{india}) for Indian children, were compared against the EMRGF in the latest entire NFHS-5 survey data. The estimates were also compared against the estimates calculated using the existing WHO global standard [6].

The statistical software R version 4.2.1 (R Core Team, 2022) was used for data analysis. The accepted false positive error for all statistical tests was set at 5%.

RESULTS

After excluding data corresponding to the upper and lower 5% of HAZ, WAZ and WHZ, validation of 10,384 children (CNNS: 1,585; NFHS-3: 1,561; NFHS-4: 3,622; NFHS-5: 3,616) were available for age, sex, height, and weight. There were 5377 boys and 5007, girls out of which 963 boys and 1011 girls were below 12 months; 1505 boys and 1444 girls were aged 12 - 23 months; 991 boys and 919 girls were aged 24 - 35 months old; 1004 boys and 884 girls were aged 36-47 months, and 914 boys and 749 girls were aged 48 to 59 months.

The mean HAZ, as calculated from the WHO standard [6], in the final analytical subsample for each survey was -0.56 (95% CI -0.61, -0.51) for the CNNS; -0.72 (95% CI -0.76,-0.69) for the NFHS-5; -0.68 (95% CI -0.72,-0.64) for the NFHS-4 and -0.74 (95% CI -0.79,-0.68) for the NFHS-3 (**Fig. 1A**). A one-way ANOVA, with post-hoc Tukey HSD comparisons, showed that the mean HAZ in the CNNS was significantly higher when compared to all the NFHS rounds. All NFHS rounds had a consistent mean HAZ in the analytical sample. In terms of HAZ variance, only 0.4% was accounted for by between-survey variance. Despite the mean HAZ in the CNNS analytical sample being 0.12 to 0.18 points higher than in the NFHS analytical sample (**Fig. 1B**), the HAZ values were pooled across all surveys, because the CNNS had a relatively smaller sample size as it was not powered for district level estimates. The pooled mean HAZ from the random effects model was -0.69 (95% CI -0.71, -0.66), and its SD was 1.16 (95% CI 1.14-1.17) (**Fig. 1B, 1C**). Further, when the age-specific mean height of the pooled (all NFHS and CNNS) sample was compared with the CNNS sample alone, no significant difference was observed between them (**Web Fig. 3A**), confirming that the pooling was appropriate.

An almost similar pattern was observed for WAZ. The mean WAZ was -0.66 (95% CI -0.71, -0.62) for the CNNS, -0.72 (95% CI -0.75, -0.69) for the NFHS-5, -0.79 (95% CI -0.82, -0.76) for the NFHS-4, and -0.79 (95% CI -0.83, -0.74) for the NFHS-3. In terms of variance, 0.36% was accounted for by between-survey variance. The pooled mean WAZ from the random effects model was estimated as -0.75 (95% CI -0.76, -0.73), and its SD was estimated as 0.93 (95% CI 0.91-0.94) (**Fig. 1B, 1C**).

The estimated mean WHZ was -0.52 (95% CI (-0.57, -0.47) for the CNNS, -0.46 (95% CI -0.50, -0.43) for the NFHS-5, -0.56 (95% CI -0.63, -0.56) for the NFHS-4, and -0.55 (95% CI -0.60, -0.55) for the NFHS-3. When the variance across surveys was compared for WHZ, only 0.24% was accounted for by between-survey variance. The pooled mean WHZ from the random effects model was estimated as -0.53 (95% CI -0.55, -0.51), and its SD was estimated as 1.07 (95% CI 1.06-1.08) (**Fig. 1B, 1C**). The pooled vs the CNNS-alone estimates for weight were also comparable (**Web Fig. 3B**).

Age-specific correction factors were obtained by fitting a hierarchical mixed model which estimated correction factors as a polynomial function of age as prominent age trends were observed on all the *z* scores (HAZ, WAZ and WHZ) within

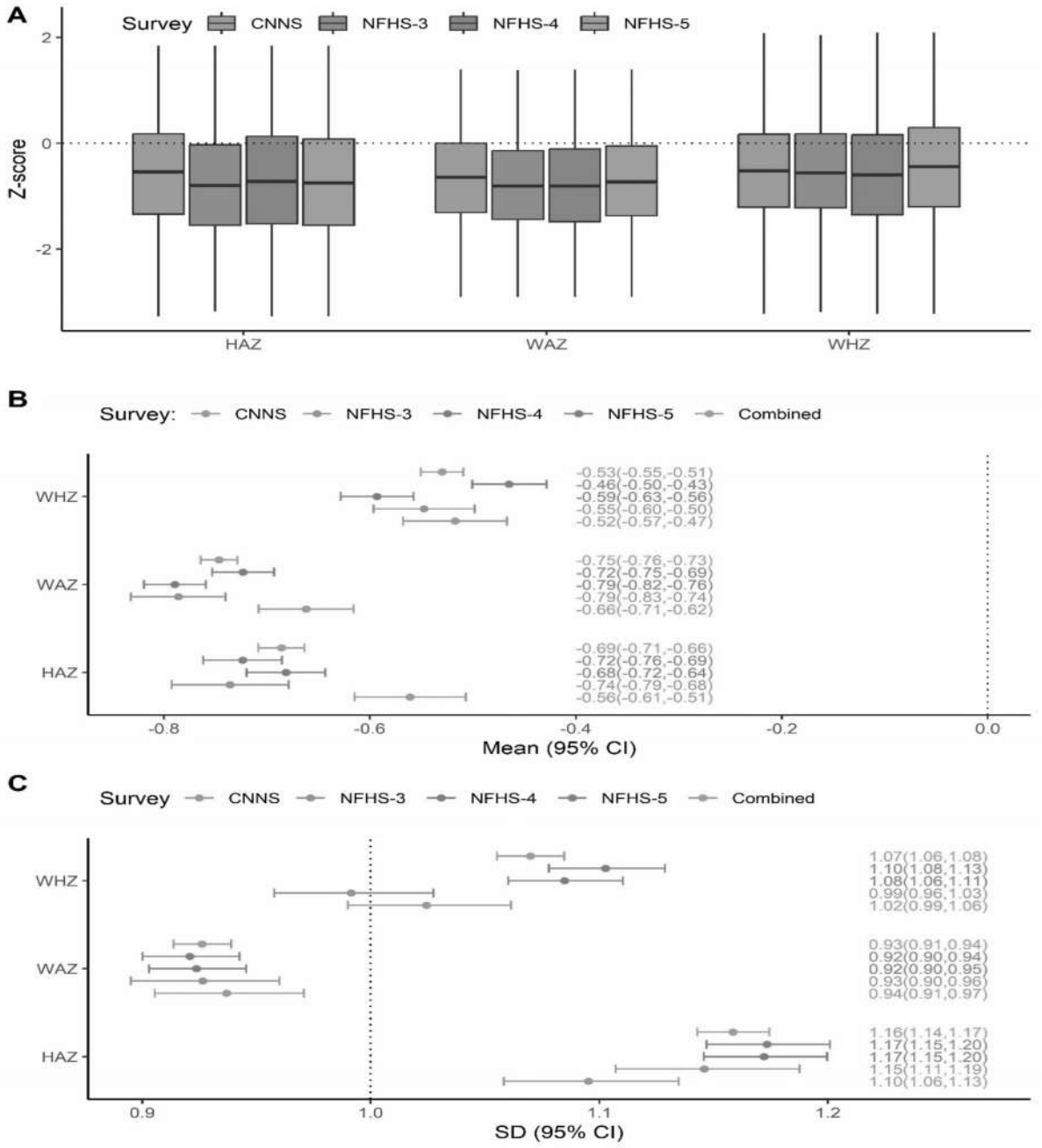


Fig. 1 Distribution of z scores of height for Age (HAZ), weight for age (WAZ) and weight for height (WHZ) in the analytical sample of healthy children across four different national surveys.

the merged analytical sample data (**Web Fig. 4**). The observed time trend was assumed to be sex invariant, and this was confirmed by fitting sex-specific curves (**Web Fig. 5**).

For HAZ

$$\hat{\mu}_{haz}(t) = 0.541 - 0.127t + 0.0035t^2 - 0.00003t^3$$

and $\hat{\sigma}_{haz}(t) = \sqrt{e^{(0.543 - 0.020t + 0.00023t^2)}}$

For WAZ, this was:

$$\hat{\mu}_{haz}(t) = 0.541 - 0.0116t + 0.0001t^2 \;\&\; \hat{\sigma}_{waz}(t) = 0.920$$

For WHZ, this was:

$$\hat{\mu}_{whz}(t) = -0.859 + 0.047t - 0.0016t^2 + 0.00001t^3$$

$$\&\; \hat{\sigma}_{whz}(t) = \sqrt{e^{(0.2365 - 0.004t)}}$$

Table I Anthropometric Indicators for Nutritional Status of Children Aged Below 5 Years in India, Estimated from NFHS-5 by Different Growth Metrics Derived in this Study

Growth metric	*Stunting*	*Underweight*	*Wasting*
Present WHO standard	35.5 (35.1, 35.8)	32.1 (31.7, 32.4)	19.2 (18.9, 19.6)
Corrected WHO standard	16.6 (16.3, 16.8)	14.9 (14.7, 15.2)	10.2 (10.0, 10.5)
EMRGF after correction	15.5 (15.3, 15.8)	15.0 (14.8, 15.3)	7.1 (6.9, 7.4)

WHO: World Health Organization; NFHS: National Family Health Surveys; EMRGF: Excess Mean Risk of Growth Faltering.
Data taken from NFHS-5 survey with 232,320 children under 5 years, from which 2,06,025 valid height for age measurements, 2,10,524 valid weight for age measurements and 2,01,687 valid weight for height measurements were available.

When age-specific correction factors were applied to the HAZ, WAZ and WHZ values in the NFHS-5, the prevalence of stunting, underweight and wasting respectively, in under-5y Indian children was half that estimated by the WHO standard (**Table I**). The EMGRF for HAZ, WAZ and WHZ was 15.5%, 15.0% and 7.1%, respectively. More granular state-specific prevalence estimates by WHO MGRS (**Web Fig. 6**), age specific corrected estimates (**Web Fig. 7**) and estimates of EMRGF for the entire NFHS-5 data, for all the three growth metrics (HAZ, WAZ and WHZ) are reported in **Fig. 2**.

DISCUSSION

Anthropometric standards are defined by the location, scale, and shape parameters of the distribution of growth indicators in defined 'healthy' children. The 2.5th percentiles of these standard distributions are defined as the diagnostic cutoff for stunting, underweight and wasting for the under-5 child population. This study showed that the distribution (mean and SD) of HAZ, WAZ and WHZ of healthy Indian children may not match the WHO growth standards as expected. Age-specific correction factors were derived for HAZ, WAZ and WHZ for Indian children, in a stringently defined 'healthy' sample of Indian children, who were most likely to have optimal or favourable conditions for growth in the local context, using criteria analogous to the WHO standards. The corrected stunting, wasting and underweight were much lower (by >50% points) than that estimated using the uncorrected, current WHO standard.

Several studies have critically examined the validity of WHO standards for different populations and a systematic review of the comparison of regional growth references against WHO standards recommended the adoption of regional standards for growth [7,11]. A method of creating synthetic growth reference charts by incorporating information from existing reference growth studies has been suggested [12]. While high undernutrition prevalence is reported in LMICs when WHO standards are used [13], very few have critically examined the appropriateness of the WHO standard by using local healthy child populations in the Indian context.

When global standards are used in any given population to measure stunting, wasting and underweight, the assumption is that the absence of sub-optimal age-appropriate diet is the main contributor to anthropometric undernutrition in that population, which in turn may have several drivers [14]. However, this assumption discounts the fact that populations may have different potentials for growth, and the possibility that the Indian population has not reached its full potential of growth but is in a path towards it as an intergenerational phenomenon. Therefore, universal standards might be unsuitable. This has been demonstrated in a sub-group of children from NFHS-2, who could presumably meet their nutritional requirements, but the prevalence of stunting was as high as 20% and that of underweight was 9.8%, based on WHO standards, which were well above the acceptable prevalence of 2.5% [15].

One important drawback of any cutoff is that the definition of disease or growth-faltering arbitrarily labels children on one side of the cut-off as 'abnormal' and on the other side as 'normal.' This is particularly troubling when (many) individuals have values close to the designated cut-off. We therefore proposed a risk-based approach, by recommending a risk metric that estimated the likelihood of growth faltering. Based on probability theory, an individual risk greater than 50% must depict the potential for growth faltering. The population estimate of growth faltering is then defined as the excess probability of faltering (EMRGF). As this metric is based on an average, it is free from the effects of over-dispersion due to random measurement error, which is particularly true for those parameters which have high potential for measurement error due to the nature of measurement, such as height/length. In the absence of any measurement error, the estimate of EMRGF and the existing descriptions like stunting will reflect population growth faltering at a similar level. This EMGRF approach draws inspiration from the probability approach that was used to assess the risk of inadequate nutrient intake, as suggested by Beaton nearly half-a-century back [16]. A similar approach has been proposed for biomarker-based nutrient deficiency as well [17]. When we estimated EMRGF using data for upper two deciles of socioeconomic index of the Indian NFHS-5, we observed values of 18.8%, 13.1% and 13.8% for stunting, underweight and wasting respectively, when using WHO global standard. The application of the age-specific correction derived here, reduced these values to 5.0%, 3.0% and 1.3%, respectively.

WHAT IS ALREADY KNOWN?

- Current World Health Organization (WHO) standards for under-5 year children may be contextually inappropriate.

WHAT THIS STUDY ADDS?

- The distribution of WHO height and weight standards in 10,384 healthy Indian under-5 children, show that the *z* scores do not follow a standard normal distribution, as expected.
- Corrected estimates of stunting, wasting and underweight, using WHO standard data, were obtained.

Based on the correction suggested here, the prevalence of stunting, underweight and wasting in India is about 50% of that measured by the current WHO standard. Using a similar probability approach on the corrected distribution, the possible risk of overweight (WHZ>1) is 15% indicating an underestimation of overweight by the current WHO standard (9%). The correction can divert policy action towards the emerging epidemic of overnutrition, beginning in this age group and in the future external validation of the corrected prevalence can be done.

A limitation of the study is that criteria on timely feeding of children and term birth could not be considered in the selection of healthy children to exactly match the WHO-MGRS selection criteria. A strength of this study is the use of data extracted from four different national surveys over different times and the age-specific mean HAZ, WAZ and WHZ of the extracted sample are consistent across upper four deciles and the uppermost decile (**Web Fig. 9**). The observed deviation of growth patterns in healthy Indian children from the WHO standard growth pattern is robust. We have suggested corrected estimates for child growth, as well as age-specific correction factors for *z* scores that are derived from the current WHO standard. We have also suggested a new growth metric which is robust to the problem of overdispersion.

In conclusion, this evidence, along with that in the systematic review [7], argues that the one-size-fits-all approach for deriving population estimates of growth faltering is misleading, and has led to misclassification in the Indian context. This is a key driver of misdirected policy and public health funding, with the constant lament that no response has occurred despite India's economic growth and policy initiatives. While these findings need validation in other contexts, Indian stakeholders may consider using the present corrected estimates for informing policy.

Ethics clearance: The Institution Ethics Review board of St. John's Medical College provided waiver of review for this secondary data analysis.

Contributors: SG, AVK: conceptualized the study; SG, AVK, TT: wrote the first draft of the paper; HPS: reviewed and edited the manuscript; SG, RM: performed the statistical analysis. All authors have approved the final version of the manuscript. SG,TT: had access to the data and have verified the data.

Funding: AVK, TT, HSS are recipients of the Welcome Trust/ Department of Biotechnology India Alliance Clinical/Public Health Research Centre Grant No. IA/CRC/19/1/610006. TT, AVK and SG are recipients of SERB POWER Grant No. SPG/ 2021/003012.

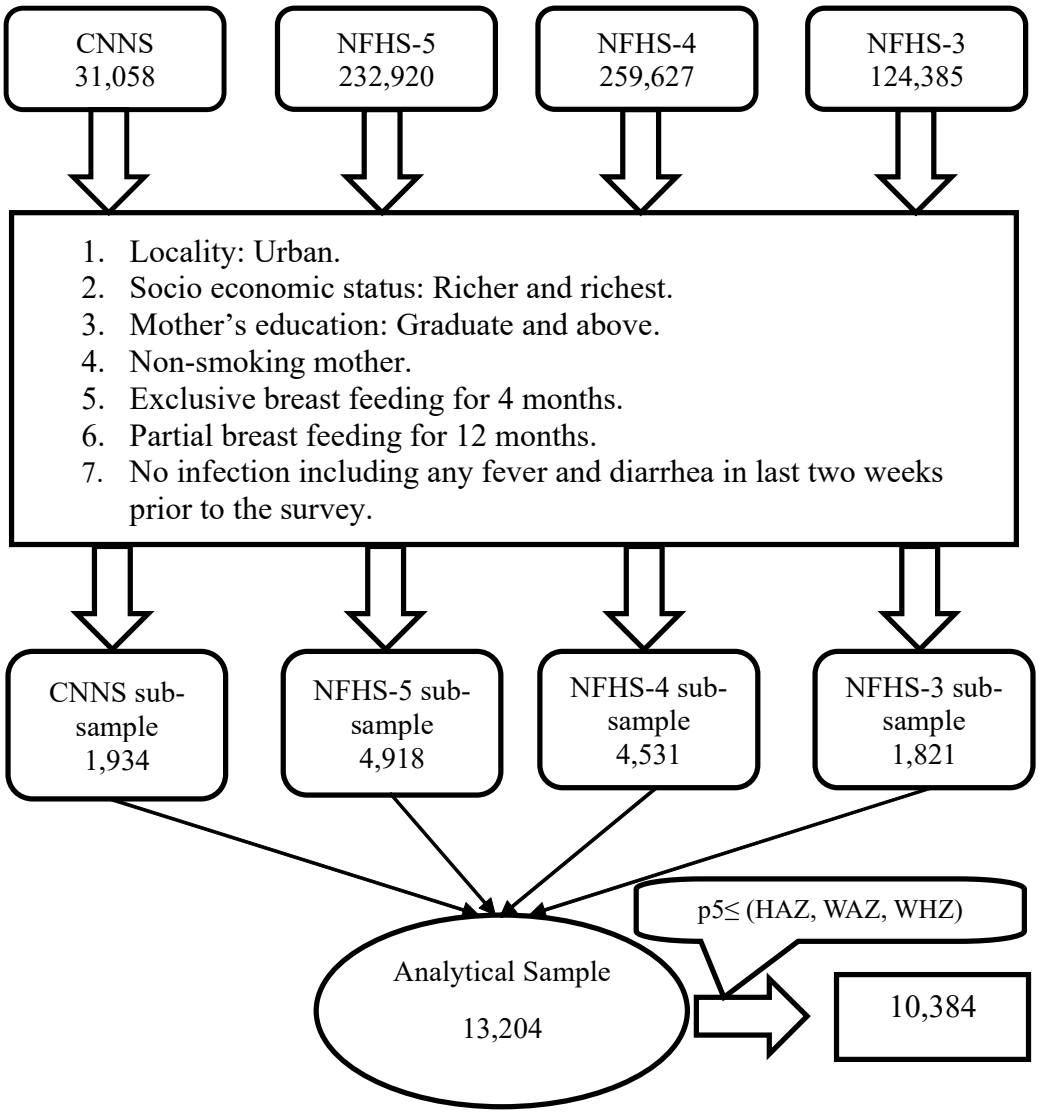
Competing interests: None stated.

Note: *Additional material related to this study is available with the online version at www.indianpediatrics.net.*

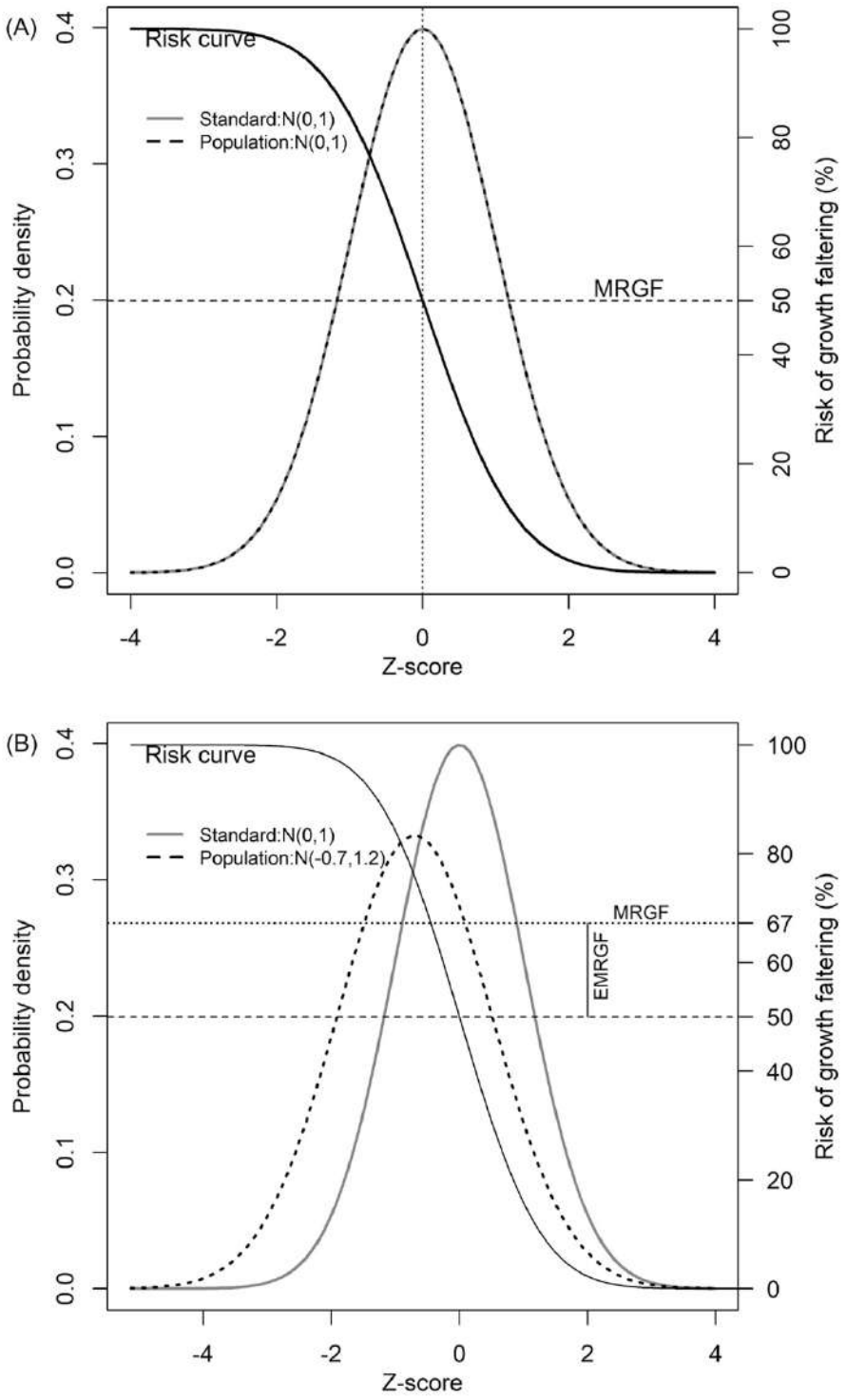
REFERENCES

1. Ministry of Health and Family Welfare, Government of India. National Family Health Survey (NFHS) 5, 2019–21. Accessed Nov 3, 2022. Available from: *http://rchiips.org/nfhs/NFHS-5_FCTS/Final%20Compendium%20of%20fact%20sheets_India%20and%2014%20States_UTs%20(PhaseII).pdf #toolbar=0&navpanes=0*
2. Ministry of Health and Family Welfare, Government of India. Comprehensive National Nutrition Survey Report (CNNS) 2016-2018. Accessed Nov 3, 2022. Available from: *https://nhm.gov.in/WriteReadData/l892s/14057960 31571201348.pdf*
3. Ministry of Health and Family Welfare, Government of India. National Family Health Survey (NFHS) 4, 2015-16. Accessed Nov 3, 2022. Available from: *http://rchiips.org/nfhs/pdf/nfhs4/india.pdf*
4. Ministry of Health and Family Welfare, Government of India. National Family Health Survey (NFHS)-3, 2005-2006. Accessed Nov 3, 2022. Available from: *https://dhsprogram.com/pubs/pdf/frind3/frind3-vol1andvol2.pdf*
5. Ministry of Women and Child Development, Government of India. Integrated Child Development Services (ICDS). Accessed Nov 3, 2022. Available from: *http://icds-wcd.nic.in/icds.aspx*
6. WHO Multicentre Growth Reference Study Group. Assessment of differences in linear growth among populations in the WHO Multicentre Growth Reference Study. Acta Paediatr Suppl. 2006;450:56-65.
7. Marume A, Archary M, Mahomed S. Validation of growth standards and growth references: A review of literature. J Child Health Care. 2022;26:498-510.
8. Ghosh S, Shivakumar N, Bandyopadhyay S, Sachdev HS, Kurpad AV, Thomas T. An uncertainty estimate of the prevalence of stunting in national surveys: the need for better precision. BMC Public Health. 2020;20:1634.
9. Rönnegård L, Shen X, Alam M. hglm: A package for fitting

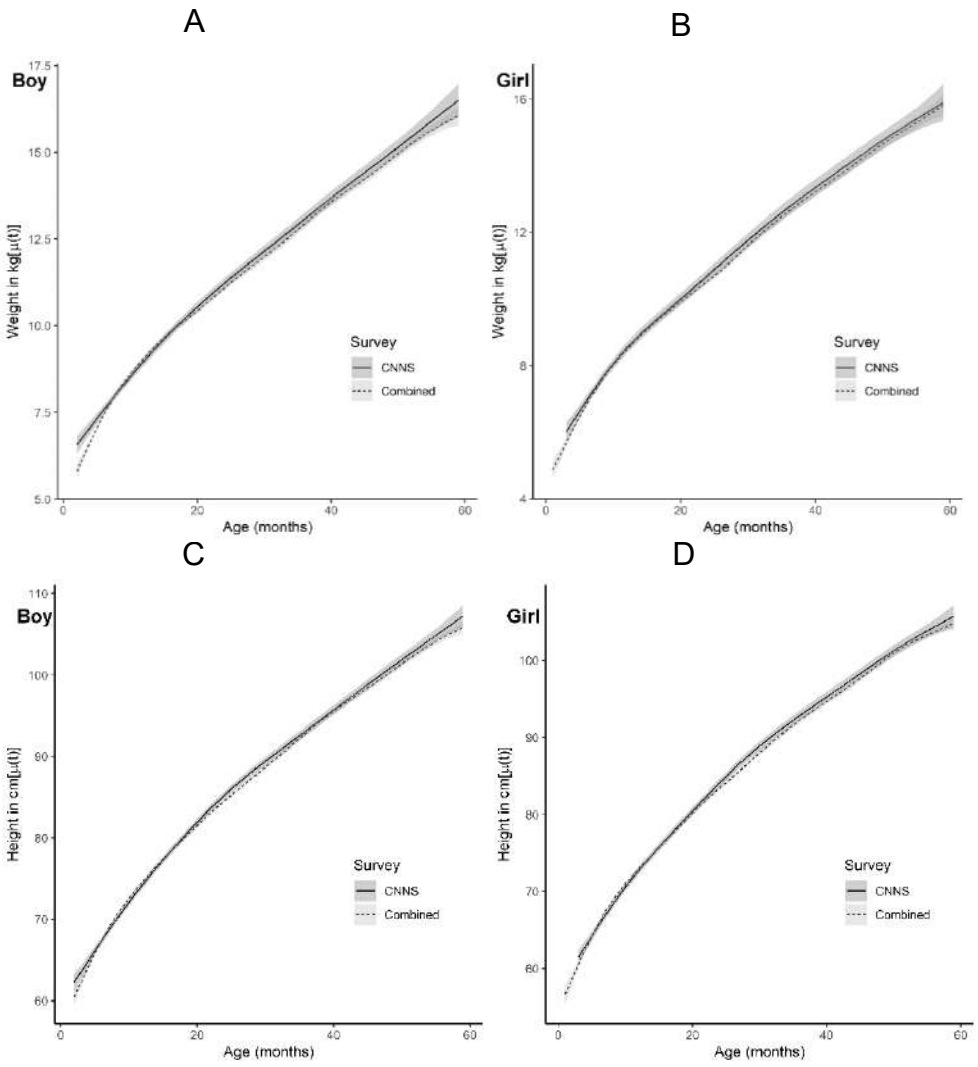
hierarchical generalized linear models. R Journal. 2010;2: 20-8.
10. Grellety E, Golden MH. The Effect of random error on diagnostic accuracy illustrated with the anthropometric diagnosis of malnutrition. PLoS One. 2016;11:e0168585.
11. Natale V, Rajagopalan A. Worldwide variation in human growth and the World Health Organization growth standards: A systematic review. BMJ Open. 2014;4:e003735.
12. Hermanussen M, Stec K, Aßmann C, Meigen C, Buuren SV. Synthetic growth reference charts. Am J Hum Biol. 2016; 28:98-111.
13. Osgood-Zimmerman A, Millear AI, Stubbs RW, et al. Mapping child growth failure in Africa between 2000 and 2015. Nature. 2018;555:41-7.
14. Panagariya A. Does India really suffer from worse child malnutrition than Sub-Saharan Africa? Economic and Political Weekly. 2013;48:98-111.
15. Tarozzi A. Growth reference charts and the nutritional status of Indian children. Econ Hum Biol. 2008;6:455-68.
16. Beaton GH. Epidemiology of iron deficiency. Vol: Iron in Bio-chemistry and Medicine. Academic Press; 1974.
17. Ghosh S, Kurpad AV, Sachdev HS, Thomas T. A risk-based approach to measuring population micronutrient status from blood biomarker concentrations. Front Nutr. 2022;9:991707.



Web Fig. 1 Steps of selection of analytical sample.



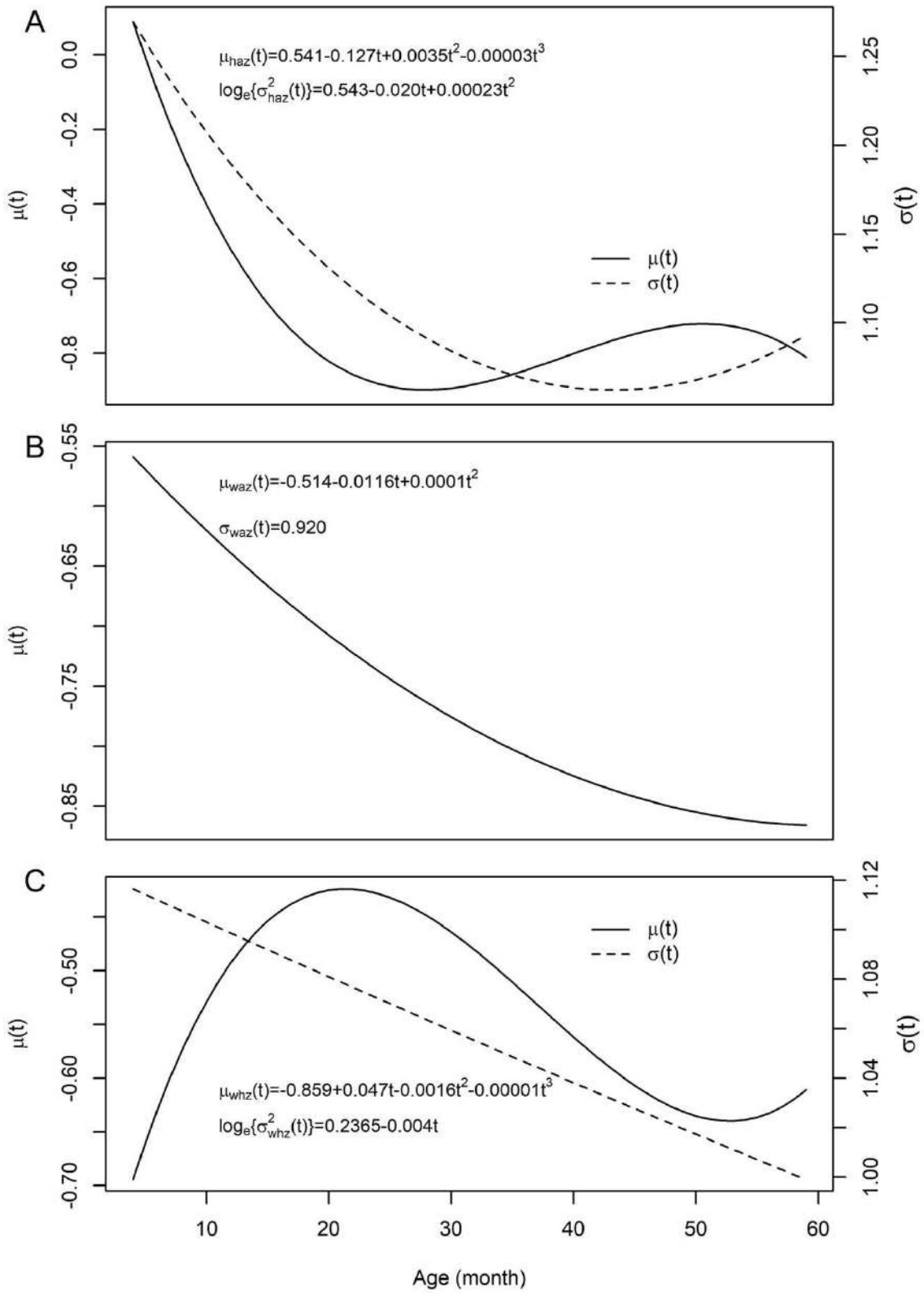
Web Fig. 2 Hypothetical comparison of distribution of *z* scores of a population with standard (unit normal) when population growth as per the standard (A) and when population has substantial growth faltering (B).



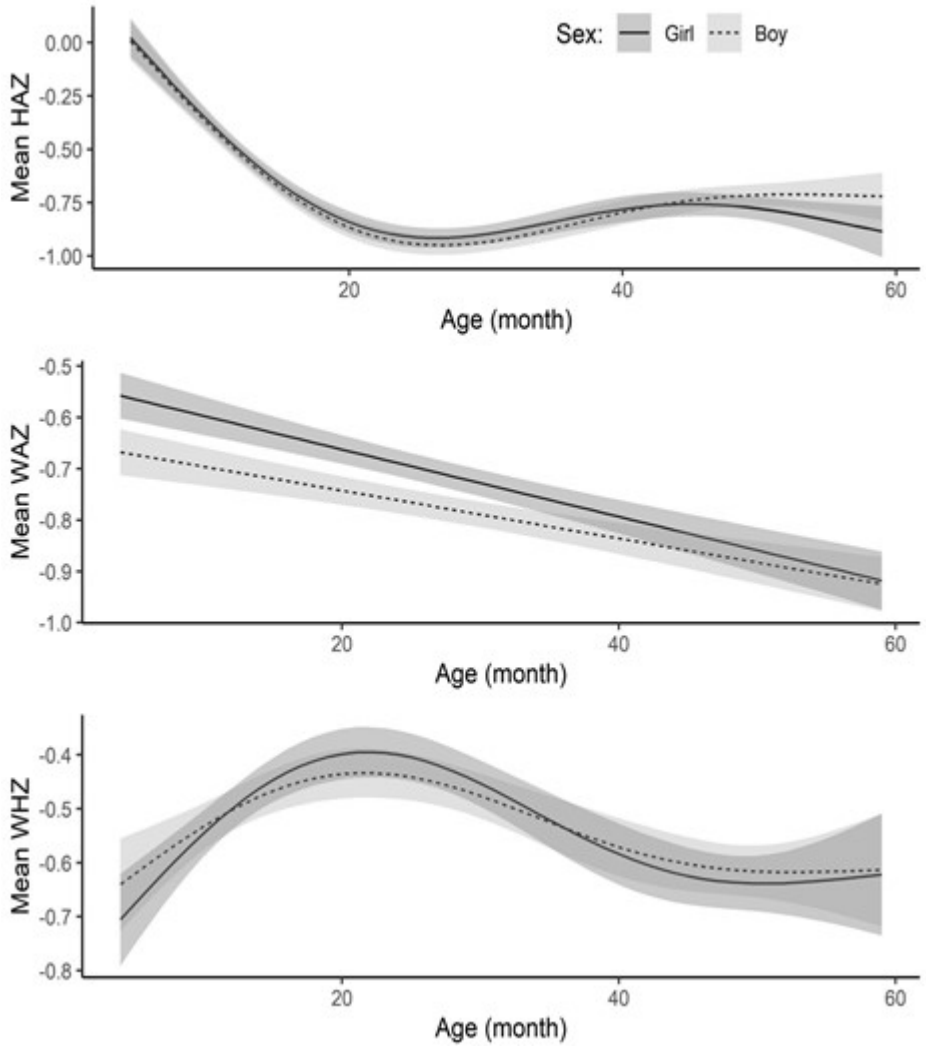
Web Fig. 3 Comparison of estimated smoothed gender specific mean height (A) and weight (B) for age between pooled sample (NFHSs and CNNS) and CNNS alone with 95% confidence band.

NFHS: National Family Health Surveys

CNHS: Comprehensive National Nutrition Survey



Web Fig. 4 Age trend of the distribution of height for age (HAZ), weight for age (WAZ) and weight for heigh (WHZ) derived by the WHO growth standard for under-5y children aged below five years.



Web Fig. 5 Age specific mean of height for age (HAZ) (A), weight of age (WAZ) (B) and weight for height (WHZ) (C) by sex of children.

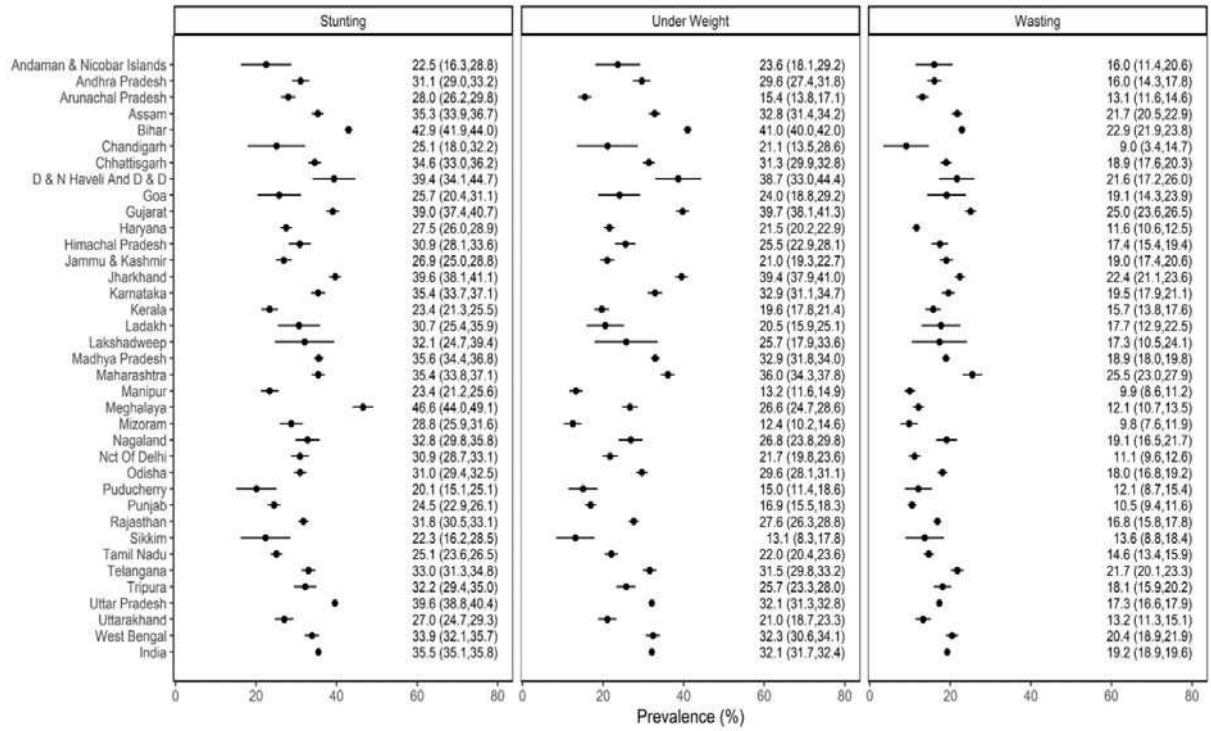
The observed time trend was confirmed to be sex invariant by fitting sex-specific curves. For HAZ, this was:

$\hat{\mu}_{haz}(t) = 0.541 - 0.127t + 0.0035t^2 - 0.00003t^3$ and $\hat{\sigma}_{haz}(t) = \sqrt{e^{(0.543 - 0.020t + 0.00023t^2)}}$.

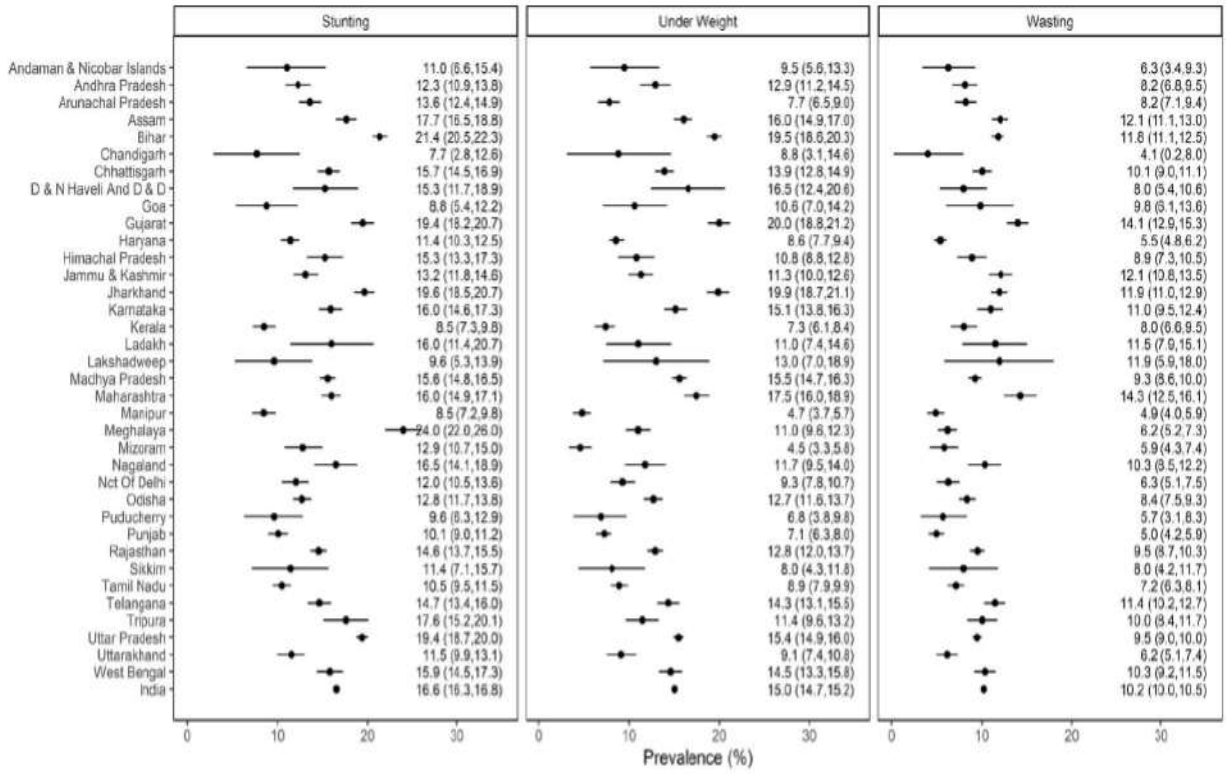
For WAZ, this was: $\hat{\mu}_{waz}(t) = 0.514 - 0.0116t + 0.0001t^2$ & $\hat{\sigma}_{waz}(t) = 0.920$.

For WHZ, this was:

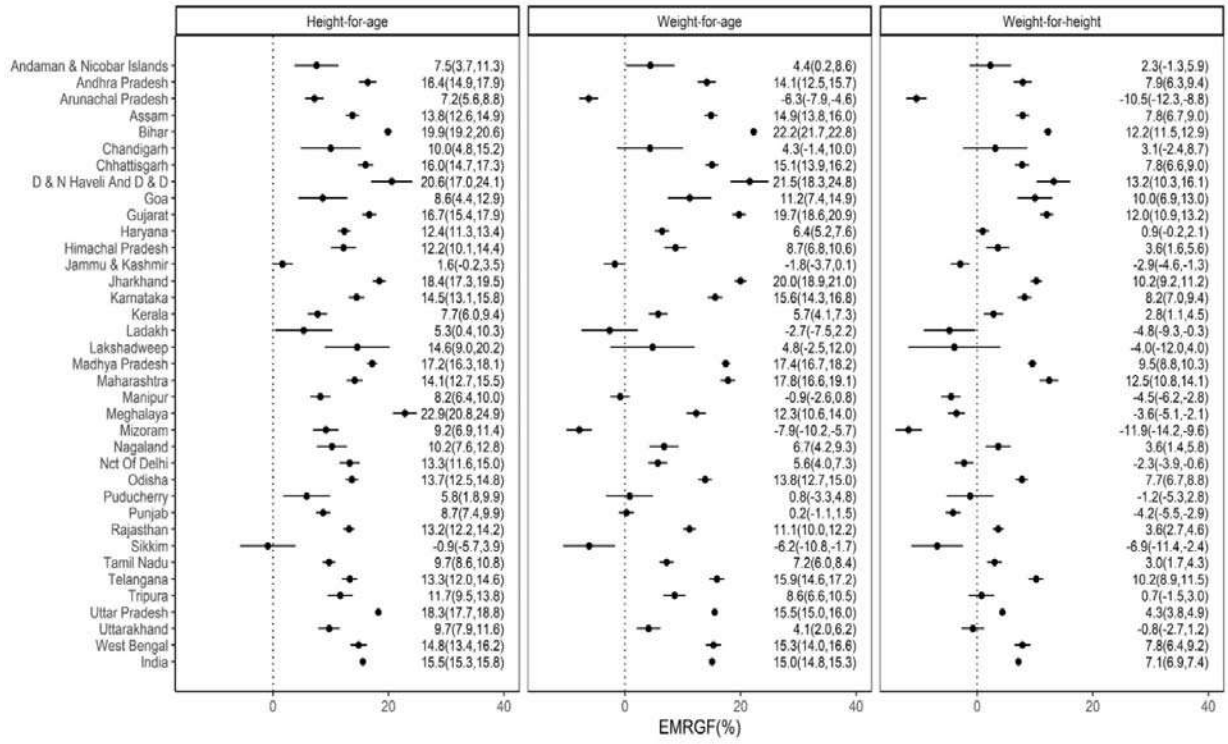
$\hat{\mu}_{whz}(t) = -0.859 + 0.047t - 0.0016t^2 + 0.00001t^3$ & $\hat{\sigma}_{whz}(t) = \sqrt{e^{(0.2365 - 0.004t)}}$



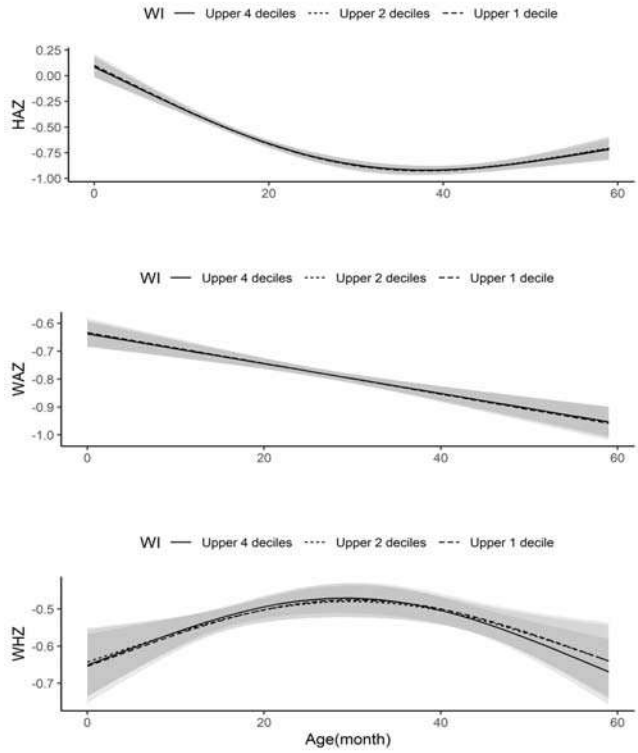
Web Fig. 6 Prevalence of stunting(A), underweight(B) and wasting(C) in states of India, based on National Family Health Surveys (NFHS-5) data using orginal World Health Organization (WHO) growth standards.



Web Fig. 7 Prevalence of stunting (A), underweight(B) and wasting(C) in states of India, based on National Family Health Surveys NFHS-5) using corrected World Health Organization (WHO) growth standards.



Web Fig. 8 Estimates of excess mean risk of growth faltering (EMRGF) for HAZ, WAZ and WHZ by state based on NFHS-5 data.



Web Fig. 9 Age sepecfic mean *z* scores of height for agd (HAZ), weight for age (WAZ) and weight for height (WHZ) of healthy children across upper 4 deciles, upper 2 deciles and upermost decile of wealth.

RESEARCH PAPER

Impact of a Brief Healthcare-based Intervention to Support Early Childhood Development in India: A Pilot Randomized Controlled Trial

DEEPA C METGUD,[1] RONITA AJGAONKAR,[2] SHUKRA CHIVATE,[1] ALAN SCHWARTZ,[3] MICHELLE FERNANDES,[4] RESHMA SHAH[5]

[1]*Pediatric Physiotherapy, KAHER Institute of Physiotherapy, Belagavi, Karnataka, India.*
[2]*Department of Pediatric Physiotherapy, KAHER Institute of Physiotherapy, Belagavi, Karnataka, India.*
[3]*Department of Medical Education, University of Illinois at Chicago, , Chicago, IL , USA.*
[4]*Faculty of Medicine, Department of Pediatrics, University of Southampton, Southampton, UK.*
[5]*Department of Pediatrics, College of Medicine, The University of Illinois at Chicago, Chicago, IL, USA.*
Correspondence to: Dr Reshma Shah, 840 South Wood St, MC 856, Chicago, IL 60612, USA. reshmamd@uic.edu.
Received: Nov 14, 2022; Initial review: Dec 18, 2022; Accepted: May 27, 2023.

Objective: To study the impact of a brief early childhood development (ECD) intervention, Sit Down and Play (SDP), integrated within routine healthcare visits on parent and child outcomes.

Methods: Between April, 2018 and March, 2019, caregivers and their infants aged 5-6 months attending a well-baby clinic were enrolled and randomized to intervention (*n*=26) or control (*n*=26) groups. Intervention families received SDP at recruitment and two subsequent immunization visits (8 months and 10 months). Control families received usual care. ECD outcomes were assessed through in-person assessments at the age of 12 months using the Stim Q subscales to assess parenting behaviors, and the Developmental Assessment Scale for Indian Infants (DASII) for neurodevelopment.

Results: There was a significant improvement in parent-child stimulation activities and verbal interactions in the intervention group compared with the control group [6.1(1.4) vs 4.9 (1.3); *P*=0.002]. Infants in the intervention group had significantly higher DASII scores in multivariable analyses [108.0 (103.0-111.3) vs 102.0 (96.8-108.0); *P*=0.04].

Conclusion: Our findings suggest a brief healthcare intervention supports opportunities for early learning among caregivers and neurodevelopmental outcomes in their infants.

Keywords: *Neurodevelopment, Nurturing care framework, Parenting, Sit down and play intervention.*

Clinical Trial Registry of India: CTRI/2018/08/015177 **Published online:** June 21, 2023; **PII**: S097475591600554

It has been estimated that at least 250 million children under 5 years of age in low- and middle-income countries (LMICs) are at risk for not achieving their development potential due to factors including exposure to infectious illnesses, malnutrition and poverty [1]. These risk factors are specifically associated with poor developmental outcomes in speech, language, and cognition [1]. As the first years of life provide a crucial foundation for future physical, mental, and emotional well-being, these early delays have important implications for young children in LMICs, including India, where an estimated 65 million children under 5 years of age are estimated to be at risk for not reaching their developmental potential [2].

The Nurturing Care Framework (NCF) highlights health, nutrition, safety, responsive caregiving, and opportunities for learning as critically important to support ECD [3]. As per World Health Organization guidelines on early childhood development (ECD), is an emphasis on supporting opportunities for learning (e.g., reading and play) and responsive caregiving, as an effective strategy to mitigate the effects of socioeconomic adversity on subsequent neurodevelopment.

Play incorporates many diverse forms and definitions, and includes imaginary activities as well as social interactions among children, peers, their caregivers and other adults [5]. Studies demonstrate that engaging in play can contribute to improved development in fine and gross motor skills, enhanced comprehension, social-emotional well-being, problem solving behavior, and better language attainment [6].

Despite these advantages, a systematic review of healthcare-based interventions targeting parenting behaviors in LMICs did not identify any published studies that originated in India [7].

Sit Down and Play (SDP) is an intervention to support opportunities for early learning as a means to improve ECD [8]. Previous studies of SDP during well-child visits in Karnataka, India have demonstrated feasibility and a positive impact in key parenting behaviors that promote ECD [9,10]. While the studies demonstrated positive pre- and post-changes in parenting behavior outcomes, neither study utilized a comparison group nor examined child

outcomes. Thus, the objective of this study was to examine the impact of SDP on child and parent outcomes at a healthcare facility at 12 months of age.

METHODS

This study was conducted at a well-baby clinic in a tertiary care hospital in Belagavi, Karnataka between April, 2018 and March, 2019. Parents and their infants attending the well-baby clinic were eligible to participate in the study if they fulfilled the inclusion criteria viz., parents were at least 18 years of age, and infants were 5-6 months of age (attending for influenza vaccination). Participants were excluded if children were acutely ill, had a known neuromotor disability, genetic disorder, congenital anomaly, metabolic disorder, a history of any surgery in the past 6 months, or had a history of neonatal intensive care unit (NICU) stay.

SDP is a brief intervention (10-15 minutes in length) which is designed to be delivered during routine healthcare visits for children in the first 2 years of life. Based upon the social cognitive theory [12] and adapted from existing parent-directed programs including Reach out Read and Care for Child Development, it aims to support a child's early social and learning experiences through parent-child play [8-10]. During each intervention session, SDP administrators discuss the importance of early learning opportunities and parent-child interactions on a child's development. SDP administrators then model examples of how to use simple toys (e.g., balls, rattle) to incorporate play and key parent-child interactions into everyday routines. Caregivers are then asked to play with their child and the administrators provide praise to positively reinforce behaviors. The caregiver is given the toy to take home with additional suggestions to incorporate play into everyday activities such as cooking and bath time. While the inter-vention is designed to be delivered by non-professionals, for this feasibility study, administrators were physical therapists.

As this was a pilot study, we were primarily interested in precise estimates of outcome variables. We aimed to recruit at least 50 participants, which exceeds the threshold for sufficiently precise estimates of the variance of change in measured outcomes in this population to use in future studies [11].

We conducted a single-blind randomized trial. Computer-generated random numbers were used to allocate participants to intervention or control groups. Sealed and opaque envelopes, which were serially numbered, were used for allocation concealment. The envelopes were opened after obtaining demographic and study measures by a research assistant who was not involved in delivering the intervention or assessing child outcomes.

Parent-child dyads in the control group received usual care, which comprised of education regarding feeding and nutrition, anthropometric assessment, developmental screening, and immunizations. Participants in the intervention group received the intervention, SDP, at enrollment and at the two subsequent immunization visits (i.e., 8 months for typhoid vaccine, and 10 months for MMR vaccine) in addition to usual care. Delivery of SDP was by a single physical therapist for all participants. In-person follow-up assessments using the Developmental Assessment Scale for Indian Infants (DASII) were completed by certified DASII evaluators who were physical therapists, for both groups at the 12-month visit (coinciding with hepatitis B vaccination). The evaluators were blinded to the group allocation study condition.

At baseline, the demographic characteristics of the study participants were obtained including information related to marital status, number of adults and children in the family, and parental level of education, age the age and sex of the infant.

The StimQ questionnaire [13] was used in this study. It is a self-report questionnaire to assess parental involvement in different activities that promote ECD. The StimQ consists of four subscales: availability of learning materials (ALM), reading-verbal scale, parental involvement in developmental advance (PIDA) scale, and parental verbal responsivity (PVR) scale. To assess areas of focus related to SDP, the PIDA and PVR subscales were selected for this study. The PIDA evaluates caregiver teaching and play activities, and the PVR assesses verbal interaction between the caregiver and their child. It has been used previously among Indian children age 12-30 months [14]. The StimQ has been reported to have good internal consistency, test-retest reliability, and criterion-related validity [15]. It also has good concurrent validity and predictive validity with measures of child development [14].

The Developmental Assessment Scale for Indian Infants (DASII) was used to examine child outcomes. The DASII is adapted from the Bayley Scales of Infant and Toddler Development for use in India. It is extensively used to assess motor and cognitive (i.e., "mental") development in Indian children aged 0-30 months and has 163 mental and 67 motor assessment items [16]. The DASII provides a development quotient which is calculated using motor and mental quotient subscales.

Institutional Review Board approval was received from the first author's institution. The protocol was registered at the Clinical Trials Registry-India (CTRI).

Statistical analysis: We assessed differences in socio-demographic characteristics between the study groups at

baseline using Chi-square tests for categorical variables (gender, education) and *t* test for continuous scores. We estimated the effects of the intervention by comparing follow-up scores between the groups using *t* tests. We used multivariate linear models to adjust for sex, education, and for PVR and PIDA score at baseline.

RESULTS

A total of 70 parent-infant dyads were screened for eligibility, of which 8 did not meet inclusion criteria and 10 declined to participate due to challenges with transportation (**Fig. 1**). After obtaining informed consent, 52 dyads (29 male infants) were enrolled and randomized into the intervention (*n*=26) or control groups (*n*=26). The characteristics of the study participants are presented in **Table I**. There were no significant differences between groups at enrollment.

There were no statistically significant differences in the mean PIDA and PVR scores between groups at enrollment (**Table I**). However, at follow-up, significant improvements in PIDA [6.1 (1.4) vs 4.9 (1.3); *P=0.002*] and PVR [Intervention 9.8 (1.5) vs 8.4 (2.0); *P*=0.006] scores were observed between groups.

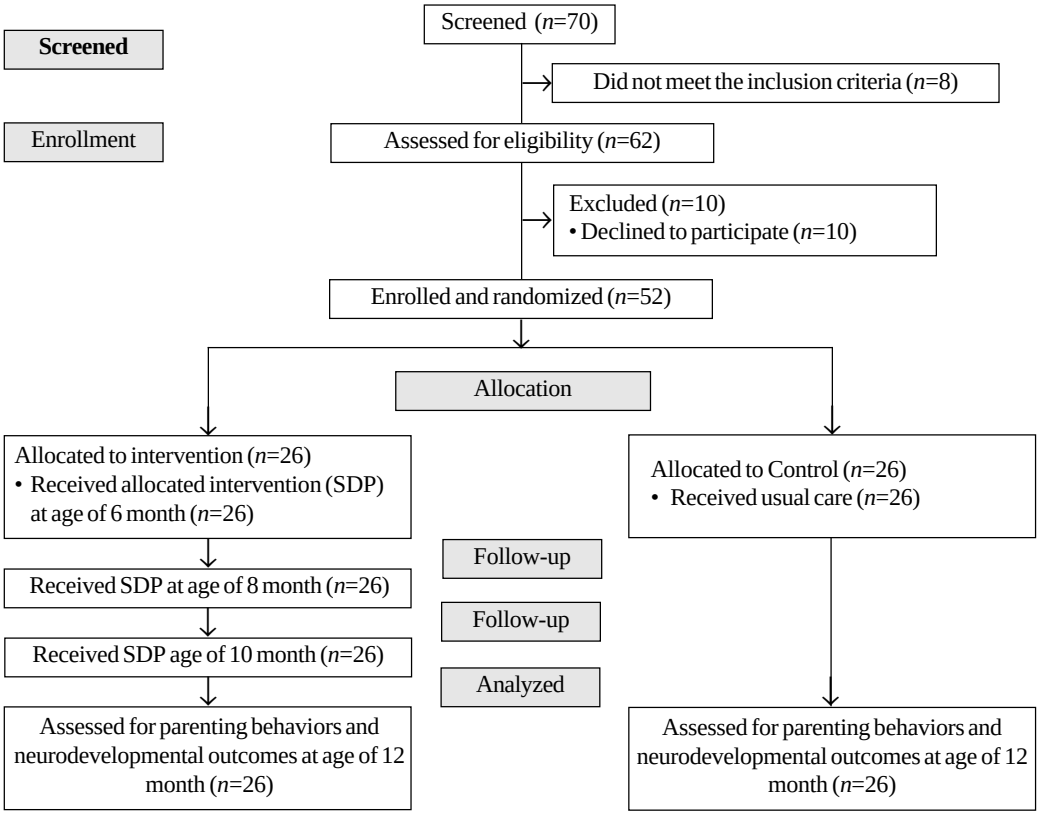
Table II shows the exploratory results of linear model analyses of SDP on parenting outcomes. At follow-up, differences between intervention and control groups were seen in PIDA [mean difference (95% CI) 1.3 (0.50-2.1); *P*=0.002] and PVR [MD (95% CI) 1.6 (0.6-2.6); *P*=0.003].

Children enrolled in the intervention group scored significantly higher on the DASII at 12 months compared with the control group as assessed by mental, motor and developmental quotients (**Table III**). This difference remained significant for the mean DASII developmental quotient (95% CI) at 12 months [108.0 (103.0-111.3) vs 102.0 (96.8-108.0); *P*=0.04] after adjusting for education and sex in multivariable analysis.

DISCUSSION

In this single-center pilot study, we found that SDP improves assessments of parenting behavior specific to supporting ECD, as well as improved neuromotor development in infants on the DASII at 12 months.

Our study adds to the recent literature that leverages the advantages of the healthcare settings to target the quality of early life experiences as a means to improve ECD [7].



SDP – Sit down and play intervention.

Fig. 1 Study flow diagram.

Table I Demographic Characteristics of the Study Participants

	Control group (n=26)	*Intervention group (n=26)*
Male sex	14 (53.8)	15 (57.7)
Maternal education		
High school <2 y	3 (11.5)	4 (15.4)
Completed high school	15 (57.7)	14 (53.8)
Some college[a]	0 (0.0)	1 (3.8)
2-year degree	3 (11.5)	1 (3.8)
Some graduate work	2 (7.7)	3 (11.5)
Graduate or postgraduate	3 (11.5)	3 (11.5)

Values in no. (%). All $P>0.05$. [a]*did not graduate.*

Similar to previously studies in other LMICs, our study utilized parent-child shared play as a means to support opportunities for learning and responsive caregiving with positive impacts on child development [15]. While these pioneering programs have capitalized on the advantages of the healthcare setting, frequent additional visits (i.e., 12-44 in a year) or use of professionals raise potential costs hampering sustainability and scalability efforts. Thus, our goal was to build on these innovative programs with a less intensive population-level healthcare-based program which could have potential for widespread dissemination for use in a low-resource setting.

Our study did have certain limitations. First, our sample was relatively small, recruited from a single site, excluded children with a complex medical history, and did not adjust for all demographic characteristics; these limitations impact the generalizability of our findings to other populations within and beyond the Indian subcontinent. Second, parenting outcomes were assessed using self-reports and as such, at risk of reporter bias and recall bias. Moreover, as families in the intervention arm could not be blinded to the condition, this may have augmented existing bias in terms of social desirability and performance bias. Nevertheless, we demonstrated successful enrollment, no attrition, and high rates of outcome measure completion from all participants. Moreover, we measured child outcomes using a valid, reliable, developmental diagnostic assessment specifically designed for use in India.

Despite these limitations, our findings provide valuable direction for future studies and for consideration for the integration of such interventions into public health policy in India. However, future studies should include larger samples and varied population groups, including those at high-risk of developmental delay such as premature infants, infants with a history of NICU stay, and those born small for gestational age. While infants with a more complex medical history may require more intensive support, an understanding of how a brief intervention may potentially impact these caregivers and their infants is necessary to examine generalizability.

SDP is designed to be delivered by nonprofessionals, but in this study it was delivered by physical therapists. The use of professionals may have contributed to the positive findings. Future studies should assess delivery with teams with basic educational qualifications which will be critical to support future scalability and dissemination efforts of the intervention. Assessing parental engagement in the intervention will be an important area for future research. Facilitators and barriers affecting parental engagement and uptake may impact intervention effectiveness and will be an important consideration in future dissemination efforts.

Table II Between Group Differences for Parenting Outcomes at Each Time Point and Multivariate Analysis at Follow-up

	Baseline			*Follow-up*			*Multivariate analysis estimated marginal means at follow-up (95% CI)[a]*		
	Control (n=26)	*Intervention (n=26)*	*P*	*Control*	*Intervention*	*P*	*Control*	*Intervention*	*P value*
PIDA	1.8 (1.6)	1.3 (1.3)	0.2	4.9 (1.3)	6.1 (1.4)	0.002	5.1 (4.3-5.9)	6.4 (5.7-7.1)	0.002
PVR	3.5 (2.5)	3.5 (2.7)	1.0	8.4 (2.0)	9.8 (1.5)	0.006	7.8 (6.8-8.8)	9.4 (8.5-10.3)	0.003

Values in mean (SD). [a]*Adjusted for respondent education, sex, and baseline scores. PIDA:parental invovement in developmental advance scale, PVR: parental verbal responsivity scale.*

Table III Between Group Differences in Child Outcomes and Multivariate Analysis

	Follow-up assessment			*Multivariate analysis estimated marginal means (95% CI)[a]*		
	Control (n=26)	*Intervention (n=26)*	*P*	*Control*	*Intervention*	*P*
Motor quotient	103.1 (14.8)	110.6 (10.5)	0.04	104.0 (96.2-111.0)	111 (103.7-118.0)	0.07
Mental quotient	97.3 (8.2)	102.5 (10.7)	0.05	101.0 (95.5-06.0)	105.0 (100.4-110.0)	0.09
Developmental quotient	100.2 (9.4)	106.5 (9.4)	0.02	102.0 (96.8-108.0)	108.0 (103.0-111.3)	0.04

Values in mean (SD). [a]*Adjusted for respondent education and sex.*

WHAT THIS STUDY ADDS?

- A brief healthcare-based intervention within existing healthcare services was effective in supporting early learning among caregivers, and neurodevelopmental outcomes in their infants.

It will be important to assess underlying mechanisms and examine factors for promoting risk and resilience in ECD outcomes. Future research focusing on these areas will be important to identify children at risk early and to identify novel targets for intervention. The frequency of touchpoints in SDP may have also reinforced the importance of partici-pating in early learning opportunities for the intervention group who received the intervention at three different timepoints at 2-month intervals. Alternatively, findings may have resulted from impacts on knowledge and attitudes regarding early learning opportunities which were also not evaluated in this study.

According to the NCF, a child's early social experiences and opportunities for learning are as important as good nutrition and access to healthcare to support ECD [3]. Our results suggest that a brief healthcare-based program may provide one strategy to promote these experiences with the potential to positively impact a child's development. Future research should focus on evaluating the generalizability of SDP to wider population groups and elucidating its underlying mechanisms.

Ethics clearance: Institutional Review Board, KLE Institute of Physiotherapy; No. 220 CTRI/2018/08/015177 dated 03/08/2018.
Contributors: DM: Conceptualized the study, developed protocol for research design, supported data collection, conducted data monitoring, and assisted with writing and editing of manuscript; RA: Conducted the literature review, supported data collection, and assisted with analysis and editing of manuscript; SC: Assisted with data collection, contributed to drafting of manuscript; MF: Developed the protocol and reviewed and revised manuscript; AS: Conducted the statistical analysis, wrote statistical section, and reviewed the manuscript; RS: Conceptualized the study, assisted with data interpretation, reviewed and revised the manuscript.
Funding: RS: Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health; Award No. K23HD086295.
Competing interests: None stated.
Note: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Black MM, Walker SP, Fernald LCH, et al. Advancing early childhood development: from science to scale 1. Lancet. 2017; 389:77-90.
2. Grantham-McGregor S, Cheung YB, Cueto S, et al. Developmental potential in the first 5 years for children in developing countries. Lancet. 2007;369:60-70.
3. Nurturing care practice guide: strengthening nurturing care through health and nutrition services, United Nations Children's Fund, and World Health Organization, 2022. [Internet]. Accessed Feb 13, 2023. Available from: *https://apps.who.int/iris/bitstream/handle/10665/365601/9789240058651-eng.pdf?sequence=1&isAllowed=y*
4. Improving early childhood development: WHO guideline. World Health Organization; 2020. Accessed May 22, 2023. Available fropm: *https://www.who.int/publications/i/item/97892400020986.*
5. Pellegrini AD, Smith PK. The development of play during childhood: forms and possible functions. Child and Adolescent Mental Health. 1998;3:51-7.
6. Kelly-Vance L, Dempsey J, Ryalls B. The effect of a parent training program on children's play. International J Psychology. 2013,13:117-38.
7. Shah R, Camarena A, Park C, et al. Healthcare-based interventions to improve parenting outcomes in lMIC: a systematic review and meta-analysis. Matern Child Health J. 2022;26: 1217-30.
8. Shah R, DeFrino D, Kim Y, Atkins M. Sit down and play: a preventive primary care-based program to enhance parenting practices. J Child and Family Studies. 2017;26:540-7.
9. Shah R, Gustafson E, Dhaded S, et al. Integrating an adapted, low-intensity program to promote early childhood development in routine health visits in rural India: A feasibility study. J Dev Behav Pediatr. 2020;41:281-8.
10. Shah R, Herekar V, Metgud D, et al. Implementing an early childhood development intervention with routine immunization visits in India: a feasibility trial. Eur J Pediatr. 2022; 181:2799-808.
11. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics. 2005;4:287-91.
12. Bandura A. Health promotion by social cognitive means. Health Edu Beh. 2004;31:143-64.
13. Mendelsohn AL, Cates CB, TamisLeMonda CS, Dreyer BP. StimQ cognitive home environment. Accessed May 22, 2023. Available at: *https:// www.videointeractionproject.org/stimq.html*.
14. Malhi P, Menon J, Bharti B, Sidhu M. Cognitive development of toddlers: does parental stimulation matter? Indian J Pediatr. 2018;85:498-503.
15. Dreyer BP, Mendelsohn AL, Tamis-LeMonda CS. Assessing the child's cognitive home environment through parental report; reliability and validity. Early Development and Parenting. 1996;5:271-87
16. Madaan P, Saini L, Sondhi V. Development assessment scale for Indian infants: A systematic review and perspective on dwindling cutoffs. Indian J Pediatr. 2021;88:918-20.
17. Hamadani JD, Mehrin SF, Tofail F, et al. Integrating an early childhood development programme into Bangladeshi primary health-care services: an open-label, cluster-randomised controlled trial. Lancet Global Health. 2019;7:e366-75.

RESEARCH PAPER

Etiology and Outcomes of Rapidly Progressive Glomerulonephritis in Children: A Retrospective Cohort Study

Bobbity Deepthi,[1] Sriram Krishnamurthy,[1] Rajesh Nachiappa Ganesh,[2] Amar Murdeshwar,[1] Sachit Ganapathy,[3] Sudarsan Krishnasamy,[1] Pediredla Karunakar[1]

[1]*Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry.*
[2]*Department of Pathology, JIPMER, Puducherry.*
[3]*Department of Biostatistics, JIPMER, Puducherry.*

Correspondence to:
Dr Sriram Krishnamurthy,
Professor, Department of Pediatrics,
JIPMER, Puducherry 605006.
drsriramk@yahoo.com
Received: January 27, 2023;
Initial review: February 25, 2023;
Accepted: March 29, 2023.

Objective: To study the clinico-etiological spectrum and outcomes of children with rapidly progressive glomerulonephritis (RPGN).

Methods: This retrospective cohort study evaluated patients <18 years with RPGN, over an 8-year period (2014-2022), for etiology and kidney outcomes.

Results: Among 68 RPGN cases [median age 10 (7,12) years], 23 (33.8%) had lupus nephritis, 21 (30.9%) C3 glomerulopathy, and 15 (22.1%) infection-related glomerulonephritis (IRGN). At presen-tation, 18 (26.4%) patients had pulmonary edema, 20 (29.4%) had hypertensive emergency and 22 (32.4%) required dialysis. Median (IQR) follow-up duration was 24.5 (12,48) months. The median (IQR) admission eGFR was 19 (10.93, 38.60) mL/min/1.73 m^2, which increased to 126 (102.7,142) mL/min/1.73m^2 at the last follow-up. At the last follow-up, 39 (57.3%) and 13 (19.1%) patients attained complete and partial renal recovery, respectively; while 16 (23.5%) progressed to CKD stage 2 and beyond. The prevalence of end stage kidney disease (ESKD) was 7.3% at 1-year and 7.7% at the last follow-up. Factors predicting kidney survival were duration of symptoms prior to presentation ≥7 days, crescents ≥37.5%, and presence of fibrous crescents/segmental sclerosis.

Conclusion: Lupus nephritis, was the commonest etiology of RPGN in children. Renal outcomes were determined by pre-admission symptoms, and percentage and stage of crescents.

Keywords: *Crescentic glomerulonephritis, Kidney survival, Lupus nephritis, C3-glomerulopathy*.

Rapidly progressive glomerulonephritis (RPGN) is a medical emergency and is histopathologically characterized by the presence of crescents [1,2]. Kidney outcomes described in this condition are heterogenous, with rates of end stage kidney disease (ESKD) ranging from 10-51% [2-6]. Though, classically defined as presence of ≥50% crescents on renal biopsy, the presence of even a single crescent may have an influence on the kidney outcomes [2,4,6,7]. Many previous studies on RPGN have used varying inclusion criteria ranging from a single crescent to ≥75% [2,4,7-13].

There is a paucity of information regarding the etiology and outcomes of children with RPGN from India. The primary objective of this study was to determine the clinico-etiological profile of RPGN, while the secondary objectives were to study the outcomes in these children and evaluate the determinants of kidney survival.

METHODS

A retrospective cohort of patients aged <18 years with suspected RPGN who underwent kidney biopsy and were under follow-up at the pediatric nephrology inpatient services of our referral hospital over an 8-year period (2014-2022) were screened and enrolled into the study. The data of the children with RPGN who died were retrieved from the medical records available in the hospital information system. The study was approved by the Institute Ethics committee and informed consent was obtained from the parents prior to inclusion of patients into the study. Eligible subjects included patients aged <18 years with rapidly progressive renal failure who underwent kidney biopsy and demonstrated at least one crescent on light microscopy in a core containing ≥10 glomeruli and had a minimum follow-up of ≥12 months [2,4]. Data regarding clinical presentation, etiology, course, therapy received, biochemical features and biopsy were recorded in a predesigned proforma. Hematuria was defined as >5 red blood cells (RBCs)/high power field in centrifuged urine [14]. Proteinuria was defined as urine dipstick 1+ or more and/or spot urine protein: creatinine ratio (Up:Uc) >0.2 mg/mg. Up:Uc was graded into nephrotic range (Up:Uc >2) and sub-nephrotic range (0.2-2) [15]. Standard definitions

were used for defining and staging hypertension [16]. Acute nephritic syndrome was defined as acute onset of hematuria (gross or microscopic) with proteinuria; in the presence of edema, hypertension, or oliguria [14]. eGFR was calculated by modified Schwartz formula [17]. Acute kidney injury (AKI) was diagnosed and staged as per KDIGO guidelines [18]. Oliguria was defined as urine volume <0.5 mL/kg/h for 6 hours [18]. End-stage kidney disease was defined as eGFR of less than 15 mL/min/1.73 m^2.

RPGN was defined as a rapid decline in renal function (50% decline in estimated glomerular filtration rate (eGFR)) within few days to weeks, in children presenting with acute nephritic syndrome, histologically characterized by the presence of at least one crescent [2,4]. Light microscopy, immunofluorescence and wherever possible, electron microscopy findings, were recorded. A crescent was defined as extra capillary proliferation of more than two cell layers involving >10% glomerular circumference [19]. Crescents were classified as cellular, fibrocellular, or fibrous. Based on the composition of the crescents, following terms were used: Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix; Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin; and Fibrocellular crescent*:* 25-75% cells and fibrin and the remainder fibrous matrix [19]. The pattern and intensity of staining for immunoglobulins (IgG, IgA, IgM, kappa, and lambda light chains), C3 and C1q on direct immunofluorescence was recorded. Standard criteria were used for diagnosing infection-related glomerulonephritis (IRGN), lupus nephritis, IgA vasculitis, IgA nephropathy, C3 glomerulopathy (C3G), immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN), anti-glomerular basement membrane (GBM) disease and pauci-immune glomerulonephritis [20-27].

Etiology of glomerulonephritis was ascertained based on clinical, serological, and histopathological data. The management of RPGN included supportive care in the form of fluid and electrolyte balance, dialysis if indicated, therapy of coexisting hypertension and infections along with definitive treatment by induction of remission and maintenance of remission. Remission was induced with three pulses of intravenous methylprednisolone followed by intravenous cyclophosphamide for 6 doses at 4-week intervals and oral prednisolone tapered to minimal alternate day dose in children. Thereafter, appropriate management was done for maintenance as per the underlying etiology (e.g., mycophenolate mofetil for 3 years for lupus nephritis) [23]. RPGN secondary to IRGN was managed with IV methylprednisolone pulses followed by tapering doses of prednisolone for 3-6 months. Additional therapies like plasma exchange (PLEX) or rituximab were used in situations such as refractory lupus nephritis.

Outcomes were categorized as: *i*) complete renal recovery (Up:Uc<0.2; serum albumin ≥3 g/dL, no hypertension and estimated GFR ≥90 mL/min/1.73 m^2), *ii*) partial renal recovery (Up:Uc 0.2-2; hypertension (BP >95th centile), and estimated GFR ≥90 mL/min/1.73 m^2), *iii*) chronic kidney disease (CKD) stage 2 and beyond, and *iv*) mortality [7]. Kidney survival time was defined as time from diagnosis till being free of CKD G2, G3a, G3b, G4, G5 or death.

Statistical analysis: Data were analyzed using SPSS version 19.0. Kolmogorov-Smirnov test was used to assess normality of continuous variables. Categorical variables were compared using Chi-square test or Fisher exact test. Continuous variables were compared using Student *t* test or Mann whitney *U* test. Spearman correlation test was used for measuring the correlation between percentage of crescents and eGFR at last follow-up and renal outcomes. Receiver operating characteristic (ROC) curve analysis was performed to find the optimum cutoff for percentage of crescents in predicting kidney survival and Youden index was calculated. The effect of etiology of the disease and percentage of crescents on kidney survival was plotted as a survival function using Kaplan- Meier curves. Log-rank test was used to compare the survival function of various etiologies on kidney survival. Kruskal-Wallis test was performed assess the difference in median eGFR levels at admission and last follow-up between different etiologies. Univariate Cox regression was performed to identify potential risk factors associated with kidney survival. The variables that were found to be significant were further included in the multiple cox regression model. Adjusted hazard ratios (HR) with 95% confidence intervals were estimated. *P* value less than 0.05 was considered as statistically significant.

RESULTS

Among the 102 kidney biopsies done for suspected RPGN during this period, 68 had atleast one crescent with adequate kidney tissue. These 68 cases (34, 50% females) with crescents were finally considered as RPGN. The 34 patients who did not have crescents on kidney biopsy were cases of IRGN with diffuse proliferative glomerulonephritis on light microscopy with IgG and C3 deposits on immunofluorescence. The median (IQR) duration of follow-up of the cohort was 24.5 (12,48) months.

The median (IQR) age at disease presentation was 10 (7,12) years. At the time of diagnosis, 64 (94.1%) were hypertensive, 37 (54.4%) had nephrotic-range proteinuria and 60 (88%) had oliguria; 27 (40%) had anasarca at presentation and and 18 (26.4%) patients had pulmonary edema, 20 (29.4%) hypertensive emergency and 22 (32.4%) required dialysis at presentation. Twelve children (17.6%) had posterior reversible encephalopathy syndrome (PRES)

Table I Baseline Characteristics of Children With Rapidly Progressive Glomerulonephritis (RPGN) (*N*=68)

Parameters	*Value*
Duration of symptoms at presentation (d)	6 (5, 11.5)
Hypertension at admission[a]	64 (94.1)
Proteinuria at admission	
Nephrotic range proteinuria (Up:Uc >2)[a]	37 (54.4)
Proteinuria (mg/mg)[b]	8.4 (2.2)
Sub-nephrotic range proteinuria (Up: Uc 0.2-2)[a]	26 (38.2)
Proteinuria (mg/mg)[b]	0.81 (0.3)
Up:Uc <0.2[c]	5 (7.35)
Serum albumin at presentation (g/dL)[b]	2.81 (0.59)
Peak serum creatinine in hospital (mg/dL)	2.67 (1.50, 4.18)
KRT requirement[a]	22 (32.4)
Duration of PICU stay (d) (*n*=21)[a]	7 (4.5, 8)
Length of hospital stay (d)	15 (12, 20)

Values in median (IQR), [a]no. (%) or [b]mean (SD). [c]These five patients had urine albumin positivity on urine dipstick (1+ or 2+). eGFR: estimated glomerular filtration rate; Up:Uc-urine protein to urine creatinine ratio; KRT: kidney replacement therapy, PICU: pediatric intensive care unit.

(**Table I**). The median (IQR) eGFR at admission in the enrolled cases was 19 (10.93, 38.60) mL/min/1.73m^2, which improved to 126 (102.7,142) mL/min/1.73m^2 at the last follow-up (*P*<0.001) (**Web Fig. 1**).

All enrolled patients had immune-complex mediated crescents. The most common etiologies included lupus nephritis [23 (33.8%)], C3G [21 (30.9%)] and IRGN [15 (22.1%)]. Other etiologies included IgA nephropathy [5 (7.4%)], IC-MPGN [3 (4.4%)], and IgA vasculitis [1 (1.5%)]. Among 23 lupus nephritis patients, eighteen children were classified as lupus nephritis class IV and five were lupus nephritis Class III. Among 21 children with C3G, electron microscopy was available for four children. Three of these showed C3 glomerulonephritis, while one showed Dense deposit disease. The median duration of symptoms prior to presen-tation was 6 (5, 11.5) days, with IRGN demonstrating the shortest periods between onset of symptoms and diagnosis [4 (3,6) days], in comparison to lupus nephritis [10 (5,14) days] and IgA nephropathy [7 (6.5-17) days] (*P*=0.003).

The median (IQR) glomeruli on kidney biopsy samples of the cohort were 16 (11,23). The median (IQR) proportion of glomeruli showing crescents was 27 (5-62) % in IgA nephropathy (*n*=5), 11 (5-40) % in lupus nephritis (*n*=23), and 9 (5-42.5) % in C3G (*n*=21). There was a significant negative correlation between the percentage of crescents and eGFR at the last follow-up [Spearman *P*=-0.281, *P*=0.02]. Based on ROC curve analysis with an area under curve (AUC) of 0.7, kidney outcomes of the study were also noted based on a crescent cutoff of 37.5% (maximum Youden index) (**Fig. 1**). The crescent threshold of 37.5% provided a sensitivity of 52% and specificity of 85% against a much lower sensitivity of 36% with percentage threshold of 50% in this cohort. 33 patients in the cohort had a single crescent, out of which 5 (7.35%) progressed to CKD 2 and beyond. Crescents involving ≥37.5%-50% glomeruli were seen in five patients, out of which two progressed to ESKD; 2 had partial renal recovery and 1 attained complete renal recovery. Crescents in >50% glomeruli were seen in 9 (13.2%) patients out of which five progressed to ESKD (3 of these patients died within 6 months of initial diagnosis), and four achieved only partial remission at the last follow-up of 12 (6,30) months. Fibrocellular and fibrous crescents were found in 14 (20.5%) children [LN (*n*=7), C3G (*n*=4) and IgA nephropathy (*n*=3]. Endocapillary hypercellularity, segmental sclerosis, acute tubular necrosis and tubular atrophy were seen in 59 (86.7%), 17 (25%), 14 (20.5%) and 3 (4.4%) patients, respectively.

Twenty-two cases (32.4%) required a median (IQR) 6 (4,9) hemodialysis sessions. PLEX was performed in one child with refractory lupus-associated thrombotic micro-angiopathy.

Of the initial cohort of 68 children, six children died during the follow-up period. Out of these, three children with lupus nephritis class IV progressed to ESKD within 100 days of initial presentation and died, while 3 other children with C3G, lupus nephritis class III, and lupus nephritis class IV

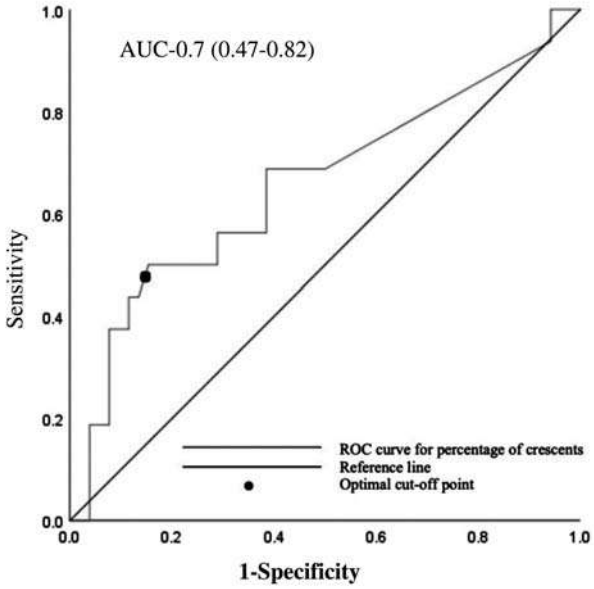


Fig. 1 Receiver operating characteristic (ROC) curve for discriminatory ability of percentage of crescents for the study outcome.

Table II Outcomes of Rapidly Progressive Glomerulonephritis in Children at the Last Follow-up (*N*=68)

Parameter	*Value*
Complete renal recovery	39 (57.3)
Lupus nephritis (*n*=23)	11 (47.8)
C3 glomerulopathy (*n*=21)	8 (38)
IRGN (*n*=15)	15 (100)
IgA nephropathy (*n*=5)	3 (60)
IC-MPGN (*n*=3)	1 (33)
IgA vasculitis (*n*=1)	1 (100)
Partial renal recovery	13 (19.1)
Persistent proteinuria	11 (16.2)
Persistent hypertension	13 (19.1)
Etiology	
Lupus nephritis (*n*=23)	5 (21.7)
C3 glomerulopathy (*n*=21)	7 (33.3)
IRGN (*n*=15)	0
IgA nephropathy (*n*=5)	1 (20)
IC-MPGN (*n*=3)	0
IgA vasculitis (*n*=1)	0
Chronic kidney disease	16 (23.5)
CKD 2	4 (5.8)
CKD 3a	1 (1.5)
CKD 3b	3 (4.4)
CKD 4	0
ESKD	8 (11.7)
eGFR (ESKD) (*n*=8)[a]	12.5 (10.75,15)
Persistent proteinuria	8 (11.7)
Persistent hypertension	11 (16.2)
Etiology	16 (23.5)
Lupus nephritis (*n*=23)	7 (30.4)
C3 glomerulopathy (*n*=21)	6 (28.5)
IRGN (*n*=15)	0
IgA nephropathy (*n*=5)	1 (20)
IC-MPGN (*n*=3)	2 (67)
IgA vasculitis (*n*=1)	0

Value in no. (%) or [a]median (IQR). of the 68 children, 6 died during follow-up. eGFR:estimated glomerular filtration rate; CKD:chronic kidney disease; ESKD: end stage renal disease; IC:MPGN: immune complex membranoproliferative glomerulonephritis; IRGN: infection related glomerulonephritis.

died at 2 years (progression to ESKD), 5 years (progression to ESKD) and 6 years (*Neisseria oblongata*- infective endocarditis) of initial presentation. Overall, by the time of the last follow-up [median (IQR) 24.5 (12,48) months], out of the 68 children, 39 (57.3%) achieved complete renal recovery, 13 (19.1%) had partial renal recovery and 16 (23.5%) progressed to CKD stage 2 and beyond (**Table II**). The median (IQR) kidney survival time in children who progressed to CKD (*n*=16) in our cohort was 3.2 (3,5) months. Kidney survival was 77.9 % at 1-year follow-up and 76.4 % at 8 years follow-up (**Fig. 2).** The prevalence of end

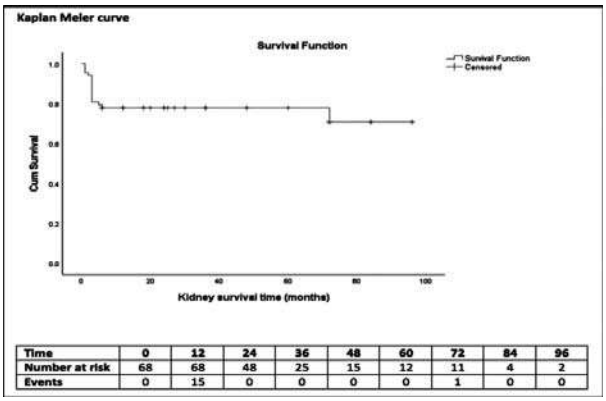


Fig. 2 Kaplan-Meier analysis curve depicting the survival function of patients with rapidly progressive glomerulonephritis (RPGN).

stage kidney disease (ESKD) was 7.3% at one-year follow-up and 7.7 % at the last follow-up.

On univariate analysis, factors predicting kidney survival were duration of symptoms prior to presentation >7 days (*P*=0.001), percentage of crescents ≥37.5%, presence of fibrous crescents (*P*=0.005) and segmental sclerosis (*P*=0.014). On multivariate analysis, duration of symptoms prior to presentation was found to be independently associated with renal survival (**Table III**). The kidney survival of the entire cohort was plotted as Kaplan-Meier survival

Table III Predictors of Kidney Survival Among Children With Rapidly Progressive Glomerulonephritis

Characteristics	*HR (95% CI)*	*P value*
Duration of symptoms >7d[a]	6.50 (2.09, 20.22)	0.001
eGFR at admission (< 60 mL/min/1.73 m^2)	-	0.308
Requirement of KRT	2.46 (0.89-6.79)	0.092
Duration of KRT ≥14 d	2.59 (0.50-13.55)	0.259
Etiology		
Lupus nephritis	1	-
C3 glomerulopathy	1.14 (0.34-3.84)	0.829
IRGN	0.32 (0.04-2.68)	0.291
IgA nephropathy	0.79 (0.09-6.53)	0.823
IC-MPGN	1.88 (0.39-9.07)	0.434
Time to resolution of oliguria ≥14 d	2.14 (0.13-34.77)	0.593
Crescents (≥37.5 %)	4.25 (1.57-11.49)	0.004
Fibrous crescents	4.22 (1.54-11.54)	0.005
Endocapillary hypercellularity	0.90 (0.25-3.16)	0.864
Segmental sclerosis	3.43 (1.28-9.18)	0.014

[a]on multivariate analysis; HR (95% CI) 5.02 (1.49-16.85); P=0.009. eGFR:estimated glomerular filtration rate; KRT: kidney replacement therapy; HR: Hazards ratio; IRGN: infection related glomerulonephritis; IC-MPGN: Immune complex mediated membranoproliferative glomerulonephritis.

WHAT THIS STUDY ADDS?

- Lupus nephritis was the commonest etiology of rapidly progressive glomerulonephritis (RPGN).
- The kidney survival and outcomes were predicted by duration of symptoms prior to presentation in RPGN.

analysis (**Fig. 2**). The effect of crescents and etiology of RPGN on kidney survival time was also analyzed (**Web Fig. 2**). The duration of symptoms prior to presen-tation >7 days (P=0.012), percentage of crescents ≥37.5% (P=0.002), presence of fibrous crescents (P=0.014) and presence of segmental sclerosis (P=0.003) were found to be higher among deaths (n=6) than survivors (n=62).

DISCUSSION

This retrospective cohort study included 68 children with RPGN. All the enrolled patients had immune-complex glomerulonephritis, lupus nephritis being the single largest group. Overall, by a median 24 month follow-up, 39 (57.3%) achieved complete renal recovery, 13 (19.1%) had partial renal recovery, and 16 (23.5%) progressed to CKD stage 2 and beyond.

The absence of pauci-immune disease in the cohort is a unique feature. It remains to be seen whether similar findings from our geographical region are replicated in other studies. Previously published studies from India have reported IRGN as the major etiological category [6-8]. However, a decade later, Sinha, et al. [7] reported pauciimmune glomerulonephritis as the major etiology in 52.7% of 36 cases, suggesting either a shifting etiology or a referral bias. A retrospective study from Saudi Arabia [13] identified lupus nephritis as the commonest etiology (54.1%). IRGN, especially due to Streptococcus, remains the dominant form of glomerulonephritis in developing countries. A recently published study [2] on 305 patients with acute glomerulonephritis and at least one crescent, showed IgA nephropathy (23%), lupus (21%), and IgA vasculitis (19%) to be the dominant causes. These differences could be potentially attributed to ethnic or environmental factors.

Many previous authors have defined children with ≥50% crescents as crescentic glomerulonephritis, while some included patients with crescents ranging from as low as 20% to as high as 75% [5-9,13]. However, there are major diagnostic and clinical implications of the presence of even one crescent on kidney biopsy [2], with only two previous pediatric studies with above inclusion criteria [2,4]. A large registry recently recruited patients with 3-100% (median 20%) crescents, and noticed adverse kidney outcomes even with 1% increase in percentage of crescents. The prevalence of ESKD was 12% at one year and 16% at last follow-up [2]. The percentage of crescents was found to be inversely related to eGFR at the last follow-up in our study, validating similar results in a German cohort [4]. The utility of 10% and 25% thresholds for cellular and fibrocellular crescents in children has been demonstrated earlier in lupus nephritis [20,28]. We found similar kidney survival rates at 1-year follow-up and at the last follow-up. Majority of our patients progressing to ESKD did so within the initial 12 months.

As expected, non-IRGN etiologies had higher rates of progression to ESKD in our study, which is in consonance with previous reports [1]. Our results were in agreement with a recent report that showed a threshold of 43% crescents as a predictor of adverse outcomes [2]. Diverse factors such as duration of disease, etiology of crescentic glomerulonephritis, presence of fibrous crescents, degree of tubular atrophy/interstitial fibrosis and necrosis on kidney biopsy, age, nephrotic syndrome, arterial hypertension, oliguria at presentation, need for dialysis and relapses have been reported earlier, to be related to outcome in crescentic glomerulonephritis [2,4,7,8].

The study being retrospective in nature has its inherent limitations. Since it is a study from a single tertiary care centre, the results may not be generalizable to the community level. Being a referral centre, we would have encountered a greater proportion of lupus nephritis, IgA nephropathy and C3 glomerulonephritis. We could not perform electron microscopy for all the C3 glomerulopathy cases, which would have helped to further classify them. Finally, the threshold of 37.5% was chosen for our cohort based on the maximum Youden index. However, the same may not have external validity and needs to be assessed in future cohorts from various ethnicities.

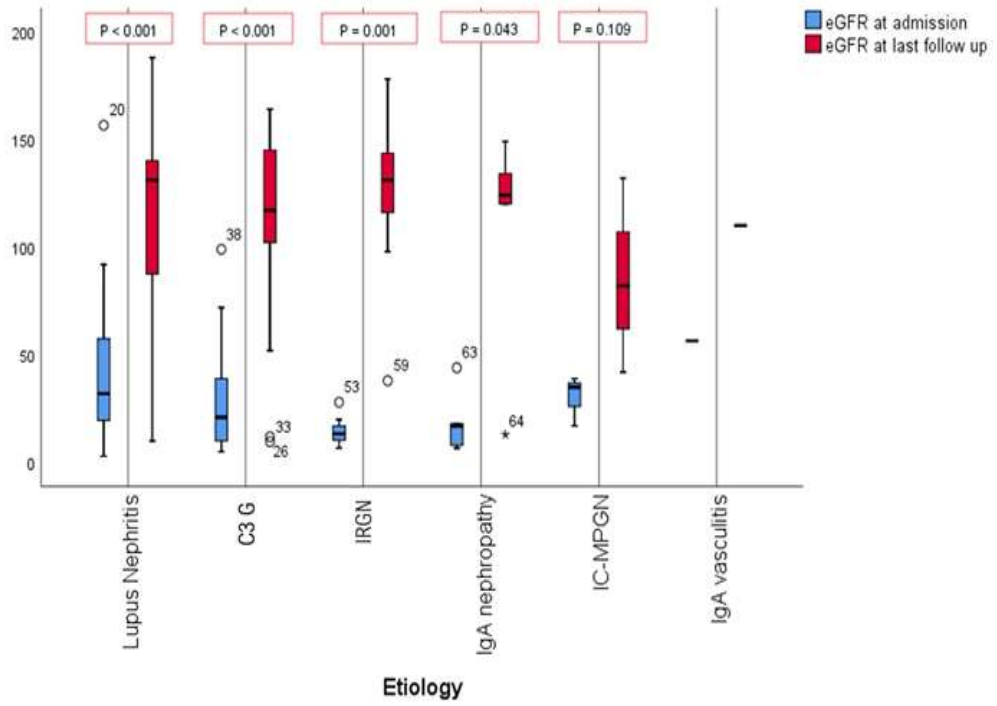
To summarize, this study showed lupus nephritis, C3G and IRGN to be the predominant etiologies of RPGN. The renal outcomes and survival in these patients were predicted only by duration of symptoms prior to presentation.

Ethics approval: Approved by the Ethics Committee of the institute; No. JIP/IEC/2022/0117 dated May 11, 2022.
Contributors: BD, SK, AM, PK, SuK: managed the patients. BD conceptualized the study design and participated in study protocol preparations, recruited patients, participated in data analysis, and drafted the first version of the manuscript. SK conceptualized the study design and critically revised the manuscript. RNG interpreted the histopathology findings. SG helped in statistical analysis. All authors contributed to drafting of the manuscript and approved the final version.

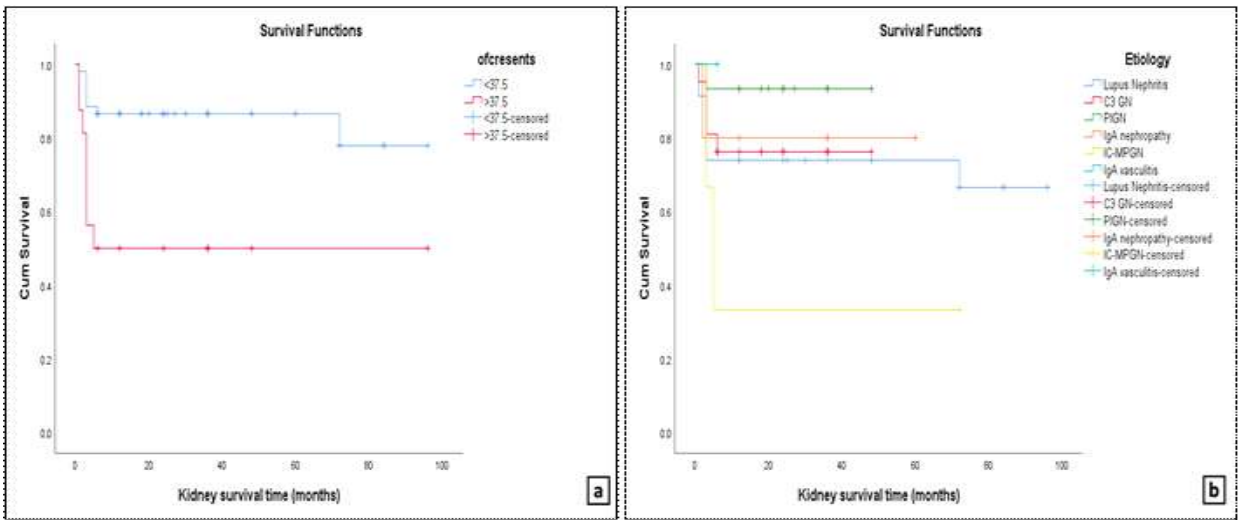
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Trimarchi H. Crescents in primary glomerulonephritis: a pattern of injury with dissimilar actors. A pathophysiologic perspective. Pediatr Nephrol. 2022;37:1205-14.
2. Maliakkal JG, Hicks MJ, Michael M, et al. Renal survival in children with glomerulonephritis with crescents: A pediatric nephrology research consortium cohort study. J Clin Med. 2020; 9:2385.
3. The Southwest Pediatric Nephrology Study Group. A clinicopathologic study of crescentic glomerulonephritis in 50 children. A report of the Southwest Pediatric Nephrology Study Group. Kidney Int.1985;27:450-58.
4. Mayer U, Schmitz J, Brasen JH, Pape L. Crescentic glomerulonephritis in children. Pediatr. Nephrol. 2020;35: 829-42.
5. Jardim HM, Leake J, Risdon RA, Barratt TM, Dillon MJ. Crescentic glomerulonephritis in children. Pediatr. Nephrol. 1992;6:231-35.
6. Srivastava RN, Moudgil A, Bagga A, et al. Crescentic glomerulonephritis in children: A review of 43 cases. Am. J. Nephrol. 1992;12:155-61.
7. Sinha A, Puri K, Hari P, et al. Etiology and outcome of crescentic glomerulonephritis. Indian Pediatr. 2013;50:283-88.
8. Dewan D, Gulati S, Sharma RK, et al. Clinical spectrum and outcome of crescentic glomerulonephritis in children in developing countries. Pediatr Nephrol. 2008;23 :389-94.
9. Ozlu SG, Caltik A, Aydog O, et al. Crescentic glomerulonephritis in children: A single centre experience. World J Pediatr. 2016;12:225-30.
10. Koyama A, Yamagata K, Makino H, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: Etiology, prognosis and treatment diversity. Clin. Exp. Nephrol. 2009;13:633-50.
11. Rampelli SK, Rajesh NG, Srinivas BH, et al. Clinical spectrum and outcomes of crescentic glomerulonephritis: A single center experience. Indian J Nephrol. 2016 ;26:252-6.
12. Gupta R, Singh L, Sharma A, et al. Crescentic glomerulonephritis: A clinical and histomorphological analysis of 46 cases. Indian J Pathol Microbiol. 2011;54:497-500.
13. Alsaad, K, Oudah N, Al Ameer A, et al. Glomerulonephritis with crescents in children: Etiology and predictors of renal outcome. ISRN Pediatr. 2011;2011:507298.
14. Vijayakumar M. Acute and crescentic glomerulonephritis. Indian J Pediatr. 2002;69:1071-75.
15. Sinha A, Bagga A, Banerjee S, et al. Expert Group of Indian Society of Pediatric Nephrology. Steroid Sensitive Nephrotic Syndrome: Revised Guidelines. Indian Pediatr. 2021;58: 461-81.
16. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017;140:e20171904.
17. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics.1976;58: 259-63.
18. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012; 2: 1-138.
19. Haas M, Seshan SV, Barisoni L, et al. Consensus Definitions for Glomerular Lesions by Light and Electron Microscopy: Recommendations From a Working Group of the Renal Pathology Society. Kidney Int. 2020;98:1120-34.
20. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society Classification for Lupus Nephritis: Clarification of Definitions, and Modified National Institutes of Health Activity and Chronicity Indices. Kidney Int. 2018;93:789-96.
21. Weening JJ, D'Agati VD, Schwartz MM, et al. International Society of Nephrology Working Group on the Classification of Lupus Nephritis; Renal Pathology Society Working Group on the Classification of Lupus Nephritis. The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. Kidney Int. 2004; 65:521-30.
22. Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis. 2006;65:936-41.
23. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;S115-S193.
24. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013; 368:2402-14
25. Leung AKC, Barankin B, Leong KF. Henoch-Schönlein purpura in children: An updated review. Curr Pediatr Rev. 2020; 16:265-76.
26. Pickering MC, D'Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013;84:1079-89.
27. Gunasekaran K, Krishnamurthy S, Mahadevan S, et al. Clinical characteristics and outcome of post-infectious glomerulonephritis in children in southern India: A prospective study. Indian J Pediatr. 2015;82:896-903.
28. Patel P, de Guzman M, Hicks MJ, et al. Utility of the 2018 revised ISN/RPS thresholds for glomerular crescents in childhood-onset lupus nephritis: A Pediatric Nephrology Research Consortium study. Pediatr Nephrol. 2022;37: 3139-45.



Web Fig. 1 Box and whisker plot showing eGFR at admission and at the last follow-up in rapidly progressive glomerulonephritis (RPGN) due to different etiologies.



Web Fig. 2. Kaplan-Meier survival curves for patients with rapidly progressive glomerulonephritis (RPGN) *a*) depicting the effect of percentage of crescents e" 37.5% and <37.5%, and b) depicting the effect of different etiologies

RESEARCH PAPER

Relationship of Serum Periostin With Asthma Control in Children: Single Center Experience

SARITA CHOUDHARY,[1] PRAWIN KUMAR,[1] MITHU BANERJEE,[2] KULDEEP SINGH,[1] JAGDISH PRASAD GOYAL[1]
[1]*Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan.*
[2]*Department of Biochemistry, All India Institute of Medical Sciences, Jodhpur, Rajasthan.*

Correspondence to:
Dr Jagdish Prasad Goyal, Professor,
Department of Pediatrics,
All India Institute of Medical Sciences,
Jodhpur, Rajasthan.
jpgoyal@rediffmail.com
Received: Mar 22, 2023;
Initial review: April 10, 2023;
Accepted: May 26, 2023.

Objective: To determine the association between serum periostin levels and asthma control in children. **Methods:** Children aged 6-17 years with physician-diagnosed asthma were enrolled in the study. Age-matched (±2 years) control children, who visited our outpatient department with non-respiratory complaints, were also enrolled. **Results:** A total of 90 children (60 with asthma and 30 control subjects) with a mean (SD) age of 12.1 (2.77) years were enrolled. Children with asthma had significantly higher median (IQR) periostin levels than the controls [23.5 (22,26) vs 22 (19.4, 22.96); *P*= 0.04]. On multivariable logistic regression analysis, serum periostin levels were associated with poor asthma control in children [OR (95% CI), 1.12 (1.01-1.24); *P*= 0.02]. Age, body mass index, IgE levels, eosinophil count, forced expiratory volume in first minute (FEV1) and presence of allergic rhinitis did not have any association with asthma control. **Conclusions:** Asthmatic children have a high serum periostin level, and its higher levels are associated with poor asthma control.

Keywords: *Airway inflammation, IgE levels, Management, Outcome.*

Published online: May 23, 2023; **PII**:S097475591600552

Asthma is a common chronic diseases in children, and type 2 airway inflammation is the primary feature of the disease. The emergence of biomarkers associated with underlying airway inflammation is an active research area in adults and children [1,2]. Searching for novel molecules for asthma phenotype found that periostin is a downstream molecule of interleukin-4/13, signature cytokines of type 2 inflammation. It is an extracellular matrix protein that belongs to the fasciculin family and acts as a matricellular protein that activates the cell by binding to its receptor on the cell surface. This critical molecule links type-2 airway inflammation and remodeling and, in the bronchial epithelial cells, is upregulated by type 2 cytokines IL-4 and IL-13 [3].

Despite the well-known interaction of periostin in asthma pathophysiology, there is a lack of evidence regarding the potential role of periostin levels in children for better asthma control. The primary objective of the study was to determine the association between serum periostin levels and asthma control in children. The secondary objectives were to determine the relationship between the blood eosinophils counts, serum immunoglobulin (IgE) levels, and pulmonary function test with the asthma control and the comparison of serum periostin levels in asthma and control groups.

METHODS

This cross-sectional study was conducted in the pediatric chest clinic at a tertiary care institute from January, 2020 to December, 2021. Ethical approval was taken from the institutional ethics committee. We took a sample of convenience of 90 children due to the available periostin kit in the market, which could perform 90 tests. We recruited 60 children with asthma and 30 unaffected children as controls.

Children aged 6-17 year diagnosed with asthma, according to the Global Initiative of Asthma (GINA) guideline [4], having completed at least 12 weeks of inhaled corticosteroid (ICS) therapy, and in follow-up in the clinic were enrolled in the study. We recruited eligible children after obtaining written informed consent from a parent and assent from children. Age-matched (±2 years) controls were taken from the otherwise well children who had come for minor complaints to the outpatient department. The children in the control group had no history of wheezing or infection during the last four weeks before the study enrolment.

Asthma control status in the study group was evaluated as per the childhood asthma control test (C-ACT) in children 4-11 years of age [5], and the asthma control test (ACT) in children 12 years and older [6]. Patients with an acute exacerbation of asthma requiring systemic corticosteroids

during the previous three months, and those with other known systemic disorders were excluded. All the patients underwent skin prick tests using common allergens. Histamine and normal saline were used as positive and negative controls, respectively. Wheal circumference greater than 3 mm than the negative control was considered positive. Children were weighed wearing minimal clothes and without shoes. Subsequently, the BMI *z* scores of participants were also calculated as per the Indian Academy of Pediatrics growth chart [7].

An automated Beckman Coulter counter determined blood eosinophil counts. The serum periostin was measured in all enrolled children by Human POSTN/OSF-2 (Periostin) ELISA Kit (Elbascience), and total IgE Elisa kit (Xema) was used to determine serum IgE levels. The kits were standardized as per the manufacturer's instructions. Pulmonary function tests were performed according to the American Thoracic Society recommendations (ATS) / European Respiratory Society (ERS) recommendations [8].

*Statistical analysis***:** All statistical analyses were performed by SPSS (22.0) (IBM SPSS Statistics for Windows, IBM Corporation). Categorical variables were expressed as frequencies. Normally distributed continuous data were expressed as mean and standard deviation, and non-normally distributed continuous data as median and interquartile ranges (IQR). The comparison of groups were carried out using Students *t* test, Mann-Whitney *U* test, as appropriate for the continuous, and the Chi-square test or Fisher test for categorical variables. The correlation coefficients between serum periostin level and other clinical variables were determined using Spearman rank correlation coefficient. Association of asthma control with different variables was examined using multivariate regression models adjusted for potential confounders. The odds ratio (OR) and 95% CI were reported. A *P* value <0.05 was considered statistically significant.

RESULTS

The mean (SD) age of the study participants was 12.1 (2.77) years. There was no significant difference in age, gender, and anthropometric parameters between the case and control groups. However, Serum periostin, eosinophil %, absolute eosinophil counts, total IgE levels, and aero-allergen sensitization were significantly higher in asthma than in the control group **(Table I)**

Most asthma patients were on step 3 of GINA asthma treatment. Of the 60 enrolled asthma patients, 26 (43.3%) had poor control based on the C-ACT/ACT scores. Serum periostin was significantly higher in the uncontrolled asthma patients as compared to control asthma patients (*P*=0.01) (**Fig. 1**). No significant difference was found in age, gender, allergic rhinitis, BMI, aeroallergen sensitization, eosinophils count/percentage, and IgE levels between well-controlled and uncontrolled asthma. We also found that patients, who were from rural areas, had poor asthma control (**Table II**)

Multivariable logistic regression analysis showed that serum periostin levels were associated with poor asthma control in children [OR (95%CI) 1.10 (1.01-1.63); *P*=0.03]. However, place of residence [OR (95%CI) 0.31 (0.06-1.63); *P*=0.17], and FEV1 [OR (95%CI) 0.97(0.94-1.00); *P*=0.08] were not significantly associated with asthma control. No correlation was found for serum periostin with age, BMI z score, C-ACT/ACT, total IgE levels, eosinophils count, and FEV1 (**Web Table I**).

Table I Baseline and Laboratory Characteristics of the Study Groups (*N*=90)

Variables	*Asthma (n=60)*	*Control (n=30)*
Age (y)	11.8 (3.04)	12.6 (2.1)
Male sex[a]	46 (76.67)	24 (80)
Height (cm)	-0.074 (1.17)	-0.16 (1.15)
Weight (kg)	-0.53 (1.10)	-0.23 (1.12)
BMI *z* score	-0.63 (1.09)	-0.17)1.14)
Serum periostin (ng/mL)[b,c]	23.5 (22,26)	22 (19.40,22.96)
Eosinophils[b,c]	6.75 (0.95,12.1)	1.25 (0.9,3.2)
Eosinophils (cells/mL)[b,c]	511.5 (75.9,765)	96.5 (35,179)
Total IgE (IU/mL)[b,c]	524 (292,1047.5)	131.35 (23.8,315)
Aeroallergen sensitization[a,c]	43 (71.67)	8 (26.67)

Values in mean (SD), [a]*no. (%), or* [b]*median (IQR) BMI: body mass index.* [c]*P<0.05.*

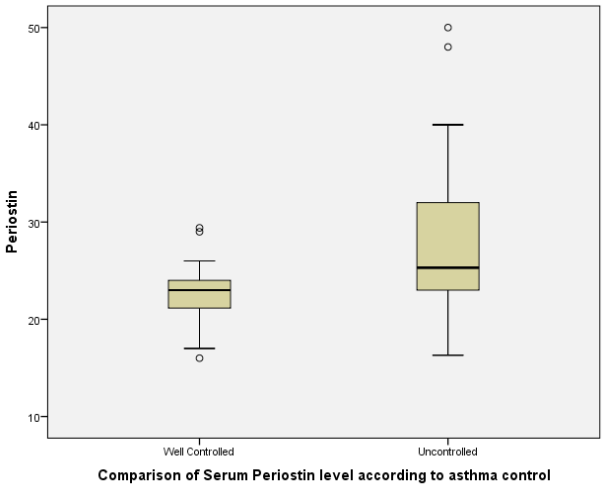


Fig. 1 Comparison of serum periostin level according to asthma control.

WHAT THIS STUDY ADDS?

- Elevated serum periostin level is associated with poor asthma control.

Table II Clinical and Laboratory Parameters of Children According to Asthma Control (*N*=60)

Variables	*Uncontrolled (n=26)*	*Controlled (n=34)*
Age (y)[a]	13 (11,14)	11 (9,14)
Male	19 (73)	27(79.4)
Rural residence[c]	23 (88.5)	22 (64.7)
Allergic rhinitis	23 (88.5)	28 (82.4)
BMI *z* score [a]	-0.53 (-1.23,0.01)	-0.42 (-1.5, 0.11)
Aeroallergen sensitization	17 (65.4)	26 (76.5)
Serum periostin (ng/mL)[a,c]	25.8 (23.2,33.5)	23 (21,24)
Eosinophils (%)[a]	9.1 (4.4, 14.3)	6.7 (3.8,10.6)
Eosinophils (per mL)[a]	739 (332, 1210)	511 (298,693)
Total IgE (IU/mL)[a]	560 (237,1047)	515 (333,996)
FEV1 (% predicted)[a,c]	80.5 (60.5,94)	93 (83,103)
C-ACT/ACT score[b,c]	16.0 (2.2)	23.4 (2.5)

Values in no. (%), [a]median (IQR) or [b]mean (SD). BMI: body mass index, FEV1: forced expiratory volume in 1 second; C-ACT: childhood asthma control test. [c]P<0.05.

DISCUSSION

This cross-sectional study found an association between serum periostin levels and poor asthma control in children. We also observed that serum periostin levels were significantly higher in children with asthma compared to age-matched control.

The findings of previous studies have demonstrated an association between serum periostin levels and asthma [9-11]. Researchers have also shown a statistically significant increase in serum periostin levels among uncontrolled asthmatic patients than those with adequately controlled asthma [12,13]. Park, et al. [14] found a statistically significant decrease in serum periostin level and bronchial wall thickness among patients with uncontrolled, asthma after being adequately and appropriately controlled, than their uncontrolled baseline states. On the other hand, Mena, et al. [15] observed that children with severe uncontrolled asthma had lower serum periostin levels as compared to children with non-severe uncontrolled asthma. The possible reasons, as cited by authors, may be that the level of serum periostin depends on the inflammatory process in asthma and this inflammatory mechanism is not a unique and isolated characteristic of each type of asthma patient. Similar to our findings, several childhood studies have demonstrated a relationship between IgE levels, eosinophil count, and asthma and found similar observations [12-14].

In this study, serum periostin did not correlate with age, BMI, total IgE level, AEC, % eosinophil, allergic rhinitis, and FEV1. The results of the correlation of serum periostin with different variables are inconsistent in the literature. An adult study [16] demonstrated that serum periostin was a better marker for eosinophilic airway inflammation in asthma, while a similar observation was not found in Indian research on children [17]. The lack of correlation in the present study might be due to the small sample size.

The current study recruited control children, in contrast to previous Indian studies, and therefore, serum periostin levels of healthy control children could be compared to those of children with asthma. We used GINA asthma criteria for the diagnosis of asthma in children and validated scores i.e., C-ACT/ACT, to evaluate asthma control.

Our sample size was small, and the study was under-powered due to convenience sampling. Moreover, periostin is a bone-derived protein secreted by osteoblasts. The fast linear development in children may impact the suggestive role of periostin in airway inflammation and asthma control. The study design was cross-sectional, and a longitudinal study would be better at exploring the effect of age.

In conclusion, we demonstrated high serum periostin levels in asthmatic children, and elevated serum periostin levels were associated with poor asthma control. It can be a better instrument in search of a biomarker that reflects the degree of inflammation in a chronic disease such as asthma. However, further longitudinal studies are required to better explain the function of periostin in the etiology of asthma and its therapeutic relevance for physicians treating children with asthma.

Ethics clearance: Institutional Ethics Committee, AIIMS; No. AIIMS/IEC/2019-20/957 dated Jan 1, 2020.
Contributors: SC: collected data and prepared the first draft of the manuscript; PK, MB: redefined the research idea and validated the data collection; KS: reviewed and edited the manuscript; JPG: developed the research idea, analyzed data, and edited the manuscript; All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: PG Thesis Grant AIIMS, Jodhpur;
Competing interests: None stated.

REFERENCES

1. Busse WW, Kraft M, Rabe KF, et al. Understanding the key issues in the treatment of uncontrolled persistent asthma with type 2 inflammation. Eur Respir J. 2021;58:2003393.
2. Licari A, Castagnoli R, Brambilla I, et al. Asthma endotyping and biomarkers in childhood asthma. Pediatr Allergy Immunol Pulmonol. 2018;31:44-55.
3. Izuhara K, Nunomura S, Nanri Y, et al. Periostin: An emerging biomarker for allergic diseases. Allergy. 2019;74:2116-28.
4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Assessed on Jan 20, 2022. Available from *www.ginaasthma.org*
5. Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol. 2007;119:817-25.
6. American Thoracic Society & European Respiratory Society. ATS/ERS recommendations for standardized procedures for the onlineand offline measurement of exhaled lower respiratory nitric oxideand nasal nitric oxide. Am J Respir Crit Care Med. 2005;171:912-30.
7. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, el al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol. 2006;117:549-56.
8. Indian Academy of Pediatrics Growth Charts Committee, Khadilkar V, Yadav S, et al. Revised IAP Growth Charts for Height, Weight, and Body Mass Index for 5- to 18-Year-Old Indian Children. Indian Pediatr. 2015; 52;47-55.
9. Yavuz ST, Bagci S, Bolat A, et al. Association of serum periostin levels with clinical features in children with asthma. Pediatr Allergy Immunol. 2021;32:937-44.
10. Song JS, You JS, Jeong SI, et al. Serum periostin levels correlate with airway hyper-responsiveness to methacholine and mannitol in children with asthma. Allergy. 2015;70:674-81.
11. Inoue T, Akashi K, Watanabe M, et al. Periostin as a biomarker for the diagnosis of pediatric asthma. Pediatr Allergy Immunol. 2016;27:521-6.
12. Al-Adawy ER, Gomaa AA, Mohamed AM. Correlation between serum periostin biomarker, spirometric airflow limitation, and airway dimensions by multidetector computed tomography in bronchial asthma. Egypt J Bronchol. 2018;12: 160-72.
13. Jia G, Erickson RW, Choy DF, et al. Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT) Study Group. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol. 2012;130:647-54.
14. Park CS, Müller NL, Worthy SA, et al. Airway obstruction in asthmatic and healthy individuals: inspiratory and expiratory thin-section CT findings. Radiology. 1997;203:361-7.
15. Habernau Mena A, Del PozoAbejón V, Rodríguez Vidigal FF, Bobadilla González P. Role of periostin in uncontrolled asthma in children (DADO study). J Investig Allergol Clin Immunol. 2017;27:291-98.
16. Jia G, Erickson RW, Choy DF, et al. Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT) Study Group. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol. 2012;130:647-54.
17. Kumar K, Singh M, Mathew JL, Vaidya PC, Verma Attri S. Serum periostin level in children with asthma. Indian J Pediatr. 2023;90:438-42.

Web Tabe I: Baseline and laboratory characteristics of the study groups (n=90)

Variables	Asthma (n=60)	Control (n=30)	p-value
Age, mean SD	11.8±3.04	12.6±2.1	0.23
Male sex, n (%)	46 (76.67)	24 (80)	0.12
Height (cm), mean SD	-0.074±1.17	-0.16±1.15	0.79
Weight (kg) , mean SD	-0.53±1.10	-0.23±1.12	0.20
BMI- Z score, mean SD	-0.63±1.09	-0.17±1.14	0.07
Serum Periostin (ng/ml), median (IQR)	23.5 (22,26)	22 (19.40,22.96)	0.04*
Eosinophils, median (IQR)	6.75 (0.95,12.1)	1.25 (0.9,3.2)	<0.01*
Eosinophils (/ml), median (IQR)	511.5 (75.9,765)	96.5 (35,179)	<0.01*
Total IgE (IU/ml), median (IQR)	524 (292,1047.5)	131.35 (23.8,315)	<0.01*
Aeroallergen sensitization n (%)	43 (71.67)	8 (26.67)	<0.01*

* Statistically significant

Web Table II Correlation Between Serum Periostin Level and Clinical Variables in Children With Asthma (*N*=60)

Variables	*Correlation coefficient*	*P value*
Age	0.068	0.06
BMI Z-score	0.170	0.19
Total IgE (IU/mL)	-0.056	0.67
Eosinophils (%)	0.092	0.48
Eosinophils (/mL)	0.055	0.67
FEV1	-0.182	0.18
Allergic rhinitis	-0.105	0.42

RESEARCH PAPER

N-Terminal Pro-Brain Natriuretic Peptide Levels in Kawasaki Disease, Sepsis and Other Febrile Illnesses

PARAMITA BANERJEE,[1] PRIYANKAR PAL,[1] SWATI CHAKRAVARTI,[1] SURUPA BASU,[2] NAZNEEN AHMED[1]

[1]*Department of Pediatric Medicine, Institute of Child Health, Kolkata, West Bengal.*
[2]*Department of Biochemistry, Institute of Child Health, Kolkata, West Bengal.*

Correspondence to:
Dr Priyankar Pal, Professor,
Department of Pediatrics,
Institute of Child Health,
11, Dr Biresh Guha Street,
Kolkata 700 017, West Bengal.
mailme.priyankar@gmail.com
Received: Jun 2, 2022;
Initial review: Aug 17, 2022;
Accepted: May 27, 2023.

Objectives: To compare the values of N-Terminal Pro–Brain Natriuretic Peptide **(**NT-proBNP) in acute phase of Kawasaki disease (KD), sepsis and other acute febrile illnesses. **Methods**: We conducted a cross-sectional study on 40 KD patients and 40 age- and sex-matched controls with sepsis and other febrile illnesses between January, 2019 and June, 2020. Complete blood count, C-reactive protein (CRP), liver and renal function tests, serum electrolytes, chest *X*-ray, NT-proBNP level, Bactec blood culture, urine microscopy and culture along with detailed physical examination was done for all cases and control. **Results**: Mean (SD) values of NT-proBNP levels in acute KD was higher than sepsis/other febrile illnesses (914.9 vs 219 pg/mL; *P*=0.001). Also, the number of KD patients whose NT-proBNP was elevated were significantly higher compared to controls (70% vs 32.5%; *P*<0.001). **Conclusions**: NT-proBNP may be useful as a biomarker in the diagnosis of acute phase KD.

Keywords: Biomarker, Diagnosis, Infection, Myocardial stress.

Published online: June 21, 2023; **PII**:S097475591600558

Kawasaki disease (KD) is an acute self-limiting vasculitis predominantly affecting medium sized arteries. In the absence of specific diagnostic tests, its diagnosis is based mainly on clinical criteria [1,2]. Due to overlapping clinical features, differentiation from sepsis and other inflammatory fevers of childhood becomes difficult. Thus we need to investigate for new markers which might help us to diagnose KD with certainty.

Brain-type natriuretic peptide (BNP) was first described in 1988 after isolation from porcine brain. Later it was found to originate mainly from the heart, representing a cardiac hormone [3]. NT-proBNP level rises in children with acute KD, but the mechanism is not clear [4,5]. Sepsis is a dreaded complication of severe trauma, extensive burns, shock, and other severe infections that result in multi-organ dysfunction. Affection of the cardiovascular system in sepsis leads to increased plasma NT-proBNP levels [6,7].

This study was undertaken to compare NT-proBNP levels in KD, sepsis and other febrile conditions to evaluate its utility, if any, as a biomarker in acute KD [8].

METHODS

This was a hospital-based cross-sectional observational study conducted at a tertiary referral hospital in eastern India. Children admitted between January, 2019 and April, 2020, with KD, sepsis and other febrile illnesses were included. Since the average number of KD admissions at the institute ranged between 35 to 40 in a year since 2015, and the study was over 16 months, we decided to enroll 40 KD patients presenting during the study period as the 'case' group. KD was diagnosed based on 2017 AHA (American Heart Association) criteria. The 'control' group comprised of another 40 children with sepsis or other febrile illnesses. Patients with structural heart disease, cardiomyopathy, renal failure, and those receiving chemotherapy/immuno-suppressive therapy were excluded.

All patients had a complete blood count, C-reactive protein (CRP), liver and renal function tests, serum electrolytes, chest *X*-ray, NT-proBNP level, Bactec blood culture, urine microscopy and culture along with detailed physical examination. KD patients as well as those with suspected cardiac dysfunction had ECG and echocardiography. Blood samples were collected at admission before administering specific therapy. NTproBNP levels were measured by Cobas e411 (Roche Diagnostics) using electro-chemiluminiscence immunoassay.

Institutional Ethics Committee clearance was taken prior to conducting the study. Since this was a pre-COVID study, patients with multi system inflammatory syndrome (MIS-C) were not included.

Statistical analysis: Data were entered into a Microsoft Excel spread sheet and then analyzed by SPSS 27.0 (SPSS Inc.) and Graph Pad Prism version 5. We used two-sample *t* test for difference in mean, and Chi-square test for difference in categorical variables. Correlation was calculated by Pearson correlation analysis. *P* value <0.05 was considered as statistically significant.

RESULTS

The median (range) age of 40 children with KD (21 boys) was 19 (3-108) months, and for the control group (24 boys), it was 44 (3-204) months. The mean (SD) duration of fever in KD was 7.8 (2.47) days, and 9.7 (2.36) days for the control group.

The control group comprised of 13 children with culture proven sepsis, 4 with pneumonia, 5 with enteric fever, 3 with systemic juvenile idiopathic arthritis, 2 with systemic lupus erythematosus, 3 with malaria, 4 with dengue, and the rest of the children had viral respiratory tract infections. Of the KD patients, 13 (32.5%) had coronary artery aneurysms at diagnosis, and 8 (20%) were intravenous immunoglobulin IVIG) resistant.

Twenty eight (70.0%) patients in KD group had high NT-proBNP levels. In control group, 13 (32.5%) had high NT-proBNP and 27 (67.5%) had normal levels. Association of frequencies of patients having NT-proBNP level above and below cutoff value between KD and control group was statistically significant (*P*<0.001).

In KD, the mean (SD) NT-proBNP level was 914.91 pg/mL, whereas amongst controls the level was 219.03 pg/mL (*P*=0.001). NT-proBNP levels were found it to be significantly positively correlated with platelet count and negatively correlated with leukocyte count, serum potassium and albumin levels (**Table I**). However, NT-proBNP levels with respect to echocardiographic findings/ IVIG resistance in the KD patients was not analyzed.

Table I Correlation Between NT-proBNP Level and Other Laboratory Parameters in Children With Kawasaki Disease (*N*=40)

Parameters	*Correlation coefficient*	*P value*
Hemoglobin	0.066	0.688
Total leukocyte count	0.315	0.048
Platelet count	0.469	0.002
Erytherocyte sedimentation rate	0.075	0.646
C-reactive protein	0.233	0.148
Serum sodium	0.110	0.500
Serum potasium	0.370	0.019
Blood urea	0.087	0.595
Serum creatinine	0.077	0.637
Serum albumin	0.660	<0.001

DISCUSSION

Diagnosis of KD depends on the recognition of a sequence of characteristic clinical findings. All clinical features may not be present at same time, and in the absence of a sensitive and specific pathognomonic laboratory test, diagnosis maybe difficult. Hence differentiation from sepsis and other autoimmune/inflammatory fevers of childhood becomes difficult [1]. The difficulty is more with incomplete and atypical presentations, consequently leading to a delayed diagnosis and increased risk of coronary artery involvement.

Several studies have explored the use of potential biomarkers to aid in the diagnosis of KD, NT-proBNP being one of the markers. Studies have shown the utility of this biomarker in diagnosis of infantile and incomplete forms of KD [10,11], and also in predicting IVIg resistance and coronary artery lesions [12,13].

BNP is synthesized as a pro-hormone (proBNP) by the myocardium. Myocardial ischemia, cytokines and endocrine (paracrine) modulation by other neurohormones are important stimulus for release of these molecules. Natriuresis or diuresis, peripheral vasodilatation, inhibition of the renin-angiotensin-aldosterone system and the sympathetic nervous system are the main physiological effects of BNP. NT-proBNP is mainly cleared from body by renal excretion, and the half-life is 120 minutes.

Sepsis being a severe complication of many critical situations, early evaluation of its severity and initiation of proper treatment is important to reduce mortality. Procalcitonin, C-reactive protein, and activated protein C, are the known predictors. Recently NT-proBNP has been included in the list; increased levels being used as a marker of cardiac insufficiency secondary to sepsis and a poor prognostic indicator.

Based on the IAP (Indian Academy of Pediatrics) Position Paper on KD, we considered values of NT-proBNP above 225 pg/mL as significant [8]. As already mentioned, the number of patients with KD who had NT-proBNP levels above cutoff value was significantly more than the number in control group. This was consistent with the results of previous studies [14,15]. It was also shown that even patients with incomplete KD had higher NT-proBNP levels than febrile control group (84% vs 4%; *P*<0.001).

There are some limitations to our study. It was a cross-sectional, single centre study, and the sample size was small. Study subjects were enrolled from the inpatient department of a tertiary hospital, thereby raising the possibility of a

WHAT THIS STUDY ADDS

- NT-proBNP measurement plays a significant role in the diagnostic algorithm of suspected Kawasaki disease, even in patients with incomplete presentations.

referral bias. We did not analyze NT-proBNP values with respect to coronary artery dimensions. Future studies with a larger sample size and longitudinal design should be able to contribute more in the diagnostic importance of NT-proBNP in KD and generate cutoff values to distinguish KD and other fevers.

To ease diagnosis of KD and for timely initiation of immunoglobulin therapy, there is need for an early diagnostic test. Like previous studies from Northern India that explored the role of NT-proBNP in KD [14], we too state that NT-proBNP measurement may play a significant role in the diagnostic algorithm of suspected KD, even in patients with incomplete presentations.

Ethics clearance: Institutional Ethics Committee, ICH, Kolkata; No. ICH/IEC/91/2018 dated Dec 29, 2018.
Contributors: PP: formulated and designed the study and provided statistical support; PB: conducted the study including preparation of proforma, data collection, blood sample collection and manuscript writing; SC: guided PB and assisted in writing the manuscript; SB: conducted the laboratory tests and interpreted them; NA helped PB in data collection and manuscript writing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Rawat A, Singh S. Biomarkers for diagnosis of Kawasaki disease. Indian Pediatr. 2015;52:473-4.
2. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and longterm management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110:2747-71.
3. Wieczorek SJ, Wu AH, Christenson R, et al. A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: A multicenter evaluation. Am Heart J. 2002;144:834-9.
4. Shiraishi M, Fuse S, Mori T, et al. N-terminal pro-brain natriuretic peptide as a useful diagnostic marker of acute Kawasaki disease in children. Circ J 2013;77:2097-01.
5. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and Nt-proBNP in clinical routine. Heart. 2006;92:843-9.
6. Li N, Zhang Y, Fan S, et al. BNP and NT-proBNP levels in patients with sepsis. Front Biosci. 2013;18:1237-43.
7. Burchardi H, Schneider H. Economic aspects of severe sepsis: A review of intensive care unit costs, cost of illness and cost effectiveness of therapy. Pharmacoeconomics. 2004;22: 793-813.
8. Shenoy B, Singh S, Ahmed MZ, et al. Indian Academy of Pediatrics Position Paper on Kawasaki Disease. Indian Pediatr. 2020;57:1040-48.
9. Rodríguez-González M, Castellano-Martínez A, Alonso-Ojembarrena A. Usefulness of age-adjusted N-terminal pro-hormone of brain natriuretic peptide level as a diagnostic marker for incomplete Kawasaki disease in children. Emergencias. 2019;31:111-4.
10. Kang JH, Hong SJ, Seo IA, et al. Early detection of Kawasaki disease in infants. Korean Circ J. 2015;45:510-15.
11. Bae HK, Do Kyung Lee JH, Kim HS, et al. Clinical characteristics and serum N-terminal pro-brain natriuretic peptide as a diagnostic marker of Kawasaki disease in infants younger than 3 months of age. Korean J Pediatrics. 2014;57:357.
12. Shao, S., Luo, C., Zhou, K. et al. The role of age-specific n-terminal pro-brain natriuretic peptide cutoff values in predicting intravenous immunoglobulin resistance in Kawasaki disease: A prospective cohort study. Pediatric Rheumatology. 2019; 17:65.
13. Zheng X, Zhang, Y, Liu L. et al. N-terminal pro-brain natriuretic peptide as a biomarker for predicting coronary artery lesion of Kawasaki disease. Scientific Reports. 2020; 10:5130.
14. Reddy M, Singh S, Rawat A, et al. Pro-brain natriuretic peptide (ProBNP) levels in north Indian children with Kawasaki disease. Rheum Int. 2016;36:551-9.
15. Dionne A, Dahdah N. A decade of NT-proBNP in acute kawasaki disease, from physiological response to clinical relevance. Children (Basel). 2018;5:141.

RESEARCH PAPER

Metabolic Bone Disease in Preterm Neonates With Fetal Growth Restriction (FGR): A Prospective Cohort Study

GURU PRASAD PERURI,[1] AMBALAKKUTHAN MURUGESAN,[1] NIVEDITA MONDAL,[1] RAM KUMAR GOVINDARAJALOU,[2] ANISH KEEPANASSERIL,[3] ZACHARIAH BOBBY,[4] SADISHKUMAR KAMALANATHAN[5]

[1]*Department of Neonatology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry.*
[2]*Department of Radiology, Jawaharlal Institute of Postgraduate Medical Education and Research , Puducherry.*
[3]*Department of Obstetrics and Gynaecology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry.*
[4]*Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry.*
[5]*Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry.*

Correspondence to:
Dr Nivedita Mondal,
Department of Neonatology,
JIPMER, Puducherry.
nive.m8@gmail.com
Received: Feb 16, 2023;
Initial review: March 26, 2023;
Accepted: June 24, 2023.

Objectives: To study the association of fetal growth restriction (FGR) with metabolic bone disease in preterm neonates. **Methodology**: This prospective cohort study included 94 preterm neonates with FGR as cases and an equal number of gestation-matched appropriate for gestational age (AGA) neonates without FGR as controls. The incidence of metabolic bone disease, and serum biochemical markers at various time intervals till 6 months corrected age were compared. The risk factors for metabolic bone disease and its association with stunting at 6 months of corrected age were studied. **Results**: The incidence of metabolic bone disease, though higher in the FGR neonates (15.5%), was not significantly different from AGA neonates (6.7%) [RR (95%CI) 0.92-5.82; *P*=0.06]. Birth weight [aOR (95%CI) 0.8 (0.64-0.98); *P*=0.03] and time to reach full feeds [aOR (95%CI) 1.17 (1.01-1.36); *P*=0.03] were significantly associated with an increased risk of metabolic bone disease after adjusting for FGR status. Mean (SD) levels of calcium, phosphorus, alkaline phosphatase, parathormone (PTH), and vitamin D were similar in both groups. No significant association existed between metabolic bone disease and stunting at 6 months of corrected age [RR (95%CI) 2 (0.75-5.4); *P*=0.16]. **Conclusion**: FGR was not found to be significantly associated with metabolic bone disease in preterm neonates.

Keywords: *Time to full feeds, Stunting, Vitamin D*.

Published online: July 20, 2023; **PII**:S097475591600561

Fetal growth restriction is regarded as a risk factor for metabolic bone disease of prematurity [1]. Metabolic bone disease is believed to be more common in newborns with fetal growth restriction (FGR) due to chronic damage to the placenta interfering with substrate transport [2]. However, studies evaluating the role of FGR in bone health have presented conflicting results [3,4]. The effect of co-existing FGR and prematurity in the causation of metabolic bone disease has not been studied extensively. We, therefore, attempted to evaluate the role of fetal growth restriction in the causation of metabolic bone disease in preterm infants.

METHODS

This prospective cohort study was conducted in the neonatal intensive care unit (NICU) of our tertiary care medical college hospital between January, 2019 and December, 2020, after obtaining institutional ethics committee clearance. As we intended to study the effect of FGR on metabolic bone disease, all preterm neonates (<37 completed weeks) with an antenatal diagnosis of FGR were included as 'exposed.' Gestational age was assigned by first-trimester ultrasono-graphy (USG) in the absence of which, the last menstrual period confirmed by the New Ballard score was taken [5]. FGR was diagnosed based on antenatal ultrasonography as estimated fetal weight (EFW) <3rd centile or EFW<10th centile with any one of the following – CPR (cerebro-placental ratio) <p5, UA (umbilical artery) pulsatility index (PI) >p95, MCA (middle cerebral artery) PI<p5, UtA (uterine artery) PI >p95 on at least one occasion. [6] The 'non-exposed' group included gestation-matched preterm neonates (<37 completed weeks) with EFW >10th centile and birth weight between 10th and 90th centile appropriate for gestational age (AGA) on the revised Fenton chart [7]. Neonates with major congenital anomalies, chromosomal abnormalities, and renal disorders were excluded. Sampling was consecutive.

Informed written consent was obtained from the parents. Feeding of neonates was done as per the unit protocol (**Table I**). Injection 10% calcium gluconate at 8 mL/kg/day (72 mg/kg/day) was given to neonates on total parenteral nutrition (TPN). Injection potassium phosphate at 0.5 mL/kg/day (provides 46 mg/kg phosphate) was given to neonates on prolonged TPN and with hypophosphatemia. Human milk fortifier (Lactodex-HMF; Raptakos, Brett & Co Ltd), 1 g to 25 mL breastmilk was added once feed volume exceeded 100 mL/kg/day to all neonates with birth weight <1800 g. Prior to discharge, HMF was stopped, and syrup calcium phosphate was prescribed at a dose of 4-5 mL/kg/day (Calcium 125 mg, Phosphorus 55 mg, and Vitamin D 200 IU per 5 mL), which was continued till 40 weeks of corrected gestation. If metabolic bone disease was diagnosed, a serial increment in the dose of the calcium phosphate syrup or separate administration of syrup calcium carbonate and oral phosphate was done. Vitamin D was supplemented as a syrup (400 IU/mL) at a total dose of 800-1000 IU/day till term age and continued at a dose of 400 IU/day till 1 year.

Metabolic bone disease was diagnosed when serum alkaline phosphatase (ALP) was >500 IU/L with phosphate <4.5 mg/dL [8]. Screening began at 3-4 weeks of age for all preterm neonates, except for those who had received TPN, bone active medications, or developed cholestasis, in whom screening began at 2 weeks of life. The screening was stopped once ALP was <800 IU/L and phosphate >5 mg/dL on two occasions, 2 months apart. Serum vitamin D levels were checked at 40 weeks corrected age (CA) using AdviaCentaur XP Chemiluminescent Immunoassay system (Siemens).

Neonates were followed-up at 40 weeks, 3 months and 6 months of corrected age. Growth monitoring was performed using modified Fenton chart [7] until 40 weeks of corrected age and then on the World Health Organization (WHO) child growth standards [9].

The incidence of metabolic bone disease and levels of serum biochemical markers (serum calcium, phosphorus, ALP, parathormone (PTH) were compared between the two groups at diagnosis and resolution of MBD and that of 25-hydroxy vitamin D (25(OH) D) at term age. Risk factors for MBD and its association with stunting at 6 months corrected age were studied.

Ramon, et al. [10] reported 15% incidence of osteopenia among preterm neonates less than 1500g or less than 32 weeks. They found osteopenia in 43.3% of FGR and 7.3% of AGA subjects. We made a conservative assumption that 10% of all preterm AGA neonates and 30% of all preterm FGRs develop metabolic bone disease. For a power of 80% at a 5% level of significance and a 1:1 ratio of exposed to non-exposed, the sample size was calculated to be 72 in each group. Assuming around 20% loss to follow-up, a final sample size of 94 per group was decided.

Table I Feeding Protocol Used for Preterm Infants Enrolled in the Study

Gestational age	*34 to 36 weeks*	*32 to 33 6/7 weeks*	*28 to 31 6/7 weeks*	*< 28 weeks*
Feeds on Day 1	Breastfeeds Switch to palladai feeds if breastfeeding is not satisfactory	60 mL/kg/day palladai feeds OG/NG feeds if poor suck-swallow coordination	30 mL/kg/day OG/NG feeds Start IV fluids	0-15 mL/kg/day Start TPN
Feed increment	Breastfeeds ad lib	30-40 mL/kg/day Start non-nutritive sucking	30 mL/kg/day	10-15 mL/kg/day x 3 days, then 20 mL/kg/day
Maximum feeds		Increase to 180 ml/kg/day; 200-220 ml/kg/day if SGA, since calculations are based on weight; > 220 ml/kg/day: discuss with SR		
Feeding interval	3 hours or ad lib	3 hours	3 hours	2 hours
AEDF/REDF on antenatal Doppler or severe SGA (birth weight <3rd centile)	Breast milk 30 mL/kg/day or higher (consider full feeds on case-by-case basis)	Start IV fluids Breast milk 20 ml/kg/day once stable	Start TPN Breast milk 10mL/kg/day once stable	Start TPN Breast milk 10mL/kg/day once stable
	Increase by 30-40 mL/kg/day after 24 hours Breastfeeds ad lib in some cases (discuss with consultant)	Increase by 30 mL/kg/day after 24 hours	Increase by 30 mL/kg/day after 48 hours	Increase by 20 mL/kg/ day after 48 hours. Increase by 30 mL/kg/day once>60 mL/kg/day of feeds are tolerated.

AEDF/REDF: absent/reduced end diastolic blood flow, SGA: small for gestational age, TPN: total parenteral nutrition.

Statistical analysis: Univariate analysis was performed to find an association between various risk factors using Mann Whitney *U* test and Student *t* test for continuous variables and Pearson Chi-square or Fisher exact tests for categorical ones. Multivariate binary logistic regression was performed for adjusted analysis. Data were evaluated using SPSS version 20.0. All statistical analyses were carried out at 5% level of significance.

RESULTS

A total of 206 newborns were assessed for eligibility, of which 188 were recruited, 94 each of preterm FGR [mean (SD) birthweight 1282 (280) grams] and preterm AGA [mean (SD) birthweight 1887 (393) grams]. Seventy nine FGR and 85 AGA preterm infants were followed-up for at corrected age of 6 months (**Fig. 1**). The mean (SD) gestational age, was 32.9 (1.8) weeks; there were no extreme preterm neonates with FGR (**Table II**). The incidence of metabolic bone disease in the entire cohort and among very low birth weight (VLBW) neonates was 10.9% (19 out of 174) and 18.5% (15 out of 81), respectively. The mean gestational age of infants with and without metabolic bone disease was 31.2 (1.9) and 33.1 (1.6) weeks, respectively. FGR neonates showed a trend towards an increased incidence of MBD [15.5% vs 6.7%; RR (95% CI) 2.32 (0.92-5.82); *P*= 0.06]. Lower birth weight, total parenteral nutrition (TPN) >1 week, sepsis, hemodynamically significant patent ductus arteriosus (hs-PDA), longer time to reach full feeds, and exposure to any bone-active medication were significantly associated with metabolic bone disease (**Table III**). After adjusting for FGR status, binary logistic regression analysis showed that birth weight [aRR (95%CI) 0.8 (0.64-0.98); *P*=0.03] and time to reach full feeds [aRR (95%CI) 1.17 (1.01-1.36); *P*=0.03] were significantly associated with an increased risk of MBD. The odds of developing metabolic bone disease decreased with every 100 g increase in birth weight [OR (95% CI) 0.8 (0.64-0.98); *P*=0.038]. On adjusted analysis, every one-day delay in reaching full enteral feeds had a 1.17 times higher odds of developing MBD [OR (95% CI) 1.17 (1.01-1.36); *P*=0.032].

Table II Baseline Characteristics, Mortality and Short-term Morbidity in the Study Groups

Characteristics	*FGR neonates (n=94)*	*AGA neonates (n=94)*
Gestational age (wk)		
28-31	21 (22.3)	21 (22.3)
32-33	35 (37.2)	35 (37.2)
34-36	38 (40.4)	38 (40.4)
Birth weight (g)		
<1000g	15 (15.9)	1 (1.06)
1000-1499	54 (57.4)	11 (11.7)
1500-2499	25 (26.6)	74 (78.7)
≥2500	0	8 (8.5)
Male babies	59 (62.8)	49 (52.1)
Delivered by LSCS	55 (58.5)	40 (42.6)
5 min APGAR[a,b]	9 (8,9)	9 (8,9)
Metabolic bone disease[b]	13 (15.5)	6 (6.7)
Time to reach full feeds[a,b,c]	3 (3,5)	3 (2,4)
Required TPN > 1 wk[c]	11 (11.7)	1 (1.1)
Received surfactant	11(11.7)	11(11.7)
Sepsis	15 (16)	9 (9.6)
Bronchopulmonary dysplasia	3 (3.2)	1 (1.1)
Hospital stay (d)[a,c]	17 (8,31)	11 (7,17.25)
Mortality	10 (10.6)	4 (4.3)

Values in no. (%) or [a]median (IQR). [b]11 neonates died (8 in FGR and 3 in Non-FGR) before reaching full feeds. [c]P<0.05. TPN: total parenteral nutrition, LSCS: lower segment cesarean section; FGR:fetal growth restriction; AGA: appropriate for gestational age.

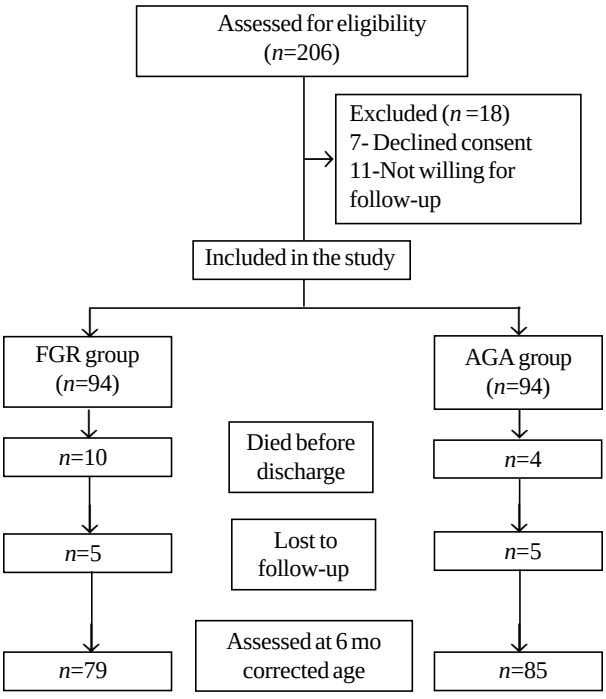


Fig. 1 Study flow chart.

The mean levels of calcium, phosphorus, ALP and PTH were similar between the two groups. The etiology of metabolic bone disease in all neonates was inadequate phosphate supplementation, confirmed by low/normal PTH levels in all cases (**Table IV**). Stunting was seen in 6 (31.6%) and 4 (2.6%) in those with and without MBD, respectively. No significant association existed between MBD and stunting at 6 months corrected age [RR (95% CI) 2 (0.75-5.4); *P*=0.16].

Table III Risk Factors Associated With Metabolic Bone Disease

Characteristics	*MBD n=19*	*No MBD n=155*	*RR (95% CI)*
Birth weight (g)[a]	1156 (304)	1660 (428)	0.66 (0.55-0.80)
Time to full feeds (d)[b,d]	7 (3,14)	3 (2,3)	1.34 (1.19-1.53)
Medications[c, f]	13 (68.4)	29 (18.7)	9.4 (3.3-26.85)
TPN >1 wk	8 (42)	4 (2.5)	9.81 (4.89-19.7)
Sepsis[g]	9 (47.3)	10 (6.4)	7.34 (3.41-15.76)
Hs-PDA	6 (31.5)	4 (2.6)	7.56 (3.66-15.65)
BPD[h]	2 (10.5)	2 (1.3)	5 (1.7-14.7)
Serum vitamin D3 (ng/mL)[b,f,h]	6.3 (27.56, 56.61)	47.5 (27.81, 71.52)	-

Values in no. (%), [a]mean (SD) or [b]median (IQR). [c]caffeine, steroids, diuretics. MBD: metabolic bone disease; TPN: total parenteral nutrition; Hs-PDA: hemodynamically significant patent ductus arteriosus; BPD: bronchopulmonary dysplasia. [d]100 mL/kg, [e]Exposure to any bone active medications, [f]level at term age, [g]either screen or culture positive. All P<0.001 except [h]P>0.05.

DISCUSSION

We demonstrated the incidence of MBD to be higher in FGR (15.5%) than in AGA neonates (6.7%); however, the difference was not statistically significant. This is likely due to the lower than expected incidence of the outcome. Mazarico, et al. [4] found bone mineral content (BMC) to be similar between AGA and FGR groups in the initial 12 months of life. Contrary to our findings, authors have reported decreased BMC in SGA infants compared to gestation-matched AGA neonates [3,11]. However, in the aforementioned studies, the authors have compared AGA vs SGA and not true FGR neonates, with SGA being defined based on birth weight alone. The overall lower incidence of metabolic bone disease in our study was due to the inclusion of preterm neonates of all gestational ages. Moreover, we have used a low phosphate cutoff (<4.5mg/dL) compared to other studies; with a higher cutoff, more infants would be labelled as suffering from metabolic bone disease.

Table IV Biochemical Parameters in Appropriate for Gestational Age (AGA) and Fetal Growth Restriction (FGR) Infants

Characteristics	*FGR (n=13)*	*AGA (n=6)*	*P value*
Postnatal age (wk)	7.0 (3.4)	5.3 (2.2)	0.27
Calcium (mg/dL)	9.7 (0.7)	9.7 (0.7)	0.88
Phosphorus (mg/dL)	3.6 (0.8)	4.0 (0.4)	0.40
ALP levels (IU/L)	830 (308)	697 (161)	0.33
PTH value (pg/mL)[a]	2.4 (0.95,4.5)	3.1 (1.6,4.4)	0.59
At resolution of MBD			
Postnatal age (wk)	13.6 (5.3)	13.2 (5.4)	0.88
Calcium (mg/dL)	10.0 (0.5)	10.1 (0.4)	0.77
Phosphorus (mg/dL)	6.0 (0.5)	5.8 (0.8)	0.59
ALP levels (IU/L)	503 (161)	436 (70)	0.34
Vitamin D level[b]	39.8 (18.5)	47.6 (27.8)	0.47

All values in mean (SD) or [a]median (IQR). [b]At term corrected age. ALP: alkaline phosphatase, PTH: parathyroid hormone.

Studies have reported a correlation between lower birth weight and BMC [12,13], which is consistent with the findings in our study. We also found sepsis to be significantly associated with MBD. The effect of sepsis on MBD is disputed, with conflicting conclusions from studies [14,15]. It is also difficult to comment if the hs-PDA or the accompanying NSAID was responsible for the association [16]. In our study, exposure to none of the three bone-active medications showed a significant association on adjusted analysis. Conventionally, TPN duration of 2-3 weeks or more has been said to be a risk factor for metabolic bone disease; however, from our results it does seem that even a week of TPN can lead to a higher risk. Longer time to reach full enteral feeds was significantly associated with MBD evidently due to the delay in initiating phosphate supplementation.

The role of vitamin D in MBD is controversial, and studies have shown calcium and phosphate absorption in preterm neonates occur independent of vitamin D intake, unlike in children and adults [17]. We found no significant association of MBD with stunting at 6 months of corrected age. Though prematurity and FGR are associated with stunting, the role of MBD in causing the same is unclear [18].

The major limitation of our study was that the incidence of MBD was lower than expected, as most of the neonates were beyond 32 weeks gestation. The sample size was not sufficient to include several risk factors in the multivariate analysis. Though a combination of biochemical parameters (serum calcium, phosphorus, ALP, PTH) was used to diagnose metabolic bone disease, DEXA, the gold standard test, could not be done.

In conclusion, FGR appears to be insignificantly associated with metabolic bone disease in preterm neonates. Birth weight and feeding practices might determine its incidence.

Acknowledgments: Ms Jeyashankari Jeswanth, Counsellor, Newborn follow-up clinic for her effort in ensuring follow-up of our patients.

Ethics clearance: Institutional Ethics Committee, JIPMER; No. JIP/IEC/2018/399 dated Dec 26, 2018.

Contributors: All authors contributed to the study design,

WHAT THIS STUDY ADDS?

- The incidence of metabolic bone disease was not significantly different between appropriate for gestational age neonates and those with fetal growth restriction.
- Birth weight and time to reach full feeds were significant determinants of metabolic bone disease.

analysis and commented on previous versions of the manuscript. GPP: data collection and analysis; AM: preparation of the first draft of the manuscript. All authors read and approved the final manuscript. NM: study conception, design, analysis and manuscript review.

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

REFERENCES

1. Abrams SA, Management of bone health in preterm infants. Hoppin AG, editor. UpToDate. UpToDate Inc. Accessed Feb 13, 2023. Available from: *https://www.uptodate.com/contents/management-of-bone-health-in-preterm-infants*
2. Holland PC, Wilkinson AR, Diez J, et al. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. Lancet. 1990;335:697-701.
3. Chen JY, Ling UP, Chiang WL, et al. Total body bone mineral content in small-for-gestational age, appropriate-for-gestational age, large-for-gestational age term infants and appropriate-for-gestational age preterm infants. Zhonghua Yi Xue Za Zhi (Taipei).1995;56:109-14.
4. Mazarico E, Martinez-Cumplido R, Díaz M, et al. Postnatal anthropometric and body composition profiles in infants with intrauterine growth restriction identified by prenatal Doppler. PLoS One. 2016;11: e0150152.
5. Smith VC. The high risk newborn: anticipation, evaluation, management and outcome. *In*: Eichenwald EC, Hansen AR, Martin CR, Stark AR, Jain N, editors. Manual of Neonatal care. Wolters Kluwer; 2021.p.92-107.
6. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther. 2014; 36:86-98.
7. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr.2013;13:59.
8. Figueras-Aloy J, Álvarez-Domínguez E, Pérez-Fernández JM, et al. Metabolic bone disease and bone mineral density in very preterm infants. J Pediatr. 2014;164:499-504.
9. World Health Organization. The WHO child growth standards. Accessed on Feb 13, 2023. Available from: *https://www.who.int/tools/child-growth-standards/standards*
10. Montaner Ramón A, Fernández Espuelas C, Calmarza Calmarza P, et al. Risk factors and biochemical markers in metabolic bone disease of premature newborns. Rev Chil Pediatría. 2017;88:487-94.
11. Kitazawa S, Itabashi K, Umeda Y, et al. Growth and bone mineralization in small-for-gestational-age preterm infants: Growth and BMC in SGA preterm infants. Pediatr Int. 2014; 56:67-71.
12. Salle BL, Braillon P, Glorieux FH, et al. Lumbar bone mineral content measured by dual energy *X*-ray absorptiometry in newborns and infants. Acta Pediatr. 1992.;81:953-8.
13. Lapillonne A, Braillon P, Claris O, et al. Body composition in appropriate and in small for gestational age infants. Acta Paediatr. 1997; 86:196-200.
14. Zhang Y, Xue C, Zhu T, et al. Serum bone alkaline phosphatase in assessing illness severity of infected neonates in the neonatal intensive care unit. Int J Biol Sci. 2011;8:30-8.
15. Eliakim A, Shiff Y, Nemet D, et al. The effect of neonatal sepsis on bone turnover in very-low birth weight premature infants. J Pediatr Endocrinol Metab. 2003;16:413-8.
16. Nuelle JAV, Coe KM, Oliver HA, et al. Effect of NSAID use on bone healing in pediatric fractures: A preliminary, prospective, randomized, blinded study. J Pediatr Orthop. 2020;40: e683-9.
17. Kovacs CS. Bone metabolism in the fetus and neonate. Pediatr Nephrol. 2014; 29:793-803.
18. Fewtrell MS, Cole TJ, Bishop NJ, et al. Neonatal factors predicting childhood height in preterm infants: evidence for a persisting effect of early metabolic bone disease? J Pediatr. 2000; 137:668-73.

RESEARCH PAPER

Growth Parameters in Adolescents With Idiopathic Nephrotic Syndrome Diagnosed at the Age of 1-6 Years

K SRIMATHI,[1] BOBBITY DEEPTHI,[1] SUDARSAN KRISHNASAMY,[1] SACHIT GANAPATHY,[2] SRIRAM KRISHNAMURTHY[1]

[1]Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry.
[2]Department of Biostatistics, JIPMER, Puducherry.

Correspondence to:
Dr Bobbity Deepthi,
Assistant Professor,
Department of Pediatrics,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006.
deepu.reddy222@gmail.com
Received: Feb 28, 2023;
Initial review: Mar 26, 2023;
Accepted: Jun 28, 2023.

Objectives: To determine the prevalence of impaired growth parameters (height and BMI *z* scores) among adolescents aged 10-19 years, with onset of idiopathic nephrotic syndrome between the age of 1 and 6 years. **Methods:** A cross-sectional study was conducted among adolescents aged 10-19 years with onset of idiopathic nephrotic syndrome between the age of 1-6 years, and under regular follow-up at our center. The data were retrieved for a 10-year period (2012-2022). The current weight, height and body mass index (BMI) were recorded and interpreted as per world Health Organization (WHO) growth standards. **Results:** 116 adolescents [60 Frequently relapsing nephrotic syndrome (FRNS)/Steroid dependent nephrotic syndrome (SDNS), and 56 Steroid resistant nephrotic syndrome (SRNS)] patients were enrolled with median (IQR) age of 133 (120,168) months and age at disease onset of 48 (26,68) months. The proportion of children with overweight (BMI for age >1*z* and cushingoid features), obesity (BMI for age >2*z*), stunting (height for age (HFA) <2*z*), and severe stunting (HFA <3*z*) were 29 (25%), 3 (2.6%), 31 (26.7%), and 7 (6%), respectively. The median (IQR) cumulative steroid dose for FRNS/SDNS and SRNS group was 19986.96 (14597.1, 26181.96) mg/m^2 and 14385 (10758.82, 21355.95) mg/m^2, respectively (P=0.003). **Conclusions**: The proportion of short stature and overweight was high among adolescents with nephrotic syndrome, emphasizing the need for measures to reduce steroid use and other measures to support growth.

Keywords: *Obesity, Overweight, Stunting, Outcome*.

Published online: July 20, 2023; **PII**:S097475591600562

Nephrotic syndrome, with onset at 2-6 years of age during the crucial years of childhood steady growth, poses significant challenges to maintenance of growth. Frequently relapsing nephrotic syndrome (FRNS) and steroid dependent nephrotic syndrome (SDNS) children with a relapsing and remitting course receive multiple courses of steroids for frequent relapses, and often develop adverse effects of steroids including growth retardation and obesity [1-7].

Previous studies have demonstrated prohibitive effects of prolonged and repeated courses of steroids on growth parameters like height, weight, and body mass index (BMI) *z* scores [2-5,8,9], while a few cohort studies have showed the preserved linear growth and weight in nephrotic children during the periods of remission and when initiated on early steroid-sparing immunosuppressive agents [9-13]. Most of these studies are from other countries and are limited by a small sample size and heterogenous population [3-5,12,13]. Hence, the current study was planned to determine the prevalence of impaired growth parameters (height and BMI *z* scores) in adolescents with idiopathic nephrotic syndrome. The secondary objective was to determine the association between cumulative steroid dose and impaired linear growth (short stature).

METHODS

The cross-sectional study enrolled adolescents aged 10-19 years with onset of idiopathic nephrotic syndrome between the age of 1-6 years, and under follow-up at the pediatric nephrology services of our institute over a 10-year period (2012-2022). The study was approved by the institute ethics committee and informed consent was obtained from the parents and assent from participants prior to enrolment. All adolescents aged 10-19 years with onset of nephrotic syndrome between 1-6 years were screened for eligibility during the study period (August to October, 2022) [14,15]. Adolescents with secondary nephrotic syndrome e.g., IgA nephropathy, lupus nephritis, C3 glomerulonephritis, and those with co-existing chronic diseases that can substantially affect the growth (like eGFR <60 mL/min/1.73m^2, diabetes mellitus, hypothyroidism) were excluded. Data regarding the age at diagnosis, number of relapses, alternate steroid-sparing agents, cumulative steroid dose, and steroid related adverse effects was recorded in a pre-designed proforma.

Sample size was calculated as 114 with an assumption that 25% children may have impaired linear growth [7] with 8% degree of variability, alpha error 0.05 and standard normal deviate 1.96. A consecutive sample size of 116 was chosen after accounting for attrition.

The current height, weight and BMI were recorded as per standard methods [14]. DS-215 electronic weighing scale (Essae-Teraoka Ltd.) was used for weight measurement and stainless steel stadiometer (Easycare) for height measurement. Standard definitions were used for defining and classifying FRNS, SDNS and steroid resistant nephrotic syndrome (SRNS) [1]. The growth standards and definitions for obesity, overweight, stunted, severely stunted were as per the WHO growth charts for adolescents [14,15]. Significant steroid toxicity was defined as hyperglycemia (Fasting blood glucose ≥100 mg/dL, post-prandial glucose ≥140 mg/dL or HbA1c >5.7%, obesity (BMI >2*z* score), HFA <2*z* score, glaucoma, cataracts, steroid myopathy, osteonecrosis, or psychosis [1].

Statistical analysis: The analysis was carried out using IBM SPSS v19.0 software. All the categorical variables were summarized using frequency or percentage and the continuous variables using mean with standard deviation or median with interquartile range. The normality of the data was assessed using Kolmogorov-Smirnov test. Association of categorical variables were carried out using Chi-square test. Continuous variables with normal distribution (weight, height, BMI *z* scores) were compared using independent Student *t* test and Mann-Whitney *U* test was used for non-normal distribution (age, cumulative steroid dose etc.). Receiver operating characteristic (ROC) curve were plotted to assess the diagnostic accuracy of cumulative dose for short stature. A *P* value <0.05 was considered statistically significant.

RESULTS

We assessed 218 adolescent for eligibility, of which 102 were excluded (66 had secondary nephrotic syndrome, 3 progressed to End stage kidney disease (ESKD), 33 had onset of disease >6 years). Finally, 116 adolescents (77 males) were enrolled for the study

The study group comprised of 39 (33.6%) children with frequently relapsing nephrotic syndrome, 21 (18.1%) with steroid dependent nephrotic syndrome, and 56 (48%) steroid resistant nephrotic syndrome. Majority (112) children in the group received one or more steroid sparing agent along with steroids (**Table I**), while 4 were on long term alternate day steroids. The proportion of children who were overweight (BMI for age *z* score >1 and cushingoid features), obese stunted (HFA *z* score <2), and severe stunted (HFA <3*z*) were

Table I Baseline Characteristics of Adolescents With Idiopathic Nephrotic Syndrome (*N*=116)

Parameters	*Value*
Age at recruitment (mo)	133 (120,168)
Age at disease onset (mo)	48 (26,68)
Cumulative dose of steroid (mg/m²) (*n*=109)	19353.6 (13447.84, 23797.2)
Duration of follow-up (mo)	96.27 (28.93)
Duration of steroid therapy (wk) (*n*=109)	99 (70, 111)
Relapses before initiation of immunosuppressants	4 (3,4)
Steroid-sparing agents	
FRNS/SDNS, *n*=60[a]	
Levamisole	48 (80)
Mycophenolate mofetil	33 (65)
Oral cyclophosphamide	28 (46)
Cyclosporine	9 (15)
Tacrolimus	1 (0.9)
Steroid resistant nephrotic syndrome, *n*=56[a]	
Cyclosporine	37 (66)
Tacrolimus	19 (33.9)
Intravenous pulse cyclophosphamide	26 (46.4)
Rituximab	3 (2.6)

Values are median (IQR) or [a]no. (%). FRNS: frequently relapsing nephrotic syndrome; SDNS: steroid dependent nephrotic syndrome.

Table II Growth Parameters in Adolescents with Idiopathic Nephrotic Syndrome (*N*=116)

Parameters	*Value*
Weight (kg)	33.8 (28.12, 47)
Weight *z* score[a,c]	-0.80 (1.24)
Normal weight (-2*z* to +2*z* score)[b]	93 (80.2)
Underweight (-2*z* to -3*z* score)[b]	21 (18.1)
Severely underweight (<-3*z* score)[b]	02 (1.7)
Height (cm)	138 (131.25, 149.5)
Height *z* score [a]	-1.35(1.25)
Normal height (-2*z* to +2 *z* score)[b]	78 (67.2)
Stunted (<-2*z* to -3*z* score)[b]	31 (26.7)
Severely stunted (<-3*z* score) [b]	07 (6)
Body mass index (BMI) (kg/m^2)	17.7 (15.27, 20.6)
BMI *z* score[a]	0.01 (1.40)
Normal BMI (- 2 *z* to +1*z* score)[b]	70 (60.3)
Overweight (> +1*z* score)[b]	29 (25)
Obese (> +2*z* score) [b]	3 (2.6)
Thinness (-2*z* to -3*z* score) [b]	10 (8.6)
Severely thinness (<-3*z* score)[b]	4 (3.4)

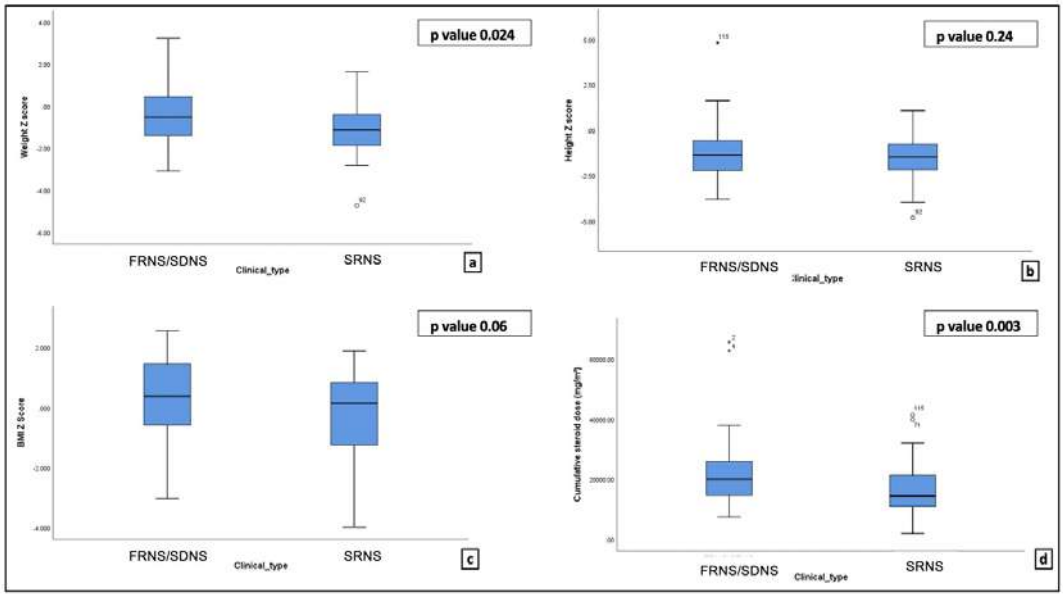
Values in median (IQR), [a]mean (SD) or [b]no. (%). [c]Weight for age z score/ SDS were calculated using IAP growth charts, 2015 [16].

29 (25%), 3 (2.6%), 31 (26.7%), and 7 (6%), respectively. The growth parameters as per WHO classification are summarized in **Table II**.

The severely stunted adolescents included four children with SRNS and three with FRNS/SDNS. The patient characteristics and comparison of growth parameters between FRNS/SDNS and SRNS is shown in **Web Table I**. The mean weight *z* scores were found to be significantly higher in FRNS/SDNS group when compared to the SRNS group (*P*= 0.024) (**Fig. 1a**), but the mean height *z* scores were comparable in both groups (**Fig. 1b**). The mean BMI *z* scores mirrored the trends of weight being significantly higher in the FRNS/ SDNS group when compared to the SRNS (*P*=0.06) (**Fig. 1c**).

The data on cumulative steroid dosage was available for 109 patients. The median cumulative steroid dose for the FRNS/SDNS group was significantly higher than the SRNS group 19986.96 (14597.1 vs 26181.96) mg/m^2 vs 14385 (10758.82, 21355.95) mg/m^2; *P*=0.003] (**Fig. 1d**).

The regression line plotted to quantify the linear relationship between cumulative steroid dose and height *z* score yielded a low coefficient of determination (r^2) (**Fig. 2**). Also, the receiver operating characteristic (ROC) curve



FRNS: Frequently relasping nephrotic syndrome; SDNS: Steroid dependent nephrotic syndrome; SRNS: Steroid resistant nephrotic syndrome.

Fig. 1 Box and whisker plot showing *a*) weight *z* score of FRNS/SDNS and SRNS, *b*) height *z* score of FRNS/SDNS and SRNS, *c*) BMI *z* score of FRNS/SDNS and SRNS, and *d*) cumulative steroid dose in FRNS/SDNS vs SRNS.

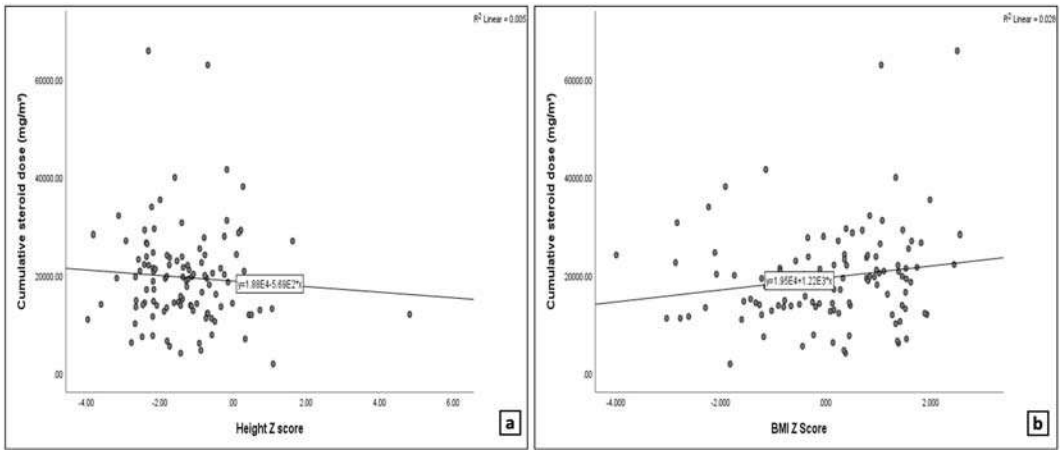


Fig. 2 Scatter plot showing linear relationship between *a*) cumulative steroid dose and height *z* score, and *b*) cumulative steroid dose and body mass index (BMI) *z* score.

plotted to assess the diagnostic accuracy of cumulative steroid dose for predicting short stature showed AUC of 0.53 (P=0.64). Significant steroid toxicity features noted in our study population included short stature (38, 32.7%), followed by cataract (19, 16.4%) and glaucoma (4, 3.4%).

DISCUSSION

Our study demonstrated relatively well-preserved weight *z* scores, though the proportion of short stature was concerning (one-third) in adolescents diagnosed with idiopathic nephrotic syndrome in early childhood. The proportion of overweight adolescents was high, though rates of obesity were negligible. Children diagnosed with FRNS/SDNS had significantly higher weight and BMI *z* scores than those with SRNS. Short stature was not shown to be correlated with cumulative steroid dose alone.

Our results are in accordance with severe growth retardation in nephrotic syndrome reported earlier; 26.5% in a French cohort [7] and 45% in an Italian cohort [17]. Catch-up growth; though, demonstrated, is usually irregular and partial [17-19]. Being a tertiary care referral centre, the proportion of difficult-to-treat nephrotic syndrome (FRNS/SDNS and SRNS) who have received steroids for a longer duration before presenting to us, could have potentially contributed to the higher proportion of short stature in our study as compared to some other studies [4,9,17]; though, conflicting results demonstrating preserved growth have been reported in few studies [9,10]. The combined prevalence of overweight and obesity was lower than most of the published literature on obesity in nephrotic syndrome (35-43%) [8,19], with one-fifth of cases being underweight. These observations could be attributed to nutritional and environmental factors.

An Indian study with 35 children showed that there was a fair correlation between steroid dose and growth retardation (height *z* scores) in SSNS [13]. However, the cumulative steroid dose did not show discriminatory ability in predicting the short stature in our study population like few earlier studies [7,12]. These findings could be explained by additional factors contributing to growth retardation like duration of steroid therapy, duration of daily continuous vs alternate day steroids, different susceptibility to steroids among individuals, and variability of pharmacokinetics. Another important observation was one-third children showing features of steroid toxicity, majority of whom had received multiple and prolonged courses of steroids at other primary centres prior to presenting to us. Most (96.5%) of our children were initiated on one or more steroid sparing agents.

Our study has some limitations. Being a study from a single tertiary-level referral centre, the results may not be generalizable and proportion of steroid side effects could have been higher than usual. The baseline pre-treatment height and data on pubertal growth spurt were not available for analysis.

To conclude, the proportion of short stature and overweight is high among adolescents with onset of nephrotic syndrome in childhood, emphasizing the need for careful monitoring of growth during the disease course. Prompt and early use of adjunctive alternate immunosuppression and rapid tapering of steroids to minimal dose possible for maintaining remission is essential.

Ethics clearance: Ethics Committee of the institute; No. JIP/IEC-OS/2022/205, dated Aug 11, 2022.
Contributors: BD and KS participated in study protocol preparations, recruited patients, participated in data analysis, and drafted the first version of the manuscript; BD: conceptualized the study design and critically revised the manuscript; SG helped in statistical analysis. All authors contributed to protocol preparation, drafting of the manuscript, and approved the final version of the manuscript, and are accountable for all aspects related to the study.
Funding: Short-term studentship (STS) program of Indian Council of Medical Research (ICMR); *Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Sinha A, Bagga A, Banerjee S, et al. Expert Group of Indian Society of Pediatric Nephrology. Steroid Sensitive Nephrotic Syndrome: Revised Guidelines. Indian Pediatr. 2021.58: 461-81.
2. Ishikura K, Yoshikawa N, Nakazato, et al. Japanese Study Group of Renal Disease in Children. Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial. Pediatr Nephrol. 2015;30: 459-68.
3. Skrzypcz KP, Panczyk-Tomaszewska M, Roskowska-Blaim M, et al. Long-term outcomes in idiopathic nephrotic syndrome: from childhood to adulthood. Clin Nephrol. 2014; 81: 166-73.
4. Valavi E, Aminzadeh M, Amouri P, et al. Effects of prednisolone on linear growth in children with nephrotic syndrome. J Pediatr. 2018;96:117-24.
5. Hung YT, Yang LY. Follow-up of linear growth of body height in children with nephrotic syndrome. J Microbiol Immunol Infect. 2006;39:422-5.
6. Larkins N, Kim S, Craig J, Hodson E. Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children. Arch Dis Child. 2016; 101:404-8.
7. Leroy V, Baudouin V, Alberti C, et al. Growth in boys with idiopathic nephrotic syndrome on long-term cyclosporin and steroid treatment. Pediatr Nephrol. 2009;24:2393-400.
8. Foster BJ, Shults J, Zemel BS, Leonard MB. Risk factors for glucocorticoid-induced obesity in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol 2006;21:

973-80.
9. Göknar N, Webb H, Waters A, Tullus K. Long-term obesity prevalence and linear growth in children with idiopathic nephrotic syndrome: Is normal growth and weight control possible with steroid-sparing drugs and low-dose steroids for relapses? Pediatr Nephrol. 2022 ;37:1575-84.
10. Simmonds J, Grundy N, Trompeter R, Tullus K. Long- term steroid treatment and growth: a study in steroid-dependant nephrotic syndrome. Arch Dis Child. 2010;95:146-9.
11. Ruth EM, Kemper MJ, Leumann EP, et al. Children with steroid-sensitive nephrotic syndrome come of age: long term outcome. J Pediatr. 2005; 147:202-7.
12. Donatti LT, Koch VH. Final height of adults with childhood-onset steroid-responsive idiopathic nephrotic syndrome. Pediatr Nephrol. 2009;24:2401-8.
13. Mohan KR, Kanitkar M. Growth in children with steroid sensitive nephrotic syndrome. Med J Armed Forces India. 2009;65:4-6.
14. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. World Health Organization, 2006. Accessed May 30, 2023. Available from: *https://www.who.int/publications/i/item/ 924154693X*
15. De Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85:660-7.
16. Indian Academy of Pediatrics Growth Charts Committee, Khadilkar V, Yadav S, Agrawal KK, et al. Revised IAP Growth Charts for Height, Weight and Body Mass Index for 5- to 18-Year-Old Indian Children. Indian Pediatr. 2015;52: 47-55.
17. Emma F, Sesto A, RiZ Z oni G. Long-term linear growth of children with severe steroid-responsive nephrotic syndrome. Pediatr Nephrol. 2003;18:783-8.
18. Motoyama O, Iitaka K. Final height in children with steroid-sensitive nephrotic syndrome. Pediatr Int 2007;49:623-5.
19. Soliman AT, Hamed N, De Sanctis V, et al. The long-term (five years) effects of prednisone therapy in children with frequently relapsing nephrotic syndrome: a controlled study of anthropometric parameters and metabolic abnormalities: growth and metabolic abnormalities in nephrotic children on prednisone therapy. Acta Biomed. 2022;93:e2022303.

RESEARCH PAPER

Short-term Outcome of Social Skills Group Therapy Intervention in School Aged Children With Autism

MONA P GAJRE, SREYASHI BISWAS, HARSHNA ASERI, SHREEYA PRADHAN
Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra.

Correspondence to:
Dr Harshna Aseri,
12/403, Tulsidham Kalyani,
Tulsidham, Off GB Road,
Next to DAV School,
Thane West 400 610, Maharashtra.
harshnaaseri@gmail.com
Received: Feb 8, 2023;
Initial Review: Apr 10, 2023;
Accepted: Jul 17, 2023.

Objective: To study the impact of social skills group training (SSGT) in children with autism aged 8-12 years. To compare baseline (T1), post-intervention immediate (T2) and 3 months post-intervention (T3) scores. **Methods**: Single-arm interventional study in 30 children with autism, aged 8-12 years with intelligence quotient >70. Interdisciplinary therapists conducted a 90-minute weekly SSGT (10 sessions) for 3 months (August-October, 2019). Outcomes were evaluated with standardized tests- Vineland Social Maturity Scale (VSMS), Vineland Social Maturity Scale- Social Quotient (VSMS-SQ), Social Communication Questionnaire (SCQ), Parent Rated Social Responsiveness Scale-2 (pSRS-2) done at baseline and at T2 and T3. **Results**: The mean (SD) scores at T1 and T3 were as follows: VSMS score at T1 was 66.63 (5.05), T3 was 71.03 (5.84) (P<0.001); SQ at T1 = 75.99 (6.399), T3 = 79.83 (8.94) (P=0.016), respectively. The mean (SD) SCQ score at T1 was 27.3 (12.28), T2 was 25.8 (6.36), T3 = 27.1 (7.16) (P>0.05 for T1- T2, T2-T3, P=0.013 for T1-T3). The mean (SD) pSRS-2 score at T1 = 83.5 (6.68), T2 = 80.1 (7.87), T3 = 76.9 (8.07) (P<0.001), showing decline in severity after SSGT. **Conclusion**: Weekly SSGT done over 3 months showed significant improvement in social skills, which were sustained up to 3 months post-intervention.

Keywords: *Group intervention, Neurodevelopment, pSRS-2, SCQ, VSMS.*

Autism spectrum disorders (ASD) are characterized by impairment in communication, reciprocal social interaction, and restricted and repetitive behaviors [1]. The Centers for Disease Control and Prevention (CDC) reports the prevalence of ASD is 1 in 44 children [2] whereas ASD prevalence in India is 1 in 89 [3]. Children with ASD receiving formal education face difficulties while adjusting to the demands of the school environment. Parents often report concerns over their child's lack of friendships, difficulties with daily routines, and problematic social behavior. Previous research shows that early interventions in autism improve core deficits and result in favorable outcomes [4].

Social skills training (SST) is a promising evidence-based aspect of intervention planning in autism [5]. A social skills group session typically includes a structured lesson on a specific skill, and common topics for the groups vary with respect to the age and functioning level of the group members. Previous studies have shown improvement in social skills after social skills group therapy (SSGT) [6]. Our study was conducted with the aim to analyze the effects of SSGT as a targeted intervention for school-aged Indian children with autism.

METHODS

This single-arm interventional study was conducted at the autism intervention center of our medical college and tertiary care hospital over 6 months (dates), after institutional review board clearance. We enrolled 30 verbal children diagnosed with autism, aged 8-12 years, with IQ >70, after consent of their parents.

Our exclusion criteria included children on new psychiatric medication (30 days), moderate to severe intellectual disability, epilepsy, self-injurious behaviors, aggressiveness, and suspected of confirmed genetic syndromes. Enrolled children underwent SSGT by certified speech-language pathologists and occupational therapists in groups of 10-15. The children received one 90-minute therapy session every week for 3 months. A total of 10 sessions were conducted, each consisting of 15 minutes free play, 60 minutes group intervention and 15 minutes wrap-up followed by parent training.

DSM-V criteria were utilized for the diagnosis of autism and grading of severity; Level 1: requiring support, Level-2: requiring substantial support, and Level-3: requiring very substantial support [7]. Only level-1 children were enrolled. Assessments were conducted at base-

line (T1), immediately after session 10 (T2) and 3 months post SSGT (T3) using the Vineland Social Maturity Scale (VSMS) [8] (along with its social quotient subscale, VSMS-SQ), the Social Communication Questionnaire (SCQ) [9], and the Social Responsiveness Scale-2 (pSRS-2) [10].

The VSMS was used by trained therapists to assess social capacities of the children through direct observation and input from primary caregivers. It was then analyzed to provide an estimate of the social quotient (SQ) to measure social maturation. Each subject required approximately 20 minutes for the test administration, followed by 10 minutes for analysis. Caregivers filled out the SCQ autoscore current form, which took 10 minutes to complete and 5 minutes to score. This test assessed the severity of ASD symptoms and was interpreted by professionals to track changes over time. The pSRS-2, a parent-rated scale, which was completed in 15-20 minutes, was used to quantify the five SRS subscales: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviors (RRBs). The tests were conducted consecutively at a single sitting.

Statistical analysis: Data were analyzed using the SPSS (version 22.0). Tests for normality were not conducted as the sample size was 30. We compared the mean (SD) of pre-test and post-test scores using the paired *t* test. Level of significance was set at 0.05

RESULTS

Out of the 160 children evaluated for eligibility at the center, 30 children were selected for enrolment in the study (60 did not meet age eligibility criteria, parent did not consent to participate in 40, and 30 did not meet the inclusion/exclusion criteria). All 30 selected children received the allocated intervention and were available for final evaluation. There were no participants lost to follow-up. The baseline demographic, socioeconomic and clinical factors are detailed in **Table I**.

Table I Baseline Characteristics of Children With Autism Enrolled in the Study

Characteristics	*No. (%)*
Male sex	22 (73.3)
Age	
8-9 y	10 (33.3)
9-11 y	18 (60)
11-12 y	2 (6.7)
Schooling	
Regular school	13 (44)
Special school	8 (26.7)
Out of school	9 (30)
Socioeconomic class[a]	
Upper	3 (10)
Upper middle	17 (56.7)
Lower middle	8 (26.7)
Upper lower	2 (6.7)
Developmental delay	
Socio-adaptive delay	28 (93.3)
Language delay	23 (76.7)
Motor delay	3 (6.7)
Severity of autism[b]	
Level 3	5 (16.6)
Level 2	15 (50)
Level 1	10 (33.3)

[a]*As per modified Kuppuswamy socioeconomic status scale [11];* [b]*as per (DSM V).*

These were significant differences in mean (SD) baseline VSMS score and VSMS-SQ scores [MD (95% CI) -3.85 (-6.92, -0.77); *P*=0.016] compared to scores at 3 months post-therapy (T3). SCQ measures autism severity, with higher scores indicating a greater intensity. There was

Table II Comparison of Outcome Measures at Baseline (T1), Immediate Post Therapy (T2) and at 3 Months Post Therapy (T3)

	Scores			*MD (95% CI); P value*		
	T1	*T2*	*T3*	*T1-T2*	*T1-T3*	*T2-T3*
VSMS	66.6 (5.05)	-	71.03 (5.84)	-	-4.40 (-5.84, -2.96); <0.001	-
VSMS-SQ	75.9 (6.39)	-	79.8 (8.94)	-	-3.85 (-6.92, -0.77); 0.016	-
SCQ	27.3 (12.28)	25.8 (6.36)	27.1 (7.16)	1.47 (-3.02, 5.95); 0.51	0.17 (-4.51,4.85); 0.94	-1.30 (-2.30, -0.30); 0.013
pSRS-2	83.5 (6.68)	80.1 (7.87)	76.9 (8.07)	3.40 (2.52, 4.28); <0.001	6.53 (5.32, 7.75); <0.001	3.13 (2.57, 3.69); <0.001

Values in mean (SD). VSMS: Vineland social maturity scale; VSMS-SQ: VSMS-social quotient; SCQ: social communication questionaire; pSRS-2: social responsiveness scale-2.

WHAT THIS STUDY ADDS?

- Social skills group therapy (SSGT) in children with autism spectrum disorders showed enhancement in social skills and overall social competence.

no difference between SCQ scores at T1 and T3. Furthermore, a progressive decline in p-SRS-2 scores was observed between T1 and T2 and T2 and T3 [MD (95% CI) -3.13 (2.57, 3.69); P<0.001] indicating a decreasing trend in the severity of social communication impairment (**Table II**).

Additionally, statistically significant differences (P<0.05) were found in the subscale scores of p-SRS-2, including social awareness, cognition, communication, social motivation, and restricted repetitive behaviors at T1, T2, and T3 (**Web Table I**).

DISCUSSION

Children with ASD face social impairments that can lead to peer rejection, mood disorders, and other psychopathologies [11]. Evidence suggests that autistic individuals without significant cognitive delays, often improve post interventions [12]. An analysis of Cochrane reviews conducted by Lyra, et al. [12] concluded that socialization groups were one of the interventions that benefited patients with ASD while highlighting the fact that there was a dearth of experimental studies to confirm this link.

We report on the efficacy of SSGT in a small number of children with autism in an Indian setting. Our results demonstrated an improvement in social quotient at 3 months post therapy. This reflected the effectiveness of the intervention, and is concordant with previous findings [14] that interventions in autistic children led to a significant difference in SQ scores. However, no changes in SCQ scores contrasted with the results of the Preschool Autism Communication Trial (PACT) study that found a significant difference in SCQ scores post intervention [15]. Our data on serial improvement of pSRS-2 scores supported the conclusion of Olsson, et al. [16], who found the SSGT to be superior to standard care. This serial improvement suggested an improvement in overall social competence and thereby indicated that these newly developed skills enhanced their day-to-day wellbeing and quality of life.

The strengths of this study include the incorporation of a follow-up and assessment period of 3 months, which allowed the evaluation of persistence of treatment effects. However, conclusions about long term maintenance could not be derived due to the unforeseen COVID-19 pandemic, which hindered the previously planned follow-ups at 12 and 18 months. As this study was a single-arm design with interventions provided to all participants, there is a possibility that some of the observed outcomes of SSGT could be influenced by a placebo effect, and potential biases may exist in parent reports. The difference noted in these scores; although significant, may not have any clinical implications, and caregiver perspective in this regard would be important in future studies.

These newly acquired behaviors post intervention can have broader implications in the community settings and thereby improve the quality of life. Additionally, this study can serve as a guide for general pediatricians who can reiterate the need of SSGT alongside the ongoing occupational therapy programs. The current findings can serve as a strong base for future clinical developments and can pave a path towards producing meaningful change in the lives of children with autism and their families.

Acknowledgments: Dr Radha Ghildiyal (Professor and Head, Department of Paediatrics, LTMMC and LTMGH) and Dr Mohan Joshi (Dean, LTMMC and LTMGH) for allowing us to conduct this research and publish it.

Ethics clearance: Institutional Ethics Committee Human Research, Lokmanya Tilak Municipal Medical College, and General Hospital; No. IEC 40/21 dated Nov 16, 2018.

Contributors: MG: conception and design, acquisition of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; SB: acquisition of data, analysis, and interpretation of data, drafting of manuscript; HA: acquisition of data, analysis, and interpretation of data, drafting of manuscript; SVP: acquisition of data, analysis, and interpretation of data, drafting of manuscript. All authors provided approval of the version to be published, and agree to be accountable for all aspects of the work.

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

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Hadeel F, Ateeqi NA, Tidmarsh L. Autism spectrum disorders. Ann Saudi Med. 2010;30:295-300.
2. Maenner MJ, Shaw KA, Bakian AV, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2018. MMWR Surveill Summ. 2021;70:1-16.
3. Arora NK, Nair MKC, Gulati S, et al. Neurodevelopmental disorders in children aged 2-9 years: Population-based burden estimates across five regions in India. PLoS Med. 2018; 15:e1002615.
4. Ke F, Whalon K, Yun J. Social skill interventions for Ayouth

and adults with autism spectrum disorder: A systematic review. Review of Educational Research. 2018;88:3-42.
5. Manohar H, Kandasamy P, Chandrasekaran V, Rajkumar RP. Early diagnosis and intervention for autism spectrum disorder: need for pediatrician-child psychiatrist liaison. Indian J Psychol Med. 2019;41:87-90.
6. Laugeson EA, Frankel F, Gantman A, et al. Evidence-based social skills training for adolescents with autism spectrum disorders: The UCLA PEERS Program. J Autism Dev Disord. 2012;42:1025-36.
7. Weitlauf AS, Gotham KO, Vehorn AC, Warren ZE. DSM-5 "levels of support:" A comment on discrepant conceptualizations of severity in ASD. J Autism Dev Disord. 2014;44:471-6.
8. Doll EA. The measurement of social competence: A manual for the Vineland Social Maturity Scale. Educational Test Bureau Educational Publishers. APA, 2022.
9. Chesnut SR, Wei T, Barnard-Brak L, Richman DM. A meta-analysis of the social communication questionnaire: Screening for autism spectrum disorder. Autism. 2017;21:920-28.
10. Bruni TP. Social Responsiveness Scale–Second Edition (SRS-2). J Psychoeduc Assess. 2014;32:365-69.
11. Sharma R. Revised Kuppuswamy's socioeconomic status scale: explained and updated. Indian Pediatr. 2017;54:867-70.
12. Weiss MJ, Harris SL. Teaching social skills to people with autism. Beh Mod. 2001;25:785-802.
13. Lyra L, Rizzo LE, Sunahara CS, et al. What do Cochrane systematic reviews say about interventions for autism spectrum disorders. Sao Paulo Med J. 2017;135:192-201.
14. Malhi P, Singhi P. A retrospective study of toddlers with autism spectrum disorder: Clinical and developmental profile. Ann Indian Acad Neurol. 2014;17:25-29.
15. Nair MK, Russell PS, George B, et al. CDC Kerala 9: Effectiveness of low intensity home based early intervention for autism spectrum disorder in India. Indian J Pediatr. 2014; 81:S115-9.
16. Pickles, Andrew, et al. Parent-mediated social communication therapy for young children with autism (PACT): long-term follow-up of a randomised controlled trial. Lancet. 2016; 388:2501-9.
17. Jonsson U, Olsson NC, Coco C. et al. Long-term social skills group training for children and adolescents with autism spectrum disorder: a randomized controlled trial. Eur Child Adolesc Psychiatry. 2019;28:189-201.

Web Table I pSRS-2 Subscales Scores At Baseline (T1), Immediate Post Therapy (T2) and 3 Months Post Therapy (T3)

pSRS-2 Subscales		Social Awareness	Social Cognition	Social Communication	Social Motivation	Restricted and Repetitive Behaviors	pSRS-2 T Score
Mean (SD)	T1	17.10 (3.71)	23.67 (7.45)	34.87 (9.10)	21.40 (5.56)	24.73(6.77)	83.5(6.68)
	T2	14.83 (3.13)	20.73 (5.47)	32.07 (8.64)	19.20 (5.26)	22.23(6.75)	80.1(7.86)
	T3	13.37 (3.01)	18.83 (5.12)	29.63(7.96)	17.47 (4.62)	20.47(6.92)	76.9(8.0)

T1: Baseline T2: immediate post therapy; T3: 3 months post therapy; T1 - T2 measures immediate treatment effect, T1 - T3 measures long-term effect; T2 –T3 measures effects sustained in home and school settings. P<0.001 for all comparisons between T1-T2, T2-T3 and T1-T3.

Adolescent Health Academy Statement on the Care of Transgender Children, Adolescents, and Youth

HARISH KUMAR PEMDE,[1] UTKARSH BANSAL,[2] PIYALI BHATTACHARYA,[3] RAM NIWAS SHARMA,[4] SANJIV KUMAR,[5] POONAM BHATIA,[6] SANJAY NIRANJAN,[7] SUHAS DHONDE,[8] JAGDISH CHANDRA GARG[9]

[1]*Department of Pediatrics, Lady Hardinge Medical College, New Delhi.*
[2]*Department of Pediatrics, Hind Institute of Medical Sciences, Safedabad, Barabanki, Uttar Pradesh.*
[3]*Department of Pediatrics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh.*
[4]*Dr RN Sharma Clinic, Agra, Uttar Pradesh.*
[5]*Shekhar Sarraf Memorial Hospital, Aligarh, Uttar Pradesh.*
[6]*Tot's 2 Teens Child Guidance Clinic, Dewas, Madhya Pradesh.*
[7]*Neo Child Clinic, Lucknow, Uttar Pradesh.*
[8]*Niramaya Nursing Home, Gwalior, Madhya Pradesh.*
[9]*Garg Nursing Home, Gwalior, Madhya Pradesh.*
Correspondence to: Dr Utkarsh Bansal, Professor and Head, Department of Pediatrics, Hind Institute of Medical Sciences, Safedabad, Barabanki, Uttar Pradesh.

Justification: The transgender community has been long stigmatized, and discriminated against, and faces numerous mental and physical problems. Certain indicators of transgender personality appear during childhood and more often before puberty begins. This puts the onus on Pediatricians to identify and offer evidence-based care for their benefit. There is an urgent and deep-felt need to understand the medical, legal, and social aspects of the care of transgender children. Hence, Adolescent Health Academy decided to release a statement on the care of transgender children, adolescents, and youth.

Objectives: To review the existing international and national guidelines and recommendations to formulate a statement for the Pediatricians on (*a*) terminologies and definitions; (*b*) legal status in India; and (*c*) implications for pediatric practice.

Process: A task force was convened by the Adolescent Health Academy as the writing committee to draft the guidelines. These were approved by all the members of the task force and the Executive Board of Adolescent Health Academy (2022).

Recommendations: Gender identity develops in childhood and adolescence as a feeling of self, and it should be respected to mitigate gender dysphoria. The law permits transgenders the right of self-affirmation and it upholds their dignity in society. The transgender community is prone to victimization, and prejudice leading to a high risk of substance abuse, suicidal ideation, and mental health issues. Pediatricians are the primary care providers of children and adolescents including those with gender incongruence, so they should be abridged with gender-affirmative practices. Gender-affirmative care involves pubertal suppression, hormonal therapy, and surgery which should be done in conjugation with the social transition, by a gender-affirmative care team.

Key Words: *Gender dysphoria, Gender-affirmative care, Gender identity, Gender incongruence, Sex.*

Published online: May 14, 2023; **PII:** S097475591600534

Gender identity is a feeling or internal sense of being a girl, a boy, both, or neither which begins to develop in early childhood and evolves to finally emerge in adolescence and youth [1]. A person can be cisgender when the gender identity is the same as the sex assigned at birth or gender-diverse/gender incongruent when the person's gender identity or expression differs from the sex assigned at birth.

Gender incongruence may also be associated with gender dysphoria or clinically significant distress in important areas of daily functioning. Gender dysphoria generally becomes more prominent as children approach puberty and adolescence (**Box I**).

Traditionally, this less-understood population faces stigma, discrimination, victimization, and significant physical and mental health issues leading to a high risk of suicide as they do not conform to the accepted social stereotypes [3,4]. Family and societal rejection or non-acceptance of transgender adolescents are few of the strongest predictors of mental health problems [5].

There is a felt need to love, value, and nurture such children as they are highly vulnerable. Affirming care in childhood can significantly improve mental health and outcomes in this community. Transgender and gender-diverse adolescents and youth face considerable barriers to accessing health information and services [6]. There is a gap

Box I Gender Dysphoria as Defined by DSM-5-TR

The DSM-5-TR defines Gender Dysphoria [2] as a marked incongruence between one's experienced/expressed gender and their assigned gender, lasting at least 6 months,

In children, as manifested by at least six of the following (one of which must be the first criterion):

- A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender)
- In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing
- A strong preference for cross-gender roles in make-believe play or fantasy play
- A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender
- A strong preference for playmates of the other gender
- In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities
- A strong dislike of one's sexual anatomy
- A strong desire for the physical sex characteristics that match one's experienced gender

In adolescents and adults, as manifested by at least two of the following:

- A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
- A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
- A strong desire for the primary and/or secondary sex characteristics of the other gender
- A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
- A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
- A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)

To meet the criteria for diagnosis, the condition must also be associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision [2].

in formal medical training confounded by almost no standardized treatment, medical interventions, or research in these children [7].

Being primary providers, pediatricians are responsible for the inclusive healthcare of transgender children, adolescents, and young adults and for providing support and guidance to their families [8,9]. In this policy statement, we bring forth the challenges faced by the transgender community and provide recommendations for pediatricians that will promote positive health and development of the youth who identify as transgender. The word 'transgender' will be used in this document to include all the words and phrases used to address the community with a gender identity that is not congruent to the sex assigned at birth.

OBJECTIVES

This statement is framed *i*) to describe the terminologies and definitions related to the transgender community; *ii*) to describe the legal status of transgender rights and their implications on Pediatric practice in India, and *iii*) to formulate recommendations for Pediatric practice related to the care of transgender children.

PROCESS

The Adolescent Health Academy (AHA) a subspecialty chapter of the Indian Academy of Pediatrics (IAP) formed a task force of pediatricians in May, 2022, on 'transgender care' to address the issues outlined above. The members comprised pediatric and adolescent experts. A series of online meetings were held periodically, the first on 7 May, 2022, to draft and finalize the recommendations.

A review of the literature was conducted by the members and relevant scientific material and research studies were shared. The main areas addressed were: *i*) definitions related to the transgender community, *ii*) gender dysphoria, *iii*) the status of transgender care, *iv*) the legal aspect of transgender care, *v*) transgender persons (protection of rights) act and rules, *vi*) the implications for pediatric practice, and *vii*) gender reaffirmation care.

Guidelines given by the World Health Organization (WHO), the United Nations (UN), the United Nations Children's Fund (UNICEF), the World Professional Association for Transgender Health (WPATH), the American Academy of Pediatrics (AAP), and the Association of Transgender Health in India (ATHI) were studied. [1,10-14]

TERMINOLOGIES AND DEFINITIONS

Sex is an individual's categorization based on the chromosomes, genitals, and reproductive tract. Gender is a social construct, made up of understandings and expectations culturally tied to people who were assigned sex as male or female at birth. Gender identity is the internal sense of self from the perspective of gender. Sexual orientation refers to

sexual attraction and is different from gender identity (**Fig. 1**). The terminologies and definitions used to describe the transgender community are given in **Box II** [12-17].

GLOBAL STATUS OF TRANSGENDER CARE

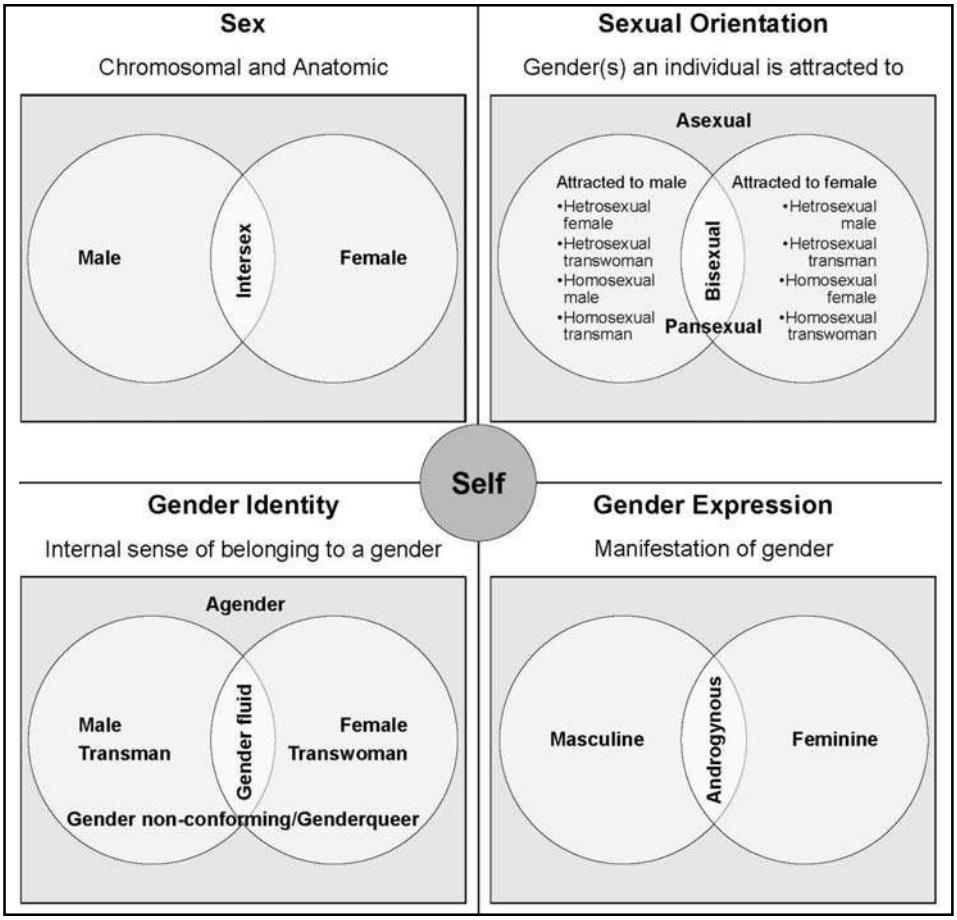
In July, 2013, the Office of the United Nations High Commissioner for Human Rights launched UN Free and Equal - an unprecedented global public information campaign to promote equal rights and fair treatment for lesbian, gay, bisexual, transgender, queer/questioning, intersex, and asexual (LGBTQIA+) people [18].

In July, 2016, the WHO re-framed "gender identity disorders" as "gender incongruence," moving diagnostic codes from the chapter on mental disorders to one on sexual health [19]. International Classification of Diseases (ICD)-11 redefined "transsexualism" and "gender identity disorder of children" (as in ICD-10's) with "gender incongruence of adolescence and adulthood" and "gender incongruence of childhood", respectively [20].

The adoption of the 2030 Agenda for Sustainable Development and its pledge to "leave no one behind" based on the normative framework of international human rights law, has reinforced the need to understand and improve the health and well-being of transgender people [21]. Many countries now have laws to guarantee the rights of equality and non-discrimination based on sex, sexual orientation, or gender identity. Marriage between same-sex couples is legally performed and recognized in 33 countries, constituting some 1.35 billion people (17% of the global population) [22].

The WPATH aims at bringing diverse dedicated professionals together for developing best practices and supportive policies globally to promote health, research, education, advocacy, respect, dignity, and equality for transsexual, transgender, and gender nonconforming people in all cultural settings [12].

The human rights council of the UN has extended States' responsible for the effective protection of all persons from



Adapted from "Health Care for Transgender and Gender Diverse Individuals: ACOG Committee Opinion, Number 823" [15].

Fig. 1 Concept of sex, sexual orientation, gender, and gender identity.

Box II Nomenclature and definitions [12-17]

Agender: term for individuals who do not identify as any gender at all.

Ally: term for individuals that support and rally the rights of LGBTQIA+ even though they don't identify within the community.

Androgynous: term for individuals with both male and female traits.

Asexual: term for individuals who don't feel sexual attraction to either sex or that don't feel romantic attraction in the typical way.

Assigned gender: the initial gender attributed to an individual after birth; for most individuals, this corresponds to the sex on their original birth certificate, aka *assigned gender, birth sex*.

Bisexual: an individual who is sexually and romantically attracted both to men and women.

Cisgender: a term for individuals whose experienced and expressed gender is congruent with their gender assigned at birth, that is, those who are not transgender.

Coming out: the act of sharing one's sexual orientation or gender identity with loved ones.

Crossdresser: These terms generally refer to those who may wear the clothing of a gender that differs from the sex which they were assigned at birth for entertainment, self-expression, or sexual pleasure, aka *drag queen or drag king*. Some cross-dressers and people who dress in drag may exhibit overlap with components of a transgender identity. The term transvestite is no longer used in the English language and is considered pejorative.

Deadname: The name that was given to a transgender individual by their family, and one by which they were identified. However, the individual may no longer use that name.

Detransition: an individual's retransition to the gender stereotypically associated with their sex assigned at birth.

Experienced gender: one's sense of belonging or not belonging to a particular gender, aka *gender identity*.

Expressed gender: how one expresses one's experienced gender.

Eunuch: an individual assigned male at birth whose testicles have been surgically removed or rendered non-functional and who identifies as a eunuch.

Gay: individuals who are sexually and romantically attracted to individuals of the same gender, aka *homosexual*.

Gender: a person's social status as male (boy/man) or female (girl/woman), or alternative category.

Gender assignment: assignment of gender to an individual. In typically developed newborns, the initial gender assignment (aka ''*birth-assigned gender*'') is usually made based on the appearance of the external genitalia.

Gender binary: a gender-categorization system limited to two options, male and female. Individuals who identify outside the gender binary may use a variety of gender identity labels, including genderqueer or nonbinary.

Gender diverse: people who do not conform to their society or culture's expectations for males and females.

Gender Dysphoria (GD) (capitalized): a diagnostic category in DSM-5, with specific diagnoses defined by age group-specific sets of criteria.

Gender dysphoria (not capitalized): the distress caused by the discrepancy between one's experienced/expressed gender and one's assigned gender and/or primary or secondary sex characteristics.

Gender expression: refers to how a person enacts or expresses their gender in everyday life and within the context of their culture and society, in the form of one's name, clothing, behavior, hairstyle, or voice, and which may or may not fit the usual frame of socially defined behaviors and characteristics associated with being either masculine or feminine.

Gender fluidity: refers to change over time in an individual's gender expression or gender identity, or both.

Gender Identity Disorder (GID): a diagnostic category in DSM-III and DSM-IV that was replaced in DSM-5 by Gender Dysphoria. Gender Identity Disorder is an obsolete term now and should not be used.

Gender identity: one's identity as belonging or not belonging to a particular gender, whether male, female, or a nonbinary alternative, aka *experienced gender*.

Gender Incongruence (capitalized): a diagnostic category (analogous to GD in DSM-5) proposed for ICD-11.

Gender incongruence (not capitalized): incongruence between experienced/expressed gender and assigned gender, and/or psychical gender characteristics.

Gender non-conforming: individuals who do not conform to either of the binary gender definitions, as well as those whose gender expression may differ from standard gender norms.

Gender perception: the objective interpretation of an individual's gender expression.

Gender role: cultural/societal definition of the roles of males and females (or of alternative genders).

Gender transition: the process through which individuals alter their gender expression and/or sex characteristics to align with their sense of gender identity.

Gender variance: any variation of experienced or expressed gender from socially ascribed norms within the gender binary.

Gender-affirmation procedures: Procedures that help an individual affirm their gender identity including social (clothes, name, pronouns), medical (hormone, laser, surgery), and legal (changing their name, and gender on identification documents), aka *gender reassignment.*

Gender-affirming surgery: surgical procedures intended to alter a person's body to affirm their experienced gender identity, aka *sex reassignment surgery*, *gender reassignment surgery*, or *gender-confirming surgery*.

Contd...

Continued from pre-page

Gendered behavior: behavior in which males and females differ on average.

Genderqueer: an identity label used by some individuals whose experienced and/or expressed gender does/do not conform to the male/female binary or who reject the gender binary.

Heterosexual: individuals who are sexually and romantically attracted to individuals of the opposite gender.

Homosexual: individuals who are sexually and romantically attracted to individuals of the same gender, aka *gay*.

Intersex conditions: a subset of the somatic conditions known as ''disorders of sex development'' or ''differences of sex development ''in which chromosomal sex is inconsistent with genital sex, or in which the genital or gonadal sex is not classifiable as either male or female. Some individuals who report their identity as ''intersex'' do not have a verifiable intersex condition.

Lesbian: Term for women sexually and romantically oriented toward other women.

LGBTQIA+: Term used to collectively refer to lesbian, gay, bisexual, transgender, questioning, queer, intersex, and asexual; and the plus sign (+) denotes inclusivity to cover all different sub-sects like allies, pansexual, non-cisgender, and non-heterosexuals, aka *LGBT*, *LGBTQ*, or *LGBTQ+*.

Misgender: when language is used that does not correctly reflect the gender with which a person identifies, aka *misgendering*.

Nonbinary: an individual whose gender identity is neither girl/woman nor boy/man.

Pansexual: an individual with a desire for all genders and sexes, aka *omnisexual*.

Pride flag: any flag that represents a segment or part of the transgender community. The colors reflect the diversity of the LGBT community and the spectrum of human sexuality and gender, aka *rainbow flag, LGBT flag,* or *queer flag*.

Pride parade: an outdoor event celebrating transgender social and self-acceptance, achievements, legal rights, and pride, aka *pride march, pride event,* or *pride festival*.

Retransition: second or subsequent gender transition whether by social, medical, or legal means.

Sex assigned at birth: the sex or gender first assigned to an individual after birth, aka *natal gender, birth-assigned sex,* or *gender assigned at birth*.

Sex: an individual's categorization as biologically male or female, usually based on the genitals and reproductive tract.

Sexual orientation: an individual's pattern of sexual attraction and physiological arousal to others of the same, other, both, or neither sex.

Sexuality: Encompasses all aspects of sexual behavior, including gender identity, orientation, attitudes, and activity. Sexuality is emotional, social, cultural, and physical. Sexuality development begins in childhood and becomes more pronounced in adolescence [42,43].

Social transition: The process by which transgender children or adolescents adopt the name, pronouns, and gender expression, such as clothing and haircuts, that match their gender identity.

They/Them/Their: Neutral pronouns used by some who have a nonbinary or nonconforming gender identity.

Trans: More recent umbrella term being increasingly used to avoid distinguishing between transgender and transsexual individuals.

Transgender: an umbrella term usually referring to individuals whose experienced or expressed gender does not conform to normative social expectations based on the gender they were assigned at birth.

Transgender man: A term to describe an individual who was assigned female at birth who identifies as a male, aka *transman, female-to-male, FTM, transgender male, transmasculine, or man of trans experience.*

Transgender woman: A term to describe an individual who was assigned male at birth who identifies as a female, aka *transwoman, male-to-female, MTF, transgender female, transfeminine, or woman of trans experience.*

Transition: the process whereby individuals usually change from the gender expression associated with their assigned sex at birth to another gender expression that better matches their gender identity.

Transphobia: negative attitudes, beliefs, and actions concerning transgender and gender-diverse peopleas a group, aka *anti-transgender bias.*

Transsexual: a term often reserved for the subset of transgender individuals who desire to modify, or have modified, their bodies through hormones or surgery to be more congruent with their experienced gender.

aka-also known as, DSM-Diagnostic and Statistical Manual of Mental Disorders, ICD-International Classification of Diseases.

discrimination based on sexual orientation or gender identity [10].

Population Estimates

The transgender population has been estimated by health systems-based studies to be 0.02-0.1%, survey-based studies of adults to be 0.3-0.5% (transgender), 0.3-4.5% (all transgender and gender diverse people), and survey-based studies of children and adolescents to be as high as 1.2-2.7% (transgender), 2.5-8.4% (all transgender and gender diverse people) [12]. The Census of India (2011), for the first time, included the "other gender" as a sex category who turned out to be 487,303 in the total estimated population of 1.247 billion [23].

Legal Aspects Related to Transgender People

For a long period, the transgender community is fighting for its legal rights. Slowly but definitely, things are going in their way. The Government and Supreme Court have taken some proactive steps to address the issues related to the transgender

community [24]. For the first time, in 2014 this community had its voice heard when the Supreme Court delivered the NALSA (National Legal Services Authority) judgement, which led to the recognition of transgender people as the "third gender" [25]. The transgender community faced deep-rooted prejudices from society, and the landmark judgement of the Supreme Court in 2018, decriminalizing Section 377 (punishment for unnatural sex) of the Indian Penal Code has given them substantive equality [26].

Recently, Madras High Court directed the Tamil Nadu Government to make a glossary with suggestions of 24 words and expressions for a dignified identity of the transgender community [27]. The court directed media to be sensitive while reporting about the transgender community and suggested arranging seminars for building a queer-friendly future, compiling words and expressions to be used while reporting, and formal training to be given to editors and reporters. The court observed that medical courses amplify queerphobia and discrimination against the transgender community and added that medical professionals should be "non-judgemental and free of moral and personal prejudices about their patient's identity on the gender spectrum, or their sexuality". The court also warned of strict action against any professional found indulging in "conversion therapy", i.e., changing anybody's sexual orientation [28].

In October 2021, Calcutta High Court allowed transgender persons to appear in Kolkata Police Recruitment Examination [27]. The Kerala High Court, in March 2021, held that transgender people should be allowed entry into National Cadet Corps (NCC) [24]. In November 2021, the Guwahati High Court directed the state government to take appropriate measures to look after the health issues of the transgender community [24]. The Delhi High Court directed the state government to construct separate toilets for transgender persons [24].

The Karnataka Government made a policy to provide reservations for transgender persons in state police recruitment and introduced a 1% reservation for the transgender community in government jobs [24]. States like Kerala, Assam, and Tamil Nadu have established Welfare Boards for transgender people [24].

TRANSGENDER PERSONS (PROTECTION OF RIGHTS) ACT AND RULES

The Transgender Persons (Protection of Rights) Act 2019 (TPA) was passed in August, 2019 and brought into effect in January, 2020 [29]. It was the first legislative effort to address the issues of the transgender community. The act has given the right to self-affirmation to individuals. In September, 2020, the Transgender Persons (Protection of Rights) Rules were notified in the Gazette of India [30]. The TPA recognizes transgender as "a person whose gender does not match with the gender assigned to that person at birth and includes trans-man or trans-woman (whether or not such person has undergone Sex Reassignment Surgery or hormone therapy or laser therapy or such other therapy), person with intersex variations, genderqueer and person having such socio-cultural identities as *kinner*, *hijra*, *aravani*, and *jogta*."

Provisions of the Transgender Persons (protection of rights) Act and Rules

1. *Certificate of Identity*: The transgender person is allowed to be recognized as such and have a self-perceived gender identity. A transgender person may make an application to the District Magistrate, in person, by post, or online, for a certificate of identity indicating the gender as 'transgender'. The application should be accompanied by an affidavit and the report of a psychologist, without any medical (*meaning thereby physical*) examination. A revised certificate may be applied only if the individual undergoes surgery, along with a certificate issued to that effect by the Medical Superintendent of the medical institution in which that person has undergone surgery, to change their gender either as a male or a female.

2. *Rights and entitlements*: The Central Government is directed to provide the following rights to the transgender community:

a. *Prohibition against Discrimination*: It prohibits the discrimination against a transgender person, including denial of service or unfair treatment concerning *i*) education; *ii*) employment; *iii*) healthcare; *iv*) access to, or enjoyment of goods, facilities, opportunities available to the public; *v*) right to movement; *vi*) right to reside, rent, or otherwise occupy the property; *vii*) opportunity to hold public or private office; and *viii*) access to a Government or private establishment in whose care or custody a transgender person is.

b. *Right of residence*: Every transgender person shall have a right to reside and be included in their household. If the immediate family is unable to care for the transgender person, the person may be placed in a rehabilitation center, on the orders of a competent court.

c. *Employment*: No Government or private entity can discriminate against a transgender person in employment matters, including recruitment, and promotion. Every establishment is required to designate a person to be a complaint officer in this regard.

d. *Education*: Educational institutions funded or recognized by the Government shall provide inclusive

education, sports, and recreational facilities for transgender persons, without discrimination.

e. Health care: The Government must take steps to provide health facilities to transgender persons including separate HIV surveillance centers, hormonal therapy, and sex reassignment surgeries. The Government shall review the medical curriculum to address the health issues of transgender persons, promote research, and provide comprehensive medical insurance schemes (covering sex reassignment surgery, hormonal therapy, laser therapy, or any other health issues) for them.

f. Reservation: Government shall notify the general category transgender persons in 'other backward classes' to enable them to avail the benefits of vertical reservation. This sub-rule shall not deny benefits to transgender persons belonging to other reserved categories.

g. Establishments: Government shall create institutional and infrastructure facilities such as separate wards in the hospital, washrooms, etc within two years from the date of commencement of these rules.

h. Awareness: Government shall carry out an awareness campaign to educate, communicate and train transgender persons to avail themselves of the benefits of welfare schemes, and their rights; eradicate stigma and discrimination against transgender persons, and mitigate its effects.

3. *Establishment of National Council for Transgender persons*: It will *i*) advise the Central Government on the formulation of policies, programs, legislation, and projects for transgender persons; *ii*) monitor and evaluate the impact of policies and programs designed for achieving equality and full participation of transgender persons; *iii*) review and coordinate the activities of all the departments of Government and other Governmental and non-Governmental organizations which are dealing with matters relating to transgender persons; *iv*) redress the grievances of transgender persons; and *v*) perform such other functions as may be prescribed by the Central Government.

4. *Offenses and penalties*: The Act recognizes the following offenses against transgender persons: *i*) forced or bonded labor (excluding compulsory government service for public purposes), *ii*) denial of use of public places, *iii*) removal from the household, and village,(*iv*) physical, sexual, verbal, emotional or economic abuse. Penalties for these offenses vary between six months and two years, and a fine.

In addition to this, the Central Government has set up shelter houses as part of the *Garima Greh* project, formulated a support scheme named Support for Marginalized Individuals for Livelihood and Employment (SMILE) under the Union Ministry of Social Justice and Employment, issued directives to conduct awareness programs for child welfare committees, juvenile justice boards, prison functionaries, healthcare officials, and media persons, and made a National Portal for transgender persons and started active training programs enabling the issuance of identity cards to transgender persons by the District Magistrate.

The TPA is criticized due to a few issues [31]:

- Not addressing the provision of reservations for transgenders completely.
- Requiring certification of identity and not acknowledging the self-identification of transgender persons.
- Using the terms transgender and intersex interchangeably, which have different meanings.
- Labor timings for transwomen should be equal to ciswomen.
- Making crimes like rape, etc against transgender persons punishable by only 6 months to 2 years.
- Violating the transgender's constitutional Right to Freedom of Residence as they must either stay with their parents or approach a court.
- Not addressing concerns about recognizing rights in marriage, divorce, and adoption.

According to Guidelines for Blood Donor Selection and Blood Donor Referral, 2017 transgender people are permanently prohibited from donating blood [32]. Despite many developments in favor of the transgender community, oppression, discrimination, queerphobia, and social stigma are still prevalent. Attitudinal change in the public is required.

Work done by NGOs

The Association of Transgender Health in India (ATHI) is conducting workshops and educational programs to sensitize medical students and healthcare professionals about the issues related to transgender health. It has developed the Indian Standards Of Care (ISOC-1) to help medical professionals to address various health issues of transgender people [14]. The Tata Institute of Social Sciences, in collaboration with Pernod Ricard India Foundation and Collective Good Foundation, launched India's first academic corporate fellowship program for transgender youth [33].

IMPLICATIONS FOR PEDIATRIC PRACTICE

A child may express gender identity at an early age or as late as adolescence but usually by 10 years of age [34]. So, these children and adolescents are brought by the parents to pediatricians who are their primary medical providers, thus

pediatricians should know how to support the child with this normal manifestation of neurodiversity.

Role of Pediatrician

Early detection, support, and intervention to initiate early gender-affirmative care by family and society. It is documented that if psychosocial gender-affirming care is started early in childhood, it promotes well-being and prevents dysphoria, which is sustained over the transition to adolescence [35].

Early pointers

Certain behavioral patterns may be noticed by parents if the child is in a dilemma leading to gender dysphoria. Younger children may express their gender identity with role play, showing interest in toys, clothing, hairstyle, and mannerisms. They get uneasy with games, and roles in social activities, disliking gender-assigned washrooms. Young children may outrightly say they are of another gender, become upset about being misgendered, not like their name, or want to get rid of their genitals. Older ones may self-harm and puberty is a stressful phase for them for obvious reasons. However, every child or adolescent with gender incongruence will have a unique presentation, and intervention options may differ for each.

Guiding Principles for Affirmative Care

The team in gender-affirmative care consists of parents, pediatricians, society, teachers, social workers, psychologists, legal and ethics members, pediatric endocrinologists, and surgeons who are interacting with each other with a focus on the child with gender incongruence. Pediatricians must team up with parents to facilitate the gender-affirmation process and the gender journey of the child to avoid gender dysphoria. Factors affecting care are enumerated in **Table I**.

Issues: Stigma, intolerance, discrimination, and aggression have an impact on the health and welfare of these children along with other medical or psychosocial co-morbidity [36]. Transgender children, adolescents, and youth have increased chances of depression, anxiety, eating disorders, self-harm, and suicide. The discrimination and bias towards them lead to an internal conflict between their appearance and identity, which is further aggravated by poor access to healthcare [6]. This ushers mental health issues and they resort to high-risk behavior and substance abuse promoting lifestyle disorders, physical and sexual abuse, and violence [37].

Creating nurturing environment: Transgender children and adolescents may face physical, emotional, and mental abuse by their family members, which may lead them to leave their own families and seek support from similar-minded community members [5]. Similarly, a discriminatory environment at school may lead to stress and dropouts. Pediatricians can help create social acceptance, nurturing environment at school, family acceptance, and social transition at the child's as well as the parents' level. Social transition initiated by the child if supported by the family and the school is beneficial in reducing emotional stress and curtailing adverse mental effects [38].

Medical and surgical management of transgender adolescents [12,39,40]

Hormonal treatment can include suppression of puberty (Gonadotrophin releasing hormone analogs, alternative progestin), or induction of pubertal changes of affirmed gender (oral estrogen for feminizing and injectable testosterone for masculinizing). Induction can be done only after the consent age i.e., 18 years. Both these interventions have advantages and disadvantages so there are stringent eligibility criteria (**Box III**). During feminization or masculinization hormonal therapy the target levels are to reach the physiological range (serum estradiol: 100-200 pg/mL and serum testosterone: 300-1000 ng/dL respectively).

Table I Factors Affecting Gender-Affirmative Care

Helpful	*Barriers*
• Address with the name, pronouns, and gender identity that the individual prefers • Supportive response • Social transition - changing of external appearance (clothing, hairstyle), name, and pronouns to match one's internal gender • Mitigate dysphoria • Support children to explore their gender • Provide information about gender-affirming medical interventions • Inform about the effects of treatments on future fertility, and options for fertility preservation • Involve gender affirmative team • Acknowledge the legal aspects	• Limited availability of gender-affirming care • Prejudice/misunderstanding of caregivers • Poor social, family, and peer acceptance of the individual's gender identity • Expensive transgender healthcare • Inappropriate use of drugs and hormones • Non-availability of health insurance and limited support from the Government • Relatively few clinical programs • Transphobia (negative attitudes, beliefs, and actions concerning transgender people) • Lack of structured training for healthcare professionals • Poor knowledge of the law and available legal support

Box III Gender-affirming Treatment of Transgender Adolescents [12, 39, 40]

Essential criteria for gender-affirming treatment	• Diagnosed as gender incongruence as per the ICD-11 • The experience of gender diversity/incongruence is marked and sustained over time. • Gender dysphoria worsened with the onset of puberty • Demonstrates the emotional and cognitive maturity required to provide informed consent/ assent for the treatment. • Mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed. • Informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility. • Reached Tanner's stage 2 of puberty. • Received at least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, unless hormone therapy is either not desired or is medically contraindicated.	
Baseline assessment	Height, weight, blood pressure, general physical examination, sexual maturity rating(SMR)	
Baseline investigations TSH)	CBC, LFT, RFT, HbA1C, Lipid profile, Hormones (LH, FSH, Estradiol, Testosterone, Prolactin,	

Pubertal suppression treatment	• Gonadotropin-releasing hormone analogs (GnRH analogs)
	  • slow-release triptorelin acetate, intramuscular 3.75 mg every 4 week
	• Progestin preparations
	  • depot medroxyprogesterone	

Gender-affirmative hormonal treatment	*Induction of female puberty* • 17β-estradiol (oral) Initiate at 5µg/kg/d and increase every 6 mo by 5 µg/kg/d up to 20 µg/kg/d according to estradiol levels Adult dose: 2-6 mg/day • 17β-estradiol (transdermal) Initial dose 6.25-12.5 µg/24 h (cutting 25 µg patch to ¼ then ½) Titrate up by every 6 mo by 12.5 µg/24 h according to estradiol levels. Adult dose: 50-200 µg/24 hours	*Induction of male puberty* • testosterone esters (IM or SC) Initiate at 25 mg/m^2/2 weeks (or half this dose weekly) Increase by 25 mg/m^2/2 weeks every 6 months until the adult dose and target testosterone levels are achieved. Adult dose: 100-200 mg every 2 week
Monitoring • *Every 3-6 months*	*Pubertal suppression treatment* height, weight, sitting height, blood pressure, Tanner's stage	*Gender-affirmative hormonal treatment* height, weight, sitting height, blood pressure, Tanner's stage
• *Every 6-12 months*	transgender males: LH, FSH, testosterone, 25OH vitamin D transgender females: LH, FSH, estradiol, 25OH vitamin D	transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin Dtransgender females: prolactin, estradiol, 25OH vitamin D
• *Every 1–2 years*	BMD using DXA Bone age on X-ray of the left hand (if clinically indicated)	BMD using DXA Bone age on X-ray of the left hand (if clinically indicated)
Gender-affirmative surgical treatment	*Core procedures in transwomen* • breast augmentation • orchidectomy • penectomy • vaginoplasty • clitoroplasty • labiaplasty • vulvoplasty • corporectomy • feminizing urethroplasty	*Core procedures in transmen* • reduction mammoplasty • hysterectomy and bilateral salpingo-oophorectomy • vaginectomy • phalloplasty • metaidoioplasty • scrotoplasty • urethroplasty • placement of a testicular prosthesis and an erectile implant/penile prosthesis
	Ancillary procedures in transwomen • hair transplants • advancement of hairline • facial feminizing surgery • rhinoplasty • thyroid chondroplasty and voice	*Ancillary procedures in transmen* • mandibular transplants • pectoral/ calf implants • facial masculinizing surgery • rhinoplasty • laryngeal and voice affirmative surgery

Contd...

Box contd from pre-page

	affirmative surgery • Thoracic shaping • Abdominoplasty, liposuction, high-definition body contouring • Non-invasive aesthetic procedures	• Thoracic shaping • Abdominoplasty, lipofilling, high-definition body contouring • Non-invasive aesthetic procedures

ICD: international classification of diseases, SMR: sexual maturity rating, CBC: complete blood count, LFT: liver function test, RFT: renal function test, HbA1C: hemoglobin A1c, LH: luteinizing hormone, FSH: follicle stimulating hormone, TSH: thyroid stimulating hormone, GnRH: Gonadotropin: releasing hormone, BMD: bone mineral density, DXA: dual-energy X-ray absorptiometry. [a]Gonadotropin and sex steroid levels are assessed for gonadal axis suppression. If the gonadal axis is not completely suppressed, the interval of GnRH analog can be shortened or the dose increased. Anthropometric measurements and X-rays of the left hand to monitor bone age are for evaluating growth and dual-energy X-ray absorptiometry scans assess the bone mineral density. [b]Sex steroid levels are assessed to ensure endogenous sex steroids are lowered and administered sex steroids are maintained at a level appropriate for the treatment goals. Erythrocytosis, hypertension, excessive weight gain, lipid changes are to be monitored in transgender males while hypertension monitoring in transgender females.

Speech therapy and voice coaching are integral parts of care. A "voice and communication specialist" help may be needed to allow transgender adolescents to converse per their gender identity.

Gender-affirmation surgery can be only performed when the transgender has attained the age of legal maturity and demonstrates the emotional and cognitive maturity required to provide informed consent. The transgender should be living in a gender-congruent role for at least 12 months before undergoing gender-affirmative surgery and the reproductive options should be discussed before. It is performed by experts in the field following all legal provisions and after an explanation of success rates and complications of various procedures. After treating a person in a pediatric setting transition to adult healthcare services is taken care of by the team.

A potentially harmful approach is reparative (conversion) therapy to the gender assigned at birth because negative reinforcement leads to substantial mental and social health consequences, thus it is not recommended and is harmful and unlawful [28, 41].

A few tools are recommended to guide families in the gender-affirming healthcare journey of their children like, finding affirming providers-medical team, being prepared to share, identifying friends and family who can support the gender journey, finding a support group (like *Sweekar: The Rainbow Parents group*), knowing the medications, getting the proper screenings for long-term health issues, having the medical history to inform the provider of risk factors and also guide gender-affirmative interventions, making the child exercise regularly and maintaining a healthy diet, especially with hormone therapy, knowing transgender rights to handle discrimination better and asking questions and building trust with the medical provider. Pediatricians should lead and employ the LEARN strategy (L - Look, Listen, and Learn from the child, the child's gender identity, E - Educate self, parents, and society, A - Advocate the rights of the child at home and educational institution, R - Resource for parents' children and society, and N- be Non-judgmental) [14].

The issue of transgender (or gender identity) should not be confused with disorders of sex development, or with sexual orientation (other than the societal norm of heterosexual orientation). In the future, gender identity may become another component for screening in the pediatrician's office for care of the families in a dignified manner as a spectrum of gender poles.

RECOMMENDATIONS

- Gender is not a binary concept with male and female being the two poles, but a whole spectrum exists between the two which may be a blend.
- Education about gender variation and fluidity should be incorporated into the school curriculum to develop a non-binary and inclusive system.
- Acceptance of LGBTQIA+ or transgender-specific diversity and providing a gender-neutral and affirming environment with awareness in society.
- Transgender people are prone to face stigma, discrimination, victimization, and abuse, which can cause significant physical and mental health issues leading to a high risk of substance abuse and suicide.
- The gender identity of an individual should be respected with a sensitive and non-judgmental approach to mitigate gender dysphoria.
- Schools, work, and public places should have gender-neutral restrooms and other facilities for gender-non-conforming individuals.
- The spectrum of gender identity variation and incongruence should be included as a part of medical education to promote training in gender-affirmative practice.

- Pediatricians dealing with a transgender child should not presume the gender identity or sexual orientation but should enquire about the client's description of self.
- Gender incongruence requires a multi-disciplinary team approach to deliver affirmative care including a pediatrician, child and adolescent psychiatrist, clinical psychologist, pediatric endocrinologist, gender-affirming surgeon, and speech therapist.
- Every trans-child will require individualized care, honoring preferred name and pronouns, and informed choices about medical gender-affirmative care.
- Medical intervention should only follow the informed assent of adolescents and the consent of their primary caretaker.
- Gender-affirmative hormonal intervention and genital surgery can be done only after the legal age of consent i.e., 18 years.

Acknowledgments: We wish to acknowledge the executive board members of AHA 2021-22 and 2022-23 including Dr. JC Garg, Dr. Harish K Pemde, Dr. Sukanta Chatterjee, Dr. Geeta Patil, Dr. RN Sharma, Dr. Suhas Dhonde, Dr. RG Patil, Dr. Ranjith P, Dr. Geeta Bansal, Dr. Prashant K Saboth, Dr. Prashant Kariya, Dr. Piyali Bhattacharya, Dr. Deepak Gautam, Dr. A Chenthil, Dr. Shamik Ghosh.

Contributors: All authors were part of the AHA Task Force on Transgender care that formulated these Guidelines. HKP, PB1, RNS, SD, JCG: conceived the Guidelines, prepared the agenda, and executed them administratively. HKP: led the discussions and all the members actively participated. HKP, UB, PB1, SN, SK, PB2: reviewed the literature. PB1, SK, PB2, SN, UB: wrote the first draft of the respective sections assigned to them. Review of literature and the first drafts were peer-reviewed by HKP, PB1, JCG. HKP, RNS, SD: provided administrative support from Adolescent Health Academy and coordinated between the team and executive board members of the Academy. UB, PB1: drafted the final document; and edited by HKP. All authors approved the final recommendations of the statement.

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

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. World Health Organization. Gender and health. Accessed May 17, 2022. Available from: *https://www.who.int/health-topics/gender#tab=tab_1*
2. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.
3. Kattari SK, Call J, Holloway BT, et al. Exploring the experiences of transgender and gender diverse adults in accessing a trans knowledgeable primary care physician. Int J Environ Res Public Health. 2021;18:13057.
4. Connolly MD, Zervos MJ, Barone CJ 2nd, et al. The Mental health of transgender youth: Advances in understanding. J Adolesc Health. 2016;59:489-95.
5. Katz-Wise SL, Rosario M, Tsappis M. Lesbian, gay, bisexual, and transgender youth and family acceptance. Pediatr Clin North Am. 2016;63:1011-25.
6. Safer JD, Coleman E, Feldman J, et al. Barriers to healthcare for transgender individuals. Curr Opin Endocrinol Diabetes Obes. 2016;23:168-71.
7. Weiselberg EC, Shadianloo S, Fisher M. Overview of care for transgender children and youth. Curr Probl Pediatr Adolesc Health Care. 2019;49:100682.
8. Landau N, Hamiel U, TokatlyLatzer I, et al. Paediatricians' attitudes and beliefs towards transgender people: A cross-sectional survey in Israel. BMJ Open. 2020;10:e031569.
9. Thomas R, Pega F, Khosla R, et al. Ensuring an inclusive global health agenda for transgender people. Bull World Health Organ. 2017;95:154-56.
10. United Nations Development Project. Discussion Paper: Transgender Health and Human Rights 2013. Accessed July 4, 2022. Available from: *https://www.undp.org/publications/discussion-paper-transgender-health-human-rights*
11. United Nations Children Fund. Eliminating discrimination against children and parents based on sexual orientation and/or gender identity. November 2014. Accessed June 21, 2022. Available from: *https://www.unicef.org/media/91126/file#:~:text=Transgender%20an%20inconsistency,expectations%20of%20gender%2Dnormative%20behaviour*
12. Coleman E, Radix AE, Bouman WP, et al. Standards of care for the health of transgender and gender diverse people, version 8. Intern J Transgend Health. 2022;23:S1-259.
13. Rafferty J, Health Committee on Psychosocial Aspects of Child and Family Health, Committee on Adolescence, Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. Pediatrics. 2018;142:e20182162.
14. Sharma S, Sharma B, John S, Bansal G, Sharma V, Sejwal V, editors. Indian Standards of Care for Persons with Gender Incongruence and People with Differences in Sexual Development/Orientation. Wisdom Publications; 2021.
15. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice; American College of Obstetricians and Gynecologists' Committee on Health Care for Underserved Women. Health Care for Transgender and Gender Diverse Individuals: ACOG Committee Opinion, Number 823. Obstet Gynecol. 2021;137:e75-e88.
16. Betts J. What Does LGBTQIA+ Stand For? Full Acronym Explained. abbreviations. yourdictionary.com. Accessed June 17, 2022. Available from: *https://abbreviations.yourdictionary.com/what-does-lgbtqia-stand-for-full-acronym-explained.html*
17. Byne W, Karasic DH, Coleman E, et al. Gender dysphoria in adults: An overview and primer for psychiatrists. Transgend Health. 2018;3:57-70.
18. Office of the High Commissioner for Human Rights. UN Free & Equal: a global campaign to promote equal rights for LGBTI people. Accessed July 21, 2022. Available from: *https://www.ohchr.org/en/sexual-orientation-and-gender-identity/un-free-equal-global-campaign-promote-equal-rights-lgbti-people*
19. World Health Organization. International Classification of

Diseases (ICD). Accessed August 14, 2022. Available from: *https://www.who.int/classifications/classification-of-diseases*
20. International Classification of Diseases 11th Revision. 17-Conditions related to sexual health. Gender incongruence. Accessed August 14, 2022. Available from: *https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f411470068*
21. United Nations Sustainable Development Group. Universal Values Principle Two: Leave No One Behind. Accessed September 2, 2022. Available from: *https://unsdg.un.org/2030-agenda/universal-values/leave-no-one-behind*
22. Wikipedia. Same-sex marriage. 2022. Accessed October 2, 2022. Available from: *https://en.wikipedia.org/wiki/Same-sex_marriage#cite_note-2*
23. Ministry of Social Justice & Empowerment, GOI. Welfare of Transgenders. Accessed July 14, 2022. Available from: *https://pib.gov.in/PressReleaseIframePage.aspx?*
24. Chacko J. Towards a gender-inclusive future: Judicial developments recognising rights of the transgender community in India. Bar and Bench - Indian Legal news. Accessed October 5, 2022. Available from: *https://www.barandbench.com/columns/towards-a-gender-inclusive-future-judicial-developments-recognising-the-rights-of-the-transgender-community-in-india-and-the-road-ahead*
25. National Legal Ser.Auth vs Union Of India & Ors thr. Secretary Ministry of Law and Justice, W. P. (Cvl.) No. 400 of 2012 (Supreme Court of India). Accessed October 17, 2022. Available from: *https://main.sci.gov.in/jonew/judis/41411.pdf*
26. Navtej Singh Johar & Ors. vs Union of India thr. Secretary Ministry of Law and Justice, W. P. (Crl.) No. 76 of 2016 (Supreme Court of India). Accessed October 19, 2022. Available from:*https://main.sci.gov.in/supremecourt/2016/14961/14961_ 2016_Judgement_06-Sep-2018.pdf*
27. Notification Regarding The Glossary For Addressing The LGBTQIA + Community. Tamil Nadu Government Gazette [G.O. Ms. No. 52, Social Welfare and Women Empowerment [SW-3(1)], 20th August 2022. Accessed Oct 24, 2022. Available from: *https://www.paalputhumai.com/wp-content/uploads/2022/08/Glossary-for-adressing-LGBTQIA-community-2022-by-TN-SW-Dept.pdf*
28. Rana R. Madras HC Issues Orders Against "Queerophobia", Demands Changes In Medical Education. thelogicalindian.com. Accessed Oct 17, 2022. Available from: *https://thelogicalindian.com/lgbtq/madras-hc-issues-orders-against-queerophobia-30527*
29. The Transgender Persons (Protection of Rights) Act, 2019. Ministry of Law and Justice, Government of India. Accessed July 2, 2022. Available from: *https://prsindia.org/files/bills_acts/bills_parliament/2019/The%20Transgender%20Persons%20(Protection%20of%20Rights)%20Act,%202019.pdf*
30. The Transgender Persons (Protection of Rights) Rules, 2020. Ministry of Social Justice and Empowerment, Government of India. Accessed July 2, 2022. Available from: *https://thc.nic.in/Central%20Governmental%20Rules/Transgender%20Persons%20(Protection%20of%20Rights)%20Rules,%202020.pdf*
31. Dhar M. Critical Analysis of Transgender Persons (Protection of Rights) Act, 2019. Law & Order. 2021. Accessed September 15, 2022. Available from: *https://www.law-order.org/post/critical-analysis-of-transgender-persons-protection-of-rights-act-2019*
32. National Blood Transfusion Council. NACO. Guidelines for Blood Donor Selection and Blood Donor Referral, 2017. Ministry of Health and Family Welfare, Government of India. Accessed Oct 15, 2022. Available from: *http://naco.gov.in/sites/default/files/Letter%20reg.%20%20guidelines%20for%20blood%20donor%20selection%20%26%20referral%20-2017.pdf*
33. Pernod Ricard India Foundation in partnership with the Tata Institute of Social Sciences launches India's 1st Academic-Corporate Fellowship Program for transgender persons. ANI News. Accessed Nov 17, 2022. Available from: *https://www.aninews.in/news/business/business/pernod-ricard-india-foundation-in-partnership-with-the-tata-institute-of-social-sciences-launches-indias-1st-academic-corporate-fellowship-program-for-transgender-persons20220414101915/*
34. Herman JL, Flores AR, Brown TNT, et al. Age of Individuals Who Identify as Transgender in the United States. Los Angeles, CA: The Williams Institute; 2017.
35. Hidalgo MA, Ehrensaft D, Tishelman AC, et al. The gender affirmative model: What we know and what we aim to learn. Human Develop. 2013;56:285-90.
36. Kuzma EK, Pardee M, Darling-Fisher CS. Lesbian, Gay, Bisexual, and Transgender health: Creating safe spaces and caring for patients with cultural humility. J Am Assoc Nurse Pract. 2019;31:167-74.
37. Gonzalez CA, Gallego JD, Bockting WO. Demographic characteristics, components of sexuality and gender, and minority stress and their associations to excessive alcohol, cannabis, and illicit (noncannabis) drug use among a large sample of transgender people in the United States. J Prim Prev. 2017;38:419-45.
38. Olson K, Durwood L, DeMeules M, McLaughlin K. Mental health of transgender children who are supported in their identities. Pediatrics. 2016;137:e20153223.
39. Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. Lancet Diabetes Endocrinol. 2017;5:816-26.
40. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;102:3869-903.
41. Telfer MM, Tollit MA, Pace CC, Pang KC. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. Med J Aust. 2018;209:132-36.
42. National Sexual Violence Resource Center. An overview of healthy childhood sexual development. Accessed December 2, 2022. Available from: *https://www.nationalcac.org/wp-content/uploads/2016/08/HealthySexualDevelopmentOverview.pdf*
43. Kar SK, Choudhury A, Singh AP. Understanding normal development of adolescent sexuality: A bumpy ride. J Hum Reprod Sci. 2015;8:70-4.

Screening and Management of Congenital Hypothyroidism – Guidelines by American Academy of Pediatrics, 2023

SUSHREE SMITA BEHURA, GANNAVARAPU PHANISRI NIKHILA, SANTOSH KUMAR PANDA

Department of Paediatrics, Kalinga Institute of Medical Sciences, KIIT DU, Bhubaneswar, Odisha.

Correspondence to: Dr Santosh Kumar Panda, Professor, Department of Pediatrics,Kalinga Institute of Medical Sciences, KIIT DU, Bhubaneswar, Odisha. doc.sant@yahoo.co.in

Guidelines for screening and management of congenital hypothyroidism in neonates have been recently updated by the American Academy of Pediatrics (AAP). This article compares new AAP guideline with the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) Guidelines, 2018 and lists the changes in screening, diagnosis, and management of congenital hypothyroidism suggested in the new guidelines, along with clinical utilization in the Indian scenario.

Keywords: *Newborn, Thyroxine, Thyroid stimulating hormone.*

Early detection of congenital hypothyroidism (CH) through newborn screening (NBS) and prompt treatment can prevent morbidities [1]. Indian infants are at higher risk of CH (approximately 1 in 1000) because of ethnicity, increased survival of very low birth weight (VLBW) neonates, and endemic iodine deficiency belts. However, countrywide NBS has not yet been established. The practice guidelines for CH in India were last given by the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) in 2018 [2,3].

Recently, the American Academy of Paediatrics (AAP) has published the clinical practice guidelines for CH [4]. The important changes in detection, diagnosis, treatment, and follow-up of children with CH, and its implication for Indian neonates are discussed in this update. The comparison between the AAP-2023 and ISPAE-2018 guidelines are enumerated in **Table I**.

NEWBORN SCREENING

The new guideline suggests CH-NBS by measuring primary thyroid stimulating hormone (TSH) in dried blood spot (DBS), preferably at 48-72 hours of age in all neonates. In the Indian setup, considering earlier hospital discharge of term healthy neonates and simultaneous screening of other metabolic disorders, DBS may be preferred over cord sample and sampling timing may be preferred at 48-72 hour rather than after 72 hour of age. However, in the clinical set-up with hospital discharge before 48 h or high chance of failure of recall, cord blood TSH may be considered. The unit of TSH value may be expressed in whole blood or serum (serum TSH is approximately 2.2 times the whole blood TSH), and all TSH values in this article are expressed in serum units.

Preterm (gestational age < 32 weeks) or VLBW infants are at risk of transient hypothyroxinemia of prematurity or delayed TSH rise, so second NBS is recommended at 2-4 week; and gestational age-specific TSH references should be followed [5]. As the peak period of delayed TSH elevation is around 8 weeks of age, further retesting after 4 weeks or at 36 weeks post menstrual age (PMA) (whichever is earlier) is recommended, if second NBS is done at <36 weeks PMA.

When NBS is collected beyond the first week of age, an age-adjusted TSH cutoff is recommended as opposed to the fixed TSH cutoff of >20 mIU/L recommended by ISPAE **Table II** [5,6]. However, by reducing the TSH cutoff with age advancement there will be a demand for confirmatory testing in a large number of neonates to identify a few mild CH cases [7]. Hence, age-specific TSH cutoff may be used in individual institutional protocols (targeting not to miss mild CH cases); and the TSH cutoff > 20 mIU/L may be adopted in national programs.

New guideline suggests measuring free thyroxine (FT4) in place of thyroxine (T4) in confirmatory testing to eliminate the false positivity in cases of thyroid binding globulin (TBG) deficiency. To avoid delay in initiation of treatment of severe CH cases, levothyroxine (L-T4) supplementation should be initiated upon NBS -TSH values above 40 mIU/L (vs NBS-TSH > 80 mIU/L recommended by ISPAE), after taking the confirmatory serum sample and for any abnormal TSH ≤40 mIU/L, a confirmatory testing is preferred earliest within 24 hours.

When the clinical symptoms favor CH, such as a large posterior fontanelle, macroglossia, umbilical hernia, prolonged jaundice, constipation, lethargy, or hypothermia,

Table I Screening and Management Guidelines of Congenital Hypothyroidism Recommended by the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)-2018 and the American Academy of Pediatrics (AAP)- 2023 Guidelines

	ISPAE, 2018 [2,3]	*AAP, 2023 [4]*
Newborn Screening (NBS) Sample	Cord blood or heel prick dried blood spot (DBS)-TSH on postnatal day 3-5.	DBS -TSH at 48-72 h of age.
NBS-TSH cutoff for confirmatory test.	• TSH >20 mIU/L in both cord blood and postnatal NBS > 48 h of age. • NBS taken 24 - 48 h of age- TSH >34 mIU/L.	• TSH- age-specific reference.
Timing of second NBS for preterm <32 wk, VLBW infant	• 2-4 wks of age	• 2-4 wks of age • If second NBS at <36 wk PMA, repeat 4 wk later or at 36 wk PMA, whichever is earlier.
TSH cutoff for preterm infant	TSH reference same as term infant.	Gestational age-specific NBS- TSH reference.
Interpretation of NBS and subsequent action	• TSH > 80 mIU/L - Take confirmatory sample, start L-T4. • TSH 40-80 mIU/L, immediate confirmatory test. • TSH 20-40 mIU/L - repeat TSH after 7- 10 days.	• TSH >40 mIU/L - Take confirmatory serum sample, start L-T4. • TSH ≤40 mIU/L - immediate confirmatory test.
L-T4 treatment on confirmatory test	• Low FT4 (<1.1 ng/dL) or T4 < 8µg/L irrespective of TSH.	• Low FT4 and raised TSH • Low FT4, Normal or low TSH- evaluation for central hypothyroidism before L-T4 treatment.
In mild CH cases	• Mild low FT4 (<1.17 ng/dL) or T4 < 10 µg/L with TSH >20 m IU/L if age <2 wk and >10 m IU/L if age >2 wk	
	• Persistently TSH >10m IU/L at age >3wk	• TSH >20mIU/L on confirmatory test. • Persistently TSH >10 mIU/L at age >4 wk
Mode of administration of L-T4	• Oral L-T4 given at a consistent time and manner.	• L-T4 should be administered consistently in the timing and manner of administration. • If enteral administration is not possible- intravenously L-T4 may be given. • Particular brand or generic preparation from single manufacturer should use.
Dose adjustment	• L-T4 dose should not be decreased with a single value of T4 above the normal range. evaluation at 2 wk of age.	• Downward adjustment may be needed to avoid overtreatment, after FT4/TSH
Follow-up	• T4/FT4 at 2 wks, then, T4/FT4 and TSH - at 1 month follow up. • Every 2 monthly up to 6 months • 6 months-3 years - every 3 monthly • After 3 years-every 3-6 months.	• FT4/TSH - 1-2 wk then every 2 wk until normal TSH. • In 1st 6 mo of life in 1-2 mo, then 2-3 monthly from 6 mo - 1 y. • Between 1-3 y 3-4 monthly. • After 3 y - every 6-12 mo.
Re-evaluation of thyroid axis	• Possibility of transient congenital hypothyroidism.	• Requiring lower dose L-T4 (<2µg/kg/d) • Absence of abnormal TSH levels during treatment.

Table II Age-specific Thyroid Stimulating Hormone Reference for Term and Preterm Infants [5,6]

Age	*TSH (mIU/L)*[a]
Term infent	
Cord	2.22-10.66
1st day	2.69-26.5
3rd day	2.8-18.6
7th day	1.34-12.08
10th day	1.19-10.72
14th day	1.72-7.87
28th day	2.02-4.9
Preterm infent[a]	
22-27wk GA	
1 wk age	14
3-4 wk age	11-11.8
36 wk PMA	9
28-31 wk GA	
1 wk age	13.1
3-4 wk age	8.2 - 9
36 wk PMA	8

[a]*95th percentile TSH level. GA-gestational age, PMA- post-menstrual age.*

measurement of TSH and FT4 in a venous sample is advised, even if NBS is normal.

EVALUATION FOR ETIOLOGY

The new guideline emphasizes on genetic testing in primary CH cases associated with syndromic infants or clinical features suggestive of a genetic condition or central CH infants or when genetic diagnosis may influence clinical management. As monogenic mutations are associated with thyroid dysgenesis, dyshormonogenesis or hypothalamic-pituitary development, genetic testing may help to identify the etiology of CH [8,9]. Based on regional facility and financial competence, imaging and genetic testing may be ordered in individual case basis.

Assessment for Permanence of Hypothyroidism

Presence of thyroid agenesis or ectopia in ultrasonography, high TSH more than 10 mIU/L after one year of treatment, or the requirement of a higher dose of L-T4 during the first year of life are predictors of permanent CH [10,11] as per AAP guidelines. If the patient is adequately treated with a low dose of L-T4 (<2 mcg/kg/day), a trial-off L-T4 supplementation should be considered at 3 years of age.

MANAGEMENT AND FOLLOW- UP

Presence of low FT4 irrespective of TSH level (low FT4 and raised TSH, or low FT4 and normal or low TSH-central hypothyroidism) on confirmatory test, suggest for L-T4 supplementation. Need for L-T4 supplementation in mild CH is explained by physiological deficit of thyroxine hormone as per hypothalamic-pituitary axis. In absence of strong evidence for treatment of mild CH cases, the TSH threshold for L-T4 initiation is based on expert opinion, and either ISPAE or AAP guidelines can be followed.

L-T4 tablet should be given in a consistent time and manner; and preferred from a particular brand or generic tablet of same manufacturer. Alternatively, intravenous L-T4 may be used when enteral administration is not feasible [12]. In CH resistance to L-T4, the addition of liothyronine (L-T3) has been suggested [13].

AAP gives more priority to close monitoring of serum TSH and FT4 during the first year of life because of the relatively rapid growth during infancy, increased metabolic clearance of thyroid hormone, and risk of overtreatment of L-T4. The initial downward adjustment of L-T4 may be attempted after 2 weeks of starting treatment to avoid overtreatment [14] as compared to suggestion of no downward adjustment of L-T4 with a single higher level of FT4 in ISPAE.

These AAP guidelines in a developed country scenario aimed to eliminate the morbidities from CH inspite of universal NBS practice and establish the etiology in diagnosed cases of CH. Whereas, we herein re-emphasize the need to implement universal NBS, and ensuring optimal treatment in diagnosed cases of CH in developing country like India.

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

REFERENCE

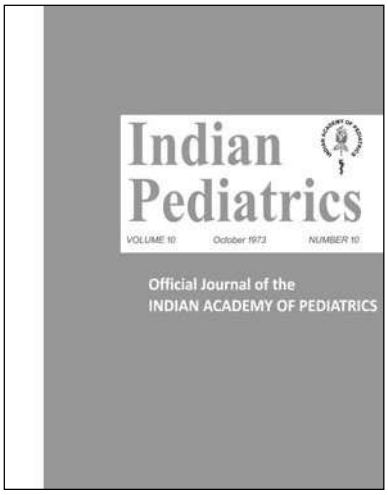
1. Donaldson M, Jones J. Optimising outcome in congenital hypothyroidism; current opinions on best practice in initial assessment and subsequent management. J Clin Res Pediatr Endocrinol. 2013;5:13-22.
2. Desai MP, Sharma R, Riaz I, et al. Newborn Screening Guidelines for Congenital Hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) - Part I: Screening and Confirmation of Diagnosis. Indian J Pediatr. 2018;85:440-47.
3. Sudhanshu S, Riaz I, Sharma R, et al. Newborn Screening Guidelines for Congenital Hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) - Part II: Imaging, Treatment and Follow-up. Indian J Pediatr. 2018;85:448-53.
4. Rose SR, Wassner AJ, Wintergerst KA, et al.; Section on Endocrinology Executive Committee; Council on Genetics Executive Committee. Congenital Hypothyroidism: Screening and Management. Pediatrics. 2023;151:e2022060419.
5. Kaluarachchi DC, Allen DB, Eickhoff JC, et al. Thyroid-stimulating hormone reference ranges for preterm infants. Pediatrics. 2019;144:e20190290.
6. MutluM, Karagüzel G, Alýyaziciolu Y,et al. Reference intervals for thyrotrophin and thyroid hormones and ultrasonographic thyroid volume during the neonatal period. J Matern

Fetal Neonatal Med. 2012;25:120-4.
7. Korada SM, Pearce M, Platt MPW, et al. Difficulties in selecting an appropriate neonatal thyroid stimulating hormone (TSH) screening threshold. Arch Dis Child. 2010;95:169-73.
8. Fan X, Fu C, Shen Y, et al. Next-generation sequencing analysis of twelve known causative genes in congenital hypothyroidism. Clin Chim Acta. 2017;468:76-80.
9. Persani L, Bonomi M. The multiple genetic causes of central hypothyroidism. Best Pract Res Clin Endocrinol Metab. 2017; 31:255-63.
10. Park ES, Yoon JY. Factors associated with permanent hypothyroidism in infants with congenital hypothyroidism. BMC Pediatr. 2019;19:453.
11. Oron T, Lazar L, Ben-Yishai S, et al. Permanent vs transient congenital hypothyroidism: assessment of predictive variables. J Clin Endocrinol Metab. 2018;103:4428-36.
12. Jonklaas J, Bianco AC, Bauer AJ, et al; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid. 2014;24:1670-751
13. Paone L, Fleisch AF, Feldman HA, et al. Liothyronine improves biochemical control of congenital hypothyroidism in patients with central resistance to thyroid hormone. J Pediatr. 2016;175:167-172.e1
14. Schoelwer MJ, Tu W, Zhou J, et al. Targeted levothyroxine therapy for treatment of congenital hypothyroidism. Endocr Pract. 2017;23:1067-71

Genetics of Short Stature: The Possibilities Grow!

AASHIMA DABAS
Associate Professor, Department of Pediatrics, Maulana Azad Medical College, New Delhi. dr.aashimagupta@gmail.com

The October, 1973 issue of *Indian Pediatrics* included an article on genetics and diagnostic aspects of short stature [1]. The article provided a logical clinical framework towards approach to short stature that was congruent to a primary genetic disorder. In the present era, molecular testing options have improved our understanding of the etiology of short stature. The reference paper [1]; however, provides an insight into a rational clinical approach for genetic short stature.



THE PAST

Wadia, et al. [1] reported observations on 62 children who were referred with short stature (defined as height below 10th centile). The diagnostic framework included pedigree analysis, developmental milestones, associated complaints, anthro-pometry, phenotype evaluation, radio-logical studies and special investigations. The authors excluded children with systemic disorders and other conditions where growth failure could be secondary to a systemic disease.

The most common etiology of short stature was osteochondrodystrophies that was suspected in disproportionate short stature and confirmed by radiography. A normal clinical phenotype suggested further work-up for hormonal deficiency that was the second most common etiology. The authors also identified chromosomal disorders like Turner syndrome and Down syndrome and a few inherited systemic disorders like sphingolipidosis [1].

The authors concluded the role of a pedigree analysis in determining the genetic basis of a disease, also mentioning alongside the fallacy of a negative family history [1]. Even though there were limited molecular services available fifty years back, a good clinical assessment including history, anthropometry and basic investigations helped achieve a diagnosis in these patients.

HISTORY

Short stature has always been a broad medical disorder, incorporating a wide range of differential diagnoses. The first few reports of people with significant short stature are of individuals who participated as artists and courtiers [2]. It was only later that the physical, psycho-social and mental well-being of children with extreme short stature (pathological) received priority as a medical condition suggesting the need for diagnosis and treatment. Further research into neuroendocrinology improved the understanding of the growth hormone (GH)-insulin like growth factor (IGF) axis in the regulation of growth. Growth monitoring was identified as a key process in pediatric care that provided impetus to generation of reference growth data.

The isolation of pituitary derived GH in 1950s, and development of recombinant human GH (rhGH) later in 1980s for treatment of growth hormone deficiency (GHD) was a major breakthrough [3]. rhGH is now also approved for use in non-GHD conditions including small for gestational age (SGA) with no catch-up, and genetic conditions namely *SHOX* gene haploinsufficiency, Turner syndrome, and Prader-Willi syndrome [3].

THE PRESENT

Height is the most heritable human trait that results with the cumulative effects of numerous genes. A large number of single-nucleotide polymorphisms (SNP) have been identified in genome wide association studies that are common in the population and account for almost 20-40% inter-individual variation in growth in different ancestries [4].

The classification of short stature has evolved to incorporate mechanism of growth failure and the underlying molecular defects. Over time, novel genetic causes for short stature have been recognized through accessibility to newer genetics testing methods. The genetic aberrations in the pituitary transcription factors (like *PROP1, HESX1, LHX3*), mechanisms governing GH release and action through GH receptors (*GHRHR, GHR, GHSR*) and signalling molecules like *STAT1, STAT3,* are now known [5].

The standard approach to a child with short stature includes a detailed clinical assessment and investigations to exclude common systemic disorders, and diagnose skeletal dysplasia or hormonal disorders. Genetic testing for short stature should be offered in children with idiopathic short stature (ISS) or short stature of undefined etiology, children born SGA particularly in the absence of maternal disease and/or placental dysfunction, in those suspected with a genetic disorder without a clear phenotype, or if there is an endocrine disorder in which a molecular diagnosis can be reached like familial GHD [5].

Genetic testing has evolved from simple karyotype and single-gene sequencing to further look for monogenic disorders or a specific group of genes. In a large European, multi-ethnic cohort of pre-pubertal children with ISS, a search for mutations in genes led to a diagnostic yield of 10% [6], consistent with other studies where yields ranged from 2-16.5% [7,8]. A few identified genes include *SHOX*, *ACAN*, *NPR2* and genes known to be involved in the GH-IGF-1 axis [7-9]. The study highlighted the need to maintain a degree of suspicion for skeletal dysplasias (*ACAN*, *MMP13* mutations) and chromosomal disorders like Noonan syndrome (*PTNPN11*). Advanced molecular investigations including targeted sequencing [8], next generation sequencing methods in candidate genes [6-8], and whole exome sequencing [8], have improved the diagnostic yield to 33% in ISS. A similar study from India [10] analyzed 455 causes of short stature and found recognizable genetic syndromes in the majority (65%) who presented with proportionate short stature. Lysosomal storage disorders or skeletal dysplasia were commonly identified in the disproportionate short stature group. The microarray provided a diagnosis in 50% cases and next-generation sequencing was helpful in one out of six cases (16%) [10]. The significance of a meticulous clinical assessment, pedigree analysis and a systematic diagnostic work-up was highlighted [10].

CONCLUSIONS

Genetic testing has deciphered new molecular mechanisms that govern growth and confirm rare genetic disorders with short stature. This reiterates the need for a judicious clinical approach in children with short stature that should be substantiated with genetic testing for a confirmatory diagnosis. Targeted gene panels for genes involved with hormones and growth axis are helpful. Similarly, targeted gene testing for skeletal dysplasia in the presence of a clinical gestalt provides a confirmatory diagnosis. Next generation deep resequencing methods have their place in the diagnostic toolkit, as does exploring the whole exome for novel mutations in both known and unknown genes related to growth. However, caution should be exercised to avoid an injudicious array of molecular investigations that may not be rewarding and may instead add to the anxiety of the clinician and the family.

REFERENCES

1. Wadia RS, Shirole DS, Deshpande N. Genetic and diagnostic aspects of shortness of stature. Indian Pediatr. 1973;10: 577-83.
2. Wu L, Zhou Y, Zhang D, Shen Y, Liu A. The portrayal of people with dwarfism in Chinese art. Am J Med Genet C Semin Med Genet. 2021;187:192-8.
3. Tidblad A. The history, physiology and treatment safety of growth hormone. Acta Pediatr. 2022;111:215-24.
4. Yengo L, Vedantam S, Marouli E, et al. A saturated map of common genetic variants associated with human height. Nature. 2022;610:704-12.
5. Perchard R, Murray PG, Clayton PE. Approach to the patient with short stature: Genetic testing. J Clin Endocrinol Metab. 2023;108:1007-17.
6. Perchard R, Murray PG, Payton A, Highton GL, Whatmore A, Clayton PE. Novel mutations and genes that impact on growth in short stature of undefined aetiology: The EPIGROW Study. J Endocr Soc. 2020;4:bvaa105.
7. Wang SR, Carmichael H, Andrew SF, et al. Large-scale pooled next-generation sequencing of 1077 genes to identify genetic causes of short stature. J Clin Endocrinol Metab. 2013;98:E1428–E1437.
8. Hauer NN, Popp B, Schoeller E, et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. Genet Med. 2018;20:630-8.
9. Hattori A, Katoh-Fukui Y, Nakamura A, et al. Next generation sequencing-based mutation screening of 86 patients with idiopathic short stature. Endocr J. 2017;64:947-54.
10. Singh K, Puri RD, Bijarnia-Mahay S, et al. Clinical and genetic profile of children with short stature presenting to a genetic clinic in Northern India. Indian Pediatr. 2022;59: 463-6.

Conjunctival Involvement in Infants as an Unusual Symptom of Omicron XBB.1.16 Driven Surge

We describe clinical characteristics of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infected children during the XBB.1.16 variant-driven surge in April, 2023 in India. A significantly higher positivity rate in young infants than in older children (37.4% vs 13.3%; *P*<0.001), and a predominance of respiratory symptoms were noticed. Notably, non-purulent conjunctivitis was found in 36.8% of SARS-CoV-2 positive infants. All recovered with symptomatic treatment as outpatients.

Keywords: *Covid-19, Eye, Outcome, SARS-CoV-2.*

A new surge of coronavirus disease (COVID-19) cases was noticed in India from the first week of March, 2023. The number of daily cases as well as active cases steadily rose with more than 11,000 cases reported on April 14, 2023, and the active case tally rose to around 50,000 [1]. A new sub-lineage of the Omicron variant of severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) called XBB.1.16 was behind this surge [2]. According to the latest INSACOG data, this sub-variant now represents 80% of all the isolates sequenced and uploaded to their site [3].

This single-centre descriptive study was conducted at a secondary level, exclusive pediatric hospital of western Uttar Pradesh, from April 4, 2023, to May 3, 2023, during the surge of COVID-19 caused by the XBB.1.16 sub-lineage. The study was conducted to describe the clinical characteristics of pediatric COVID-19 during this surge. All outdoor pediatric cases visiting this hospital with a respiratory or febrile illness were asked to undertake a SARS-CoV-2 reverse transcriptase – polymerase chain reaction (RT-PCR) or rapid antigen test (RAT). Both RAT and RT-PCR were employed to confirm a case. However, all RAT-positive samples were re-analyzed with RT-PCR to assess cycle threshold (Ct) values. Key demographic characteristics like age, sex, weight, contact history, presenting signs and symptoms, and comorbidities of all these children were recorded. SARS-CoV-2 positive children were grouped into four cohorts based on their age: infants (0-11 months), young children (12-59 months), older children (above 60-143 months), and adolescents (144-215 months).

Out of 258 children with suspected features who presented during the study period, the parents of 196 (91 younger than one year and 105 older) could get the RAT or RT-PCR test done for the SARS-CoV-2. Of these, 48 (24.49%) children had either of these two tests positive. All these 48 positive cases improved with the symptomatic treatment on an outdoor basis. The total duration of acute illness was 1-3 days. The detailed clinical features have been described into two groups – young children (0-59 months) and older children (60 months and above) **(Table I).** On sub-group analysis, it was noted that infants below one year had a significantly higher positivity rate than older children (37.4% vs 13.3%, *P*<0.001).

Like the third wave of COVID-19 in India, this outbreak also caused mild brief symptomatic illness in children [4,5]. Most affected children only had a mild respiratory illness characterized by fever, cold and cough that resolves within one to three days. Acute respiratory symptoms were prominent in all except six children. Expectedly, symptoms like headache, muscle pains and body aches, throat pain were seen exclusively in older children. Unlike the previous BA.2 Omicron wave in which the gastrointestinal symptoms predominated in young infants; mainly respiratory symptoms were noticed dominating the clinical picture of this surge [4]. None of the older children complained of anosmia or loss of taste.

Though, we could not perform genetic sequencing, we believe that most positive cases represented XBB.1.16 sub-variant infection. The cycle threshold values for nucleocapsid and *ORF1ab* genes on positive RT-PCR varied from 18 to 23. Although, we could notice a fine erythematous rash in three infants, no case resembling the features of multisystem

Table I Clinical Characteristics of Children With Coronavirus Disease (COVID-19) in Bijnor, April-May, 2023

Clinical features	*0-59 mo (n=38)*	*≥60 mo (n=10)*
High fever (>102 °F)	3 (7.9)	0
Rhinorrhea	26 (68.4)	2 (20)
Conjunctival involvement	14 (36.8)	0
Throat pain	0	2 (20)
Cough	22 (57.9)	6 (60)
Loose stools	6 (15.8)	0
Vomiting	10 (26.3)	2 (20)
Pain in abdomen/colic	11 (28.9)	0
Fine rash	3 (7.9)	0
Myalgia/bodyaches	0	3 (30)
Headache	0	4 (40)

All values in no. (%).

inflammatory syndrome was seen. Family history of similar acute illness was present in only four children.

One notable finding of the study was the presence of itchy, non-purulent conjunctivitis with mucoid discharge and sticky eyelids in 14 infants (36.8%). This manifestation was not seen amongst infants during the past COVID-19 waves, especially in this region; although, frank conjunctivitis was a common clinical presentation of COVID-19 during the early part of its emergence in some regions [6]. Later, this clinical sign was not considered to be a key finding of COVID-19. Many respiratory viruses like adenovirus, influenza, RSV, measles, etc are more commonly associated with conjunctival involvement [7]. However, unlike in these viral infections, the conjunctival affliction was mild and not associated with marked redness and purulent discharge in the current outbreak. One limitation of the current study is the inability to test all children with suggestive symptoms.

Contributors: VMV conceptualize and conducted the study, analyzed, and prepared the initial draft of the manuscript. PK helped in drafting and data analysis, gave valuable inputs in the interpretation of the data, and helped in editing the manuscript. Both authors approved the final version of the manuscript.
Ethics clearance: IEC, Mangla Hospital & Research Centre, Bijnor; No. MHRC/IEC/2023/03, dated April 3, 2023.
Funding: None; *Competing interests*: None stated.

VIPIN M VASHISHTHA,[1]* PUNEET KUMAR[2]
[1]Department of Pediatrics, Mangla Hospital & Research Center, Shakti Chowk, Bijnor, Uttar Pradesh.
[2]Kumar Child Clinic, KM Chowk, Sector 12, Dwarka, New Delhi.
**vipinipsita@gmail.com*

REFERENCES

1. Huge jump in COVID-19 cases! Over 11,000 infections reported in last 24 hours. Accessed on April 15, 2023. Available from *https://www.businesstoday.in/coronavirus/story/huge-jump-in-covid-19-cases-over-11000-infections-reported-in-last-24-hours-377357-2023-04-14*
2. XBB.1.16, new Arcturus variant behind India's COVID-19 surge. Accessed on April 15, 2023. Available from *https://health.economictimes.indiatimes.com/news/industry/xbb-1-16-new-arcturus-variant-behind-indias-covid-19-surge/99495285*
3. The Indian SARS-CoV-2 Genomics Consortium (INSACOG). Accessed on July 22, 2023. Available from *https://inda.rcb.ac.in/insacog/statreportlineagegraph*
4. Sarkar M, Ghosh A, Konar MC, Roy O, Mahapatra MK, Nandi M. Clinical characteristics of children with SARS-CoV-2 infection during the third wave of the pandemic: single center experience. Indian Pediatr. 2022;59:531-4.
5. Muthusamy S, Sarojam B, Sugunan S, et al. Clinical Profile and short-term outcome of children with acute SARS-CoV-2 infection during the first and second waves of the pandemic. Indian J Pediatr. 2022:1–7.
6. Güemes-Villahoz N, Burgos-Blasco B, García-Feijoó J, Sáenz-Francés F, Arriola-Villalobos P, Martinez-de-la-Casa JM, et al. Conjunctivitis in COVID-19 patients: frequency and clinical presentation. Graefes Arch Clin Exp Ophthalmol. 2020 Nov;258:2501-7.
7. Belser JA, Rota PA, Tumpey TM. Ocular tropism of respiratory viruses. Microbiol Mol Biol Rev. 2013;77:144-56.

Urachal Anomalies During Infancy: A Case Series

Persistent embryonic remnants of allantois represent urachal anomalies. Incomplete involution at either end can give rise to patent urachus, umbilical-urachal sinus, vesicourachal diverticulum, and urachal cyst. We came across a series of urachal anomalies during a 6 months period at a tertiary hospital with 1500 deliveries annually. This clinical encounter with a presumed rare entity triggered the review of evidence, focusing on presentation and management. Parental consent was obtained for reporting non-identifying data.

The individual presentation is elaborated below and summarized in **Table I**.

Case 1: Ultrasonography of the abdomen done during the fourth week of life for a preterm female (30 weeks 2 days) with delayed detachment of the umbilical cord (**Fig. 1A**), showed a 24 mm long hypoechoic tract, extending from the umbilicus to the dome of the urinary bladder. Excision and umblicoplasty was advised by surgeon. Surgical explo-ration ruled out patency at the level of bladder. Histopatho-logy of the excised tract showed fibro-myxoid tissue with blood vessel, muscle bundle, and lymphoplasmacytic infiltrate, consistent with an urachal remnant. She made a quick recovery post operatively.

Case 2: An 18-days-old presented with features of omphalitis (**Fig. 1B$_1$**). Antibiotics were started after sending septic workup. Peculiarly wide and wet appearance (**Fig. 1B$_2$**) intrigued the need for ultrasonography which showed a 29.4 mm inflamed hypoechoic tract from the umbilicus to the bladder. Repeat ultrasound after 5 days showed increased collection (size 34.9 mm) consistent with clinical worsening and rising inflammatory markers, confirming a complicated urachal sinus. Pus was drained and the infected sinus excised surgically. She was discharged as her clinical condition improved on antibiotics as per culture sensitivity pattern.

Case 3 and 4: Routine visit at 6 weeks drew attention to peculiar appearance of umbilicus (**Figs. 1C, 1D**). Ultrasound confirmed the UA, managed conservatively.

Case 5: A late preterm with purulent umbilical discharge, and polypoid structure (**Fig. 1E**) within the umbilicus presented at 1 month. Ultrasonography showed a small urachal sinus, which was managed conservatively.

Case 6: A 1-year-old boy with intermittent umbilical discharge had a wet-appearing, erythematous umbilicus with a tubular structure at the base (**Fig. 1F**). Ultrasonography

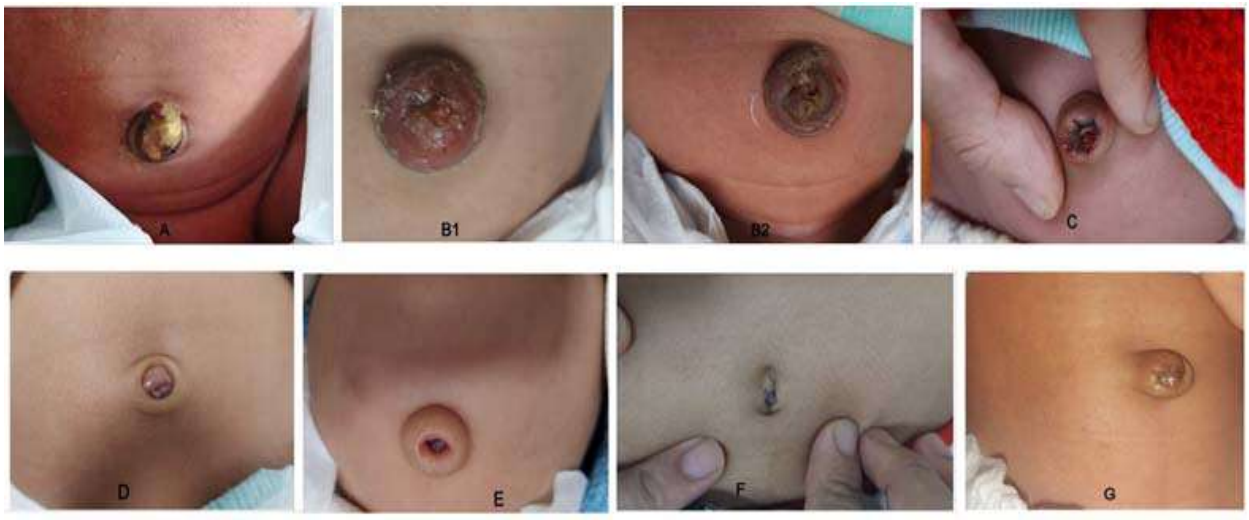


Fig. 1 Spectrum of abnormal appearance of umbilicus as an indicator of underlying urachal anomaly. *a*) Case 1: wet appearing umbilical stump with failure to separate at the base even at 3 weeks of age; *b*) Case 2: wide, swollen umbilicus with periumbilical erythema and induration in a neonate; *c*) Case 2: reddish granuloma like structure at the base of the umbilicus at 6 weeks of age; *d*) Case 3: granulomatous structure at the base of umbilicus at 6 weeks of age; *e*) Case 4: small pinkish polypoid structure seen within the umbilicus in a 1 month infant; *f*) Case 5: a small tubular structure seen at the base of wet appearing umbilicus in an infant; *g*) Case 6: small polypoid structure seen at the base of the umbilicus at 4 weeks of age.

revealed a well-defined, anechoic, thin-walled urachal cyst. He was treated with a short course of oral antibiotics.

Case 7: A small urachal sinus was detected incidentally on the scan done at 4 weeks of age for inguinoscrotal swelling. A subsequent umbilical examination revealed a small polypoid structure at the base (**Fig. 1G**).

Urachal anomalies have been visualized in 99% of the asymptomatic children screened using abdominal ultrasonography [1]. Whereas, in a population based study from Canada, 1% of all screened patients were noted to have a urachal remnant, with a male preponderance [2,3]. Urachal anomalies are often detected incidentally [4]. The size, location, and the age of the patient determine the clinical presentation. Typically, a patent urachus manifests at birth, while the others tend to be asymptomatic or present later [3,5]. Symptoms range from umbilical discharge, urinary leakage, polyp or granulation tissue to abdominal discomfort, swelling, fever, and recurrent urinary tract infections [4]. A detailed physical examination along with imaging can establish the diagnosis in most cases [6]. We found an atypical appearance of the umbilicus in form of wide diameter, persistent granulomatous or polypoid structure at the base, edematous or wet appearance, and delayed stump healing as pointers to underlying urachal anomalies, akin to a previous report [7].

Plain ultrasonography is the best screening modality with a high diagnostic accuracy of 90% [6]. UA are seen as luminal, hypoechoic structure visualized till the level of bladder; while the normal obliterated urachal remnant (median umblical ligament) is visualised as a non-luminal fibrous grey band [3]. Patent vitellointestinal (VI) duct is an important differential diagnosis seen as a tubular, fluid filled structure with a blind end. Asymptomatic urachal remnants which are smaller than 22.5 mm in length (95th centile) can be considered physiological [1]. Infection is the most

Table I Clinical, Radiological, and Management Details of Babies With Urachal Anomalies

Case	*Age at diagnosis*	*GA (wk)*	*Gender*	*Presentation*	*Length, width (mm)*	*Differential diagnosis*	*Final diagnosis*	*Management*
1	3 wk	30 + 2	female	Delayed cord detachment beyond 3 wk of age, wet appearing stump	24, 11.5	Patent urachus, omphalitis	Symptomatic urachal sinus	Surgical excision done for failure of cord healing. Discharged home after feeding transition and weight gain.
2	18 d	38 + 1	female	Umbilical swelling, pus discharge and irritability	34.9, 18	Omphalitis	Complicated urachal sinus	Surgical drainage and excision, pus culture grew MRSA. Doing well on follow-up.
3	6 wk	37 + 2	male	Umbilical granuloma with bleeding	10.5, 5	Umblical granuloma	Small urachal sinus	Managed conservatively, follow-up scan at 3 mo age confirmed obliteration.
4	6 wk	38 + 2	female	Asymptomatic	13.1, 11	Umblical polyp	Small urachal sinus	Managed conservatively Follow-up scan at 3 mo of age confirmed obliteration.
5	4 wk	36 +3	male	Umbilical discharge, erythema, and small pinkish polypoid structure	10.7, 9	Umblical polyp	Small urachal sinus	Oral antibiotics and close follow-up. Resolution at 6 mo on review scan.
6	1 y	39	male	Intermittent umbilical discharge	5, 4.5	Omphalitis	Small urachal cyst	Oral antibiotics and under close follow-up.
7	4 wk	35 + 4	male	Asymptomatic, incidental finding	8, 5.5	Umblical granuloma	Small urachal sinus	Resolved on follow-up.

MRSA: methicillin resistant staphylococcus aureus.

common complication of urachal anomalies, followed by urinary tract injury, hemorrhage, rupture, bowel obstruc-tion, and malignancy [4,5], with up to 25% of cases of patent urachus having an underlying bladder outlet obstruction [8].

In the absence of consensus guidelines, the usual practice is to intervene surgically to avoid the risk of complications, recurrent infection, and possible malignant transformation. However, there has been a gradual shift towards a conservative approach for most forms of urachal anomalies [9]. Researchers have reported spontaneous regression in majority of the cases younger than 6 months, children being at lower risk for morbidities. A proposed treatment algorithm [9] also advocates conservative mana-gement in most cases. The risk of malignant transformation, primarily adeno-carcinoma appears very low to justify elective excision [10]

Our experience supports that urachal anomalies are under-diagnosed and most remnants obliterate during infancy. Abnormal appearance of the umbilicus can be an indicator of underlying urachal anomalies. However, any infant with suspected urachal anomalies should undergo screening ultrasound with complete evaluation of the genitourinary tract. Pediatric healthcare professionals including surgeons need to be cognizant of the possible complications and evaluate each case with a meticulous physical examination. Initial management should consist of observation irrespective of its presentation. Follow-up every 3-6 months till 5 years may be necessary to detect possible complications at the earliest [9]. Early detection with timely elective surgery when conservative approach fails is the preferred management strategy.

DEEPIKA RUSTOGI,[1*] JAI BHARAT PANWAR,[1] MAMTA MOTLA,[2] KARUNESH KUMAR[3]

[1]Department of Pediatrics, Yashoda Superspeciality Hospital, Kaushambi, Ghaziabad, Uttar Pradesh.

[2]Department of Radiology, Yashoda Superspeciality Hospital, Kaushambi, Ghaziabad, Uttar Pradesh.

[3]Department of Pediatrics & Pediatric Gastroenterology, Indraprastha Apollo Hospitals, Sarita Vihar, Delhi.

**drdeepikaneo@gmail.com*

REFERENCES

1. Ozbek SS, Pourbagher MA, Pourbagher A. Urachal remnants in asymptomatic children: gray-scale and color Doppler sonographic findings. J Clin Ultrasound. 2001;29:218-22.
2. Keçeli AM, Dönmez MÝ. Are urachal remnants really rare in children? An observational study. Eur J Pediatr. 2021;180: 1987-90.
3. Yu JS, Kim KW, Lee HJ, et al. Urachal remnant diseases: spectrum of CT and US findings. Radiographics. 2001;21: 451-61.
4. Wilson AL, Gandhi J, Seyam O, et al. Urachal anomalies: a review of pathological conditions, diagnosis, and manage-ment. Transl Res Anat. 2019;16:100041.
5. Parada Villavicencio C, Adam SZ, Nikolaidis P, et al. Imaging of the urachus: anomalies, complications, and mimics. Radiographics. 2016;36:2049-63.
6. Cilento BG, Bauer SB, Retik AB, et al. Urachal anomalies: defining the best diagnostic modality. Urology. 1998;52:120-22.
7. Espírito Santo R, Alcafache M, Almeida SR, Tavares A. Abnormal appearance of the umbilicus: an indicator of urachal anomalies. BMJ Case Rep. 2016;2016:bcr2016215374.
8. Taher H, Ramnarine S, Smeulders N, et al. Patent urachus and bladder outflow obstruction–chance or consequence? A study of a cohort of patients with complete patent urachus presenting to a tertiary urological center and a review of literature. Ann Pediatr Surg. 2021;17:2.
9. Lipskar AM, Glick RD, Rosen NG, et al. Nonoperative management of symptomatic urachal anomalies. J Pediatr Surg. 2010;45:1016-19.
10. Gleason JM, Bowlin PR, Bagli DJ, et al. A comprehensive review of pediatric urachal anomalies and predictive analysis for adult urachal adenocarcinoma. J Urol. 2015;193:632-36.

Hematemesis: A New Manifestation of Adenovirus Infection?

Adenovirus belongs to the adenoviridae family, and is a double stranded DNA virus, which is known to cause very mild to moderate respiratory illness in the healthy, and can lead to moderate to severe illness in the vulnerable and immuno-compromised [1]. We discuss the clinical features of seven children who presented with hematemesis and associated respiratory symptoms, who later tested positive for adeno-virus infection on reverse transcriptase-polymerase chain reaction (RT-PCR) sample of their respiratory swabs. None of these children had a significant drop in their hemoglobin or needed admission to intensive care. There was no history of excessive non-steroidal anti-inflammatory drug (NSAID) usage elicited from the parents, and none of these children had any comorbidity.

We prospectively analyzed data in children who underwent emergency upper gastrointestinal endoscopy (n=23) for hematemesis at our tertiary care children hospital during February-April, 2023. Seven children, who had severe erosive pan-gastritis endoscopically, tested positive for adenovirus in the respiratory PCR swab (BioFire Respiratory 2.1 Panel, Biomériux Inc.), done as part of the associated respiratory symptoms. These children were treated with intravenous proton pump inhibitors (PPI) and discharged home on oral PPIs, as there were no further episodes during the next 48 hours of observation. Upper gastrointestinal serial biopsies (esophagus, antrum and duodenum) had no abnormalities, and did not show any viral or inclusion bodies. The hematological parameters were normal for cell counts, red blood cell indices, liver function tests and coagulation profile.

These children were all previously well, had no co-morbidities, did not consume or had an overdose with NSAIDs, and their nutritional status was within normal limits. The mean age of this cohort was 7.8 years, male to female ratio was 3:4, and none had any previous gastro-intestinal symptoms. The average hemoglobin in our cohort was 11.7 g/dL.

Upper gastrointestinal endoscopy in these children was indicated due to the sudden onset of hematemesis in previously well children. All children were hemodynamically stable before and after endoscopy/and none needed blood transfusion during their hospital stay. All children were well on their follow-up visits with negative stool occult blood.

Only isolated reports of a possible association between adenovirus and hematemesis have been reported previously [2,3]. We have presented these cases to suggest a possible association between adenovirus infection and hematemesis, which may need confirmation by larger prospective studies.

Dhanasekhar Kesavelu,* Nithya Franklyn, Sarah Nalliannan
Apollo Childrens Hospital, Shafee Mohamed Road, Chennai, Tamil Nadu.
**drdskgastro@gmail.com*

REFERENCES

1. Centers for Disease Control and Prevention. Adenoviruses. CDC, 2023. Accessed May 1, 2023. Available from: *https://www.cdc.gov/adenovirus/hcp/diagnosis.html*
2. Bye AM, Rice SJ, Koh TH, Brown RJ, Price EH. Haematemesis as a presentation of adenovirus type 7 infection. Aust Paediatr J. 1983;19:184.
3. Gupta SK, Fitzgerald JF. Gastric erosions in children: is adenovirus the cause? Gastro-intest Endosc. 2000;51:AB128.

Confounding Factors Influencing Growth

We read with interest the article on growth parameters in adolescents [1], and would like to point few observations regarding the study.

There are numerous unaccounted confounding factors that could have influenced the observed growth patterns like duration since the last relapse, the cumulative relapse-free interval, the current use of steroids and the duration of last consecutive steroid-free periods. Furthermore, the study missed capturing the baseline anthropometric parameters of the participants, which are arguably the most significant variables affecting the outcome measures. These parameters

would have been essential for comparing current anthropometric data. A more comprehensive assessment including mid-parental height, bone age, and the evaluation of pubertal status using SMR staging would have provided a clearer picture of the participants' growth potential and could have identified physiological variations. Therefore, there is a risk of over diagnosing pathological stunting in the studied population.

The usage of WHO growth charts for adolescents in this study could have led to overestimation of short stature and underweight. Instead, our population-specific IAP growth charts, would have provided a more accurate assessment for Indian children [2]. Several studies have emphasized the importance of utilizing appropriate and population-specific growth charts for the correct identi-fication of growth abnormalities [3].

The authors used the BMI cut-offs of >+1 *z* and >+2 *z* scores for defining overweight and obesity, respectively, as opposed to IAP growth chart BMI cut-offs of 23rd and 25th adult equivalent centiles which correspond much lower BMI *z* scores (+0.55 *z* for males and +0.67 *z* for females for overweight and, +1.33 SD for females and +1.63 SD for females for obesity), which would have led to the under-estimation of their respective prevalence. As it is well-documented that Indian children tend to have higher central adiposity compared to Western populations and are at a higher risk of cardiovascular morbidities and hence have lower BMI cut-offs.

The authors have concluded that 32.7% prevalence of short stature among adolescents with nephrotic syndrome at their center was high, without comparing it to a normal population. However, previously published population-specific data have shown even higher rates of stunting in "normal" adolescents, ranging from 25-51% [4].

MAHESH VENKATACHARI,
THIRUNAVUKKARASU ARUN BABU*
Department of Pediatrics,
AIIMS, Mangalagiri, Andhra Pradesh.
**babuarun@yahoo.com*

REFERENCES

1. Srimathi K, Deepthi B, Krishnasamy S, Ganapathy S, Krishnamurthy S. Growth parameters in adolescents with idiopathic nephrotic syndrome diagnosed at the age of 1-6 years. Indian Pediatr. 2023 Jul 20:S097475591600562.
2. Khadilkar VV, Khadilkar AV, Choudhury P, et al. IAP growth monitoring guidelines for children from birth to 18 years. Indian Pediatr. 2007;44:187-97.
3. Singh P, Gandhi S, Malhotra RK, Seth A. Impact of using different growth references on interpretation of anthropometric parameters of children aged 8-15 years. Indian Pediatr. 2020;57:124-8.
4. Haboubi GJ, Shaikh RB. A comparison of the nutritional status of adolescents from selected schools of South India and UAE: a cross-sectional study. Indian J Community Med. 2009;34:108-11.

AUTHORS' REPLY

We would like to thank the authors of this correspondence for their interest in our manuscript. Our study design was a cross-sectional study and hence has its inherent bias; baseline pre-treatment anthropometry was not available for analysis in majority of children. While we agree that constitutional and familial short stature could be contributory to some degree, these factors are relatively minor when one considers the high cumulative steroid-dose intake with median duration of steroids being 99 (70, 111) weeks, which is very likely capable of growth-retardation [1,2], being much higher than other studies [3, 4]. While some studies have demonstrated catch-up growth during the periods on lower doses of prednisolone, most of this preserved growth was seen at prednisolone doses below 0.25 to 0.75 mg/kg/day [3, 4].

However, cumulative steroid dose alone did not show discriminatory ability in predicting the short stature in our study population unlike some previous studies [2]. These findings could be explained by additional confounding factors like duration of steroid therapy, duration since the last relapse, the cumulative relapse-free interval, the current use of steroids, the duration of last consecutive steroid-free periods, duration of daily continuous vs alternate-day steroids, different susceptibility to steroids, and variability of pharmacokinetics. Also, the pubertal growth spurts in similar group of children have been previously demonstrated to be attenuated and delayed [5], though the same was not done in the index study which could have further shed insights on growth patterns. We acknowledge these factors as limitations.

Our objective was to measure linear growth (height *z* scores) and BMI *z* scores in adolescents with idiopathic nephrotic syndrome (INS). Since the upper limit of the enrolled adolescents was 19 years, WHO growth-charts were chosen for defining primary outcomes (height z score and BMI *z* scores). The additional data (weight-for-age *z* scores for 5-18 years) were expressed as per IAP growth-charts in the absence of reference data beyond 10 years in WHO growth charts. We acknowledge that the proportion of children diagnosed to have short stature might be marginally high in using different growth charts; but these children need careful growth monitoring and a chart with higher sensitivity might be more beneficial. The combined prevalence of overweight and obesity as per WHO (27.5%) and IAP charts (30.1%) was not statistically different in our study. Also, being a high-risk population who had received steroids for long duration, comparing them with physiological short

stature in general population was not considered appropriate.

Availability of data on pre-treatment baseline anthropometry, genetic potential of the child and pubertal growth spurt would have provided a more detailed picture on growth parameters in adolescents with INS; however, being a cross-sectional study, we reported only the prevalence of short stature, overweight and obesity at our canter; with appropriate acknowledgment of limitations.

BOBBITY DEEPTHI, SRIRAM KRISHNAMURTHY*
Department of Pediatrics, JIPMER, Pondicherry,
**drsriramk@yahoo.com*

REFERENCES

1. Emma F, Sesto A, Rizzoni G. Long-term linear growth of children with severe steroid-responsive nephrotic syndrome. Pediatr Nephrol. 2003;18:783-8.
2. Donatti LT, Koch VH. Final height of adults with childhood-onset steroid-responsive idiopathic nephrotic syndrome. Pediatr Nephrol. 2009;24:2401-8.
3. Simmonds J, Grundy N, Trompeter R, Tullus K. Long-term steroid treatment and growth: a study in steroid-dependent nephrotic syndrome. Arch Dis Child. 2010;95:146-9.
4. Göknar N, Webb H, Waters A, Tullus K. Long-term obesity prevalence and linear growth in children with idiopathic nephrotic syndrome: is normal growth and weight control possible with steroid-sparing drugs and low-dose steroids for relapses? Pediatr Nephrol. 2022;37:1575-1584.
5. Donatti TL, Koch VH, Fujimura MD, Okay Y. Growth in steroid-responsive nephrotic syndrome: a study of 85 pediatric patients. Pediatr Nephrol. 2003;18:789-95.

NEWS IN BRIEF

Nirsevimab to Prevent Severe RSV Infection

The American Academy of Pediatrics has just recommended the use of Nirsevimab for all infants under 8 months entering their first respiratory syncytial virus (RSV) season. This is not a vaccine but a long acting monoclonal antibody. It binds to a prefusion F protein of the virus preventing entry into humans. Besides infants it has also been recommended for children between 8-19 months entering their second RSV season if they are immuno-compromised, have chronic lung disease of prematurity or lung disease due to cystic fibrosis.

This is a single intramuscular injection unlike the previously available monoclonal antibody palivizumab which needed to be given monthly for the 5 months of the RSV season between October and March. Phase 3 clinical trials in 1490 African infants published in 2022 demonstrated a 73% decline in the number of lower respiratory tract infections due to RSV though the number of hospitalizations were not significantly different.

Monoclonals are effective in prevention of severe disease in children but not in geriatrics because of the larger doses required in adults. An effective vaccine for RSV is still awaited. (*Centers for Disease Control; 3 August, 2023*)

Indian Doctor Wins Ramon Magsaysay Award

No one expected the head of surgical oncology in Adyar Cancer Institute in Chennai, Dr Ravi Kannan to leave the hustle and glamour of a metro to relocate to a remote town in Assam at 42 years of age. Till then he had followed a rather humdrum path of graduate medical education in Tamil Nadu, post-graduation in Delhi, followed by an MCh in Surgical Oncology in Chennai. In early 2006, the director of the Cacher Cancer Hospital & Research Centre (CCHRC), Silchar, Assam started interacting with Kannan and referring him patients. Much to Dr Kannan's surprise he then invited him to relocate to Silchar as the Director of CCHRC. Despite many misgivings regarding the risk of insurgency and communal riots in Assam, his family supported his decision to translocate.

It has been a long road in CCHRC over 17 years from 23 employees to 451. From a hospital with limited facilities when he came on board, it now has 28 departments covering Oncology, Pathology, Radiology, Microbiology, Epidemiology, Tumor Registry, Palliative Care, and other services and specializations.

He has transformed cancer care in Assam by persistent patient education, subsidizing costs and building a network of peripheral hospitals which take health care to the doorstep of the patients.

This year he has been awarded the Ramon Magsaysay Award 2023 for "*his combination of skill, commitment, and compassion in pushing the boundaries of people-centered, pro-poor healthcare and cancer care, and for having built, without expectation of reward, a beacon of hope for millions in the Indian state of Assam, thus setting a shining example for all*." (*The Indian Express; 9 September, 2023*)

Chimeric Human-Pig Kidneys

There has been an interesting breakthrough to overcome shortages in organ transplants. Scientists in China have been able to grow humanized kidneys in pig embryos. It is a first for a solid organ with both human and animal cells to grow inside another species.

The procedure is complex to say the least. First pig embryos are subjected to CRISPR/Cas9 gene editing technology at the one cell stage to remove the 2 genes required for kidney formation. Once the embryo starts developing, human induced pluripotent cells (iPCS's) are introduced into the appropriate position. Usually human iPC's are often doomed to destruction in this alien environment. This is overcome by further tweaking their genes to avoid apoptosis.

Researchers from Guangzhou Institute of Biomedicine and Health experimented on 1800 embryos which were implanted in surrogate sows. On day 28 they harvested 5 embryos to check the development. All five had fully developed kidneys with 50-60% human cells. It is possible that further in gestation the percentage of human cells may increase. Ideally a 100% human kidney will be perfect for organ transplants. Another finding in the study was the development of some human iPC's into neural cells. This needs to be corrected since it may have ethical repercussions in the long term.

This development is a big advance in the science of organ transplant with a ripple effect in all spheres. (*Science News; 7 September, 2023*)

Smart Bandages for Wound Healing

Given the giant strides medicine has taken, the way we treat wounds is antiquated. A mere shielding of the wound with no real time monitoring of whether sepsis, bleeding or gangrene is setting in, seems bizarre in today's world.

Now across the world scientists are racing to develop an artificial intelligence enhanced smart bandage. These paper thin special materials will be embedded with sensors which monitor bleeding, infection and the progress of wound healing. They will have the ability to alert the physician and maybe even intervene with medications or other laser pulses. Some will be capable of monitoring temperature, pH, oxygen content, glucose, proteins etc. Tiny cameras will take pictures which are evaluated using AI to assess healing. Some even have light emitting diodes which emit ultraviolet rays and aid in reducing infection rates. Electric stimuli to enhance healing has also been experimented with, and phase 1 trial in rodents have been successful and further work is on to bring it to the bedside. (*Medscape News; 6 September, 2023*)

GOURI RAO PASSI
gouripassi@hotmail.com

CLIPPINGS

Dextromethorphan antitussive efficacy in children with acute cough due to common cold (Pediatr Pulmonol. 2023;58:2229-39)

A variety of home remedies and pharmacological treatments are available to mitigate or suppress cough. However, high quality evidence in the form of randomized controlled trials demonstrating the effectiveness of these treatment options is lacking. Efficacy of dextromethorphan hydrobromide (DXM), a nonopioid cough suppressant was demonstrated in this multiple-dose, double-blind, placebo-controlled, randomized, pilot clinical study conducted in children, aged 6-11 years, with cough due to the common cold. 128 children (aged 6-11 years), experiencing acute onset cough due to common cold, were enrolled and fitted with the VitaloJAK cough counting monitor, which recorded continuous digital audio. Subjects received DXM (7.5 mg/5mL) or placebo syrup every 6-8 h for nine doses, apart from acetaminophen as needed for pain or fever. Total cough count over the first 72 h of treatment was noted. They reported a 21% reduction in the 24 h cough frequency for DXM group in comparison to placebo, while the daytime cough frequency was reduced by 25.5%, both were statistically significant. In the secondary outcomes, the DXM group also had a statistically significant greater reduction in cold severity than the placebo group (P=0.025), while the adverse effects profile remained comparable between the groups. The authors note that these treatment effects are clinically more relevant in children, as reductions in daytime cough rates with DXM relative to placebo (<~20%-30%) was much more than reduction observed in adults (<~13%). Therefore, they concluded that DXM antitussive efficacy was shown in children using objective and subjective assessment tools validated in pediatric populations. Diurnal variation of cough frequency over 24 h reduced the assay sensitivity needed to detect treatment differences at nighttime, as coughs/hour decreased during sleep for both groups. The strengths of the current study are its prospective nature, placebo controlled randomized design, and implementation of validated assessment tools which could enable accurate determination of the antitussive efficacy of DXM.

Characterizing the phenotypes of prematurity-associated lung disease (Thorax. 2023;78:895-903)

This prospective study was done with the aim to characterize phenotype of prematurity associated lung disease among preterm born children. 768 children between 7-12 years, including 565 children in the preterm group (gestation <34 weeks) and 203 children in the term (gestation >37 weeks) group, were invited to join for home or hospital visit to obtain perinatal and respiratory history, anthropometry measurements, fractional exhaled nitric oxide (FENO) measurement, and lung function test using spirometry before and after bronchodilator administration. Based on abnormality in spirometry variables, children were categorized into four phenotype groups. The Preterm group was divided into two groups: group one (16.7%) with FEV_1 < lower limits of normal (LLN) and group two (83.3%) FEV_1>LLN. Preterm children with FEV_1<LLN were further classified into (7.7%) Obstructive phenotype (prematurity associated obstructive lung disease, PLOD) with FEV1/FVC <LLN and (9.0%) PRISm phenotype (prematurity associated preserved ration of impaired spirometry) with FEV1/FVC>LLN. The preterm PLOD group was further divided into PLOD reversible (4.4%) and PLOD fixed (3.3%) based on the bronchodilator reversibility test. Preterm children with FEV1>LLN and FEV1/FVC<LLN were classified as pDysanapsis group (5.9%), and remaining preterm children whose FEV1>LLN, FEV1/FVC> LLN were considered as the control group (77.4%) for preterm. PLODS reversible group children had more FENO levels, bronchopulmonary dysplasia (BPD), and intrauterine growth restriction, whereas the PLOD fixed group was associated with BPD. pDysanapsis group children had bronchodilator response, increased FENO, and were associated with postnatal weight gain. PRISm group showed bronchodilator response. The author concluded that by identifying the phenotype of prematurity-associated lung disease, long-term outcomes can be improved by providing targeted therapy.

Dexamethasone vs methylprednisolone for critical asthma (Pediatr Pulmonol. 2023;58:1719-27)

Qualitative data reveals 96% of pediatric intensivists prescribe intravenous methylprednisolone using clinical experience as the basis for preferred drug and dosage and only few prescribe dexamethasone in patients presenting with acute severe asthma. The authors did a single center, open-label, two-arm, parallel-group, nonrandomized trial among children aged 5-17 years hospitalized in the PICU for critical asthma and compared the clinical efficacy and safety of dexamethasone vs methylprednisolone. 31 children (intervention arm) received intravenous dexamethasone 0.25 mg/kg/dose (max: 15 mg/dose) every 6 h for 48 h and 61 children (standard care arm) received intravenous methylprednisolone 1 mg/kg/dose every 6 h (max dose: 60 mg/dose) for 5 days. They found that regarding efficacy and safety endpoints, no differences were noted in hospital length of stay, continuous albuterol duration, adjunctive asthma intervention rates or corticosteroid-related adverse events. Compared to the intervention arm, participants in the standard care arm were more frequently prescribed corticosteroids at discharge (P<0.001). They concluded that among children hospitalized for critical asthma, dexamethasone appears safe and warrants further investigation to fully assess clinical efficacy and potential advantages over commonly prescribed agents such as methylprednisolone.

AMIT DEVGAN
dramitdevgan@gmail.com

IMAGE

Gingival Cysts at Birth

Cystic gum swellings were seen in a full-term newborn (gestation 40 weeks, and birthweight 3600 g) at birth. These were one cm sized oval in appearance and with a smooth surface. These swellings commonly known as gingival cysts, are benign in nature and regress by three months of age. They do not interfere with future tooth eruption or feeding. These are inclusion cysts similar to Bohns nodules over gums or Epstein pearls over hard palate.

Gingival cysts are usually small cysts; however, the index infant's oral lesions were larger than reported. They often occur as solitary cystic swellings on the alveolar edges or gums or base of tongue. These are also known as dental laminar cysts as they are lined by odontogenic epithelia containing dental lamina and keratin. These are prone to be confused with impacted or uninterrupted tooth in a newborn. No treatment is required in most cases as they regress spontaneously. Parental reassurance is of importance. Definitive diagnosis is by histopathology, which shows keratin and islands of dental laminae.

Anisha Rosilyn Abraham,[1] Chetan Khare[2]
Departments of [1]Pediatrics and [2]Neonatology

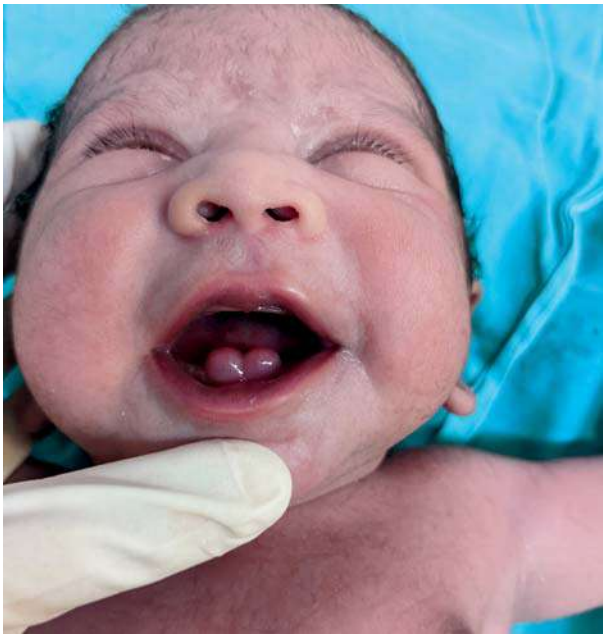
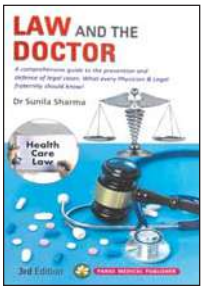


Fig. 1 Two midline gingival cysts in a fullterm newborn at birth.

All India Institute of Medical Sciences,
Bhopal, Madhya Pradesh.
**drchetankhare@gmail.com*

BOOK REVIEW



Law and the Doctor

Dr. Sunila Sharma
Paras Medical Publishers, 2023
Pages: 476; *Price: 501/-.*

This book is a sincere attempt on a very important and vital topic. The author has made a good attempt to compile various basic issues and information. This is the third edition and additional details have been included. However, some of the topics could have been restricted or merged. The Consumer Protection Act (CPA) 1986 should have been curtailed with more emphasis on CPA 2019. There is also a lot of overlap between the MCI Act and National Medical Commission. Some of the important references are from the Internet or Facebook, which may have questionable credibility or authenticity.

In the present era when numbers of readers of any book are decreasing, this book has adequate features to maintain the interest of the readers. Proper editing would have provided more relevant information. Many books are now available on these topics, but this one stands out for being a comprehensive, solo author book for the beginners to have awareness about medico-legal issues.

Satish Tiwari
Dr PDM Medical College,
Amravati, Maharashtra.
drsatishtiwari@gmail.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

Mankind
Serving Life

THE RARE PROBIOTIC

Entromax

2 Billion *Bacillus Clausii* Spores

Suspension

- **R** Reliable
- **A** Affordable
- **R** Rapid Action
- **E** Efficacy & Safety

In
- Infectious Diarrhea
- Antibiotic Associated Diarrhea (AAD)

For Billion Smiles

ASSURED GOODNESS

Gudcef-100

Cefpodoxime 100mg / 5ml

Dry Syrup

Good @ Efficacy
Micronised Cefpodoxime

Good @ Compliance
Palatable Orange Flavour

Good @ Affordability

In RTIs • Acute Otitis Media • Typhoid Fever

Orangilicious Choice for Kids