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Karnataka Paediatric Journal

Editorial

Bye Bye anaemia – Raise your hands for blood health

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Dear Readers,

Anaemia is a significant public health issue in India, affecting many people, especially women and children. Iron deficiency is a significant nutritional deficiency that affects individuals all over the world, particularly in developing countries. Iron deficiency anaemia has been the main cause of health burden in India for the past decade, based on a review of previous Global Burden of Disease surveys. Poverty, illiteracy and poor sanitation are the principal reasons for anaemia in India. As per the Global Nutrition Assessment 2016, India is among the countries with the highest rates of iron deficiency, placing 170th out of 180 for women's anaemia. Anaemia caused by an abnormal iron metabolism is connected with poverty and malnutrition.

Iron needs are higher for expectant mothers, new-borns, children and teenagers who are at the potential of becoming iron deficient. Low iron bioavailability in food is the most prevalent cause of iron deficiency in developing countries. A shortage of iron causes iron deficiency anaemia, which affects roughly 4–5 million individuals each year. It affects people of all ages, but the most vulnerable are children, pregnant or menstrual women and those who need renal dialysis. The concept which describes a condition in which the body's iron stores are depleted and there is evidence of a decreased iron transport to tissues is 'iron deficiency'. Anaemia caused by an abnormal iron metabolism is the most common micronutrient deficiency in the world, influencing the human health and economic well-being of countless men, women and children. As per the World Health Organization, anaemia caused by an abnormal iron metabolism is a significant community health issue that demands immediate attention from governments, researchers and healthcare practitioners.

Prevalence of anaemia in India – according to the National Family Health Survey-5, 57% of women aged 15–49 and 25% of men aged 15–49 in India have anaemia. It is more common in women and children in most states and union territories. Anaemia is more common in poorer women, and the prevalence decreases with increased education and wealth. It is more common in adolescent girls and pregnant women. Anaemia is more common in the eastern, north-eastern and central regions of India.

The government of India has implemented a number of initiatives to reduce anaemia:

- Strengthening the supply chain and logistics
- Developing training modules for healthcare providers
- Working with other departments and ministries
- Engaging the National Centre of Excellence and Advanced Research on Anaemia Control at AIIMS, Delhi.

The country's present health data infrastructure should be combined with a constant monitoring and assessment methodology. Although there are still significant technological hurdles in detecting anaemia in the general population, identifying its occurrence and severity is crucial. Studies are being conducted to produce a procedure that is relatively precise, quick and inexpensive, and that can be administered with equipment that is not easily broken and does not rely on power.

The government of India has set out Rs. 36,707 crore toward nutritional programs, including National Health Mission's Integrated Child Development Scheme. This might be $700 million less than the estimated needs, according to a nutrition evaluation. Other dietary programs, such as the welfare schemes and the Mahatma Gandhi Rural Employment Guarantee Act, receive about Rs. 2.07 lakh crore from the government; however, the system has serious flaws. According to a report published in January 2016, over half of the food given never reached its intended recipients.

Another program to combat this situation is the 'National Nutrition Anemia Prophylaxis Programme'. The purpose of the initiative, which started in 1970, was to avoid nutritional anaemia in mothers and children. Expectant and nursing mothers, as well as birth control users, are given one iron and folacin capsule containing 60 mg elementary iron, which has also been doubled to 100 mg elementary iron, but the folacin dose has not changed. This program is overseen by the Ministry of Health and Family Welfare's Maternal and Child Health Division. It is now part of the Reproductive and Child Health initiative. The program follows few actions to have a change. The following are the actions done to combat anaemia as part of the National Health Mission:

In 2018, Anaemia Mukt Bharat (AMB) was launched as part of the Strengthened Nationwide Iron Plus Initiative Project to lower anaemia rates by one to three percentage points each year. Children aged 6–59 months, 5–9 years, teenagers aged 19 years, reproductive age group women (15–49 years), expecting women and breastfeeding women are the target demographics for AMB.

The Weekly Iron and Folic Acid Supplementation (WIFS) Program is conducted to address problems of teenage girls and boys having a great due to the rising prevalence of anaemia. The WIFS approach entails 52 weeks of weekly iron-folic acid (IFA) tablet distribution under supervision (a single IFA tablet consists of 100 mg elemental iron and 500 g folic acid). A health information system and a mother-infant surveillance system are being implemented to identify and track cases of anaemic and extremely anaemic pregnant women.

Most interventions rely on people's active engagement to succeed. Because iron deficiency is widespread, it is critical to inform and educate the public, particularly through social mobilisation initiatives. As a public, professional strategy, it should be planned with the people that we are dealing with and other aspects in mind. Many nations have long-standing programs aimed at preventing and controlling iron deficiency anaemia, but only a handful have a well-coordinated plan to address the disease. In many countries, the expansion of primary health care has provided a valuable chance to control iron deficiency anaemia by using an approach that is direct, economical and easy. Food fortification is incredibly successful, but it can only be done in places with the necessary industrial infrastructure. It is usually not a good idea to base any anaemia management strategy just on any of those methods; it is unlikely to be effective enough on its own.

World Anaemia Awareness Day is observed globally to raise awareness about anaemia, its cause, prevention and treatment. The day highlights the importance of addressing anaemia, particularly among women, children and vulnerable populations, as it significantly impacts public health, productivity and quality of life. The theme for World Anaemia Awareness Day in 2025 is 'Raise Your Hands for Blood Health'.

Key points about the 2025 theme:
Focus on the action: The theme emphasises the importance of taking proactive steps to maintain good blood health.

Slogan: 'Know Your Number, Break the Silence on Anaemia' is often used alongside this theme.

World Anaemia Awareness Day was created in 2022 in response to the global issues of anaemia and iron deficiency, mainly affecting women and children. It is marked on 13 February as 13, representing the ideal haemoglobin number for optimal blood health. The 2024 global campaign successfully reached an audience of over 50 million. The campaign focus is to keep the problem of anaemia and iron deficiency in the spotlight. It is especially for the general public as it is a problem often overlooked by medical professionals. World Anaemia Awareness Day aims to be a platform for raising awareness of anaemia and iron deficiency and a global driver to promote the importance of preventative action to support blood health. Central Indian Academy of Pediatrics (IAP) and IAP Karnataka have done commendable work in this regard by conducting awareness programs across the country. Let's join hands to achieve the goal of anaemia free India.

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Karnataka Paediatric Journal

Original Article

Assessment of neurodevelopmental outcomes in preterm infants using risk stratification score

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ABSTRACT

Objectives: Preterm birth, defined as delivery occurring before 37 weeks gestation, poses a significant public health challenge, as an increasing number of infants who survive face neurodevelopmental disabilities. Preterm infants face various health challenges, including anaemia, hyperbilirubinaemia, feeding and respiratory difficulties, retinopathy and intracranial haemorrhage, which often lead to long-term cognitive, learning and behavioural impairments due to structural brain abnormalities. (1) To study risk stratification tools based on intrauterine and neonate insult. (2) To study and predict major neuro-developmental disability like cerebral palsy, mental retardation, blindness, deafness at 1 year of age.

Material and Methods: The study included 30 preterm infants, categorised by risk levels, after obtaining ethical clearance and parental consent. Developmental follow-up assessments were adjusted for prematurity and conducted using tools such as the Amiel-Tison angle (ATA), scarf sign, Denver developmental screening test (DDST) and Vineland social maturity scale (VSMS). Visual and hearing assessments were checked for retinopathy and deafness. Primary outcomes at 1 year included death or major neurodevelopmental delays, such as cerebral palsy, mental impairment, blindness and profound hearing loss.

Results: In this study of 30 preterm infants, 83% weighed over 1.5 kg with a mean birth weight of 1.73 kg, and amongst those under 1.5 kg, 80% had abnormal developmental outcomes. The mean gestational age was 32 ± 1 weeks. Major neurodevelopmental delays (NDD), including cerebral palsy and global developmental delay, was observed in 16.6% of the infants, while 30% experienced minor NDD. Preterms with major NDD had higher intervention needs, with 40% requiring positive pressure ventilation and intubation, and 20% requiring chest compressions, 26.6% having abnormal ATAs. Statistically significant perinatal risk factors for poor neurodevelopmental outcomes included extreme prematurity (≤32 weeks), birth weight (<1.7 kg), need for resuscitation and prolonged ventilation (>7 days).

Conclusion: The study identified extreme prematurity, low birth weight, need for resuscitation and prolonged ventilation as key predictors of poor neurodevelopmental outcomes in preterm infants. Infants were stratified into low and high-risk groups to plan follow-up intensity and early intervention. Tools such as ATA, DDST, and VSMS aid in the early detection of neurodevelopmental disabilities, emphasising the importance of standardised follow-up programmes in neonatal units to improve outcomes for high-risk infants.

Keywords: Amiel-Tison angle, Denver developmental screening test, Neuro-development outcome, Preterm birth, Vineland social maturity scale

INTRODUCTION

Preterm birth, defined as delivery before 37 weeks of gestation, presents a major public health challenge, with many surviving infants facing neurodevelopmental disabilities.[1] Despite

advancements in neonatal intensive care unit technology that has improved survival rates and reduced severe neonatal complications, the risk of neurodevelopmental and behavioural impairments remains significant.[1] Prematurity and low birth weight are leading causes of neonatal mortality worldwide, particularly in low-income regions such as Asia and sub-Saharan Africa[1]. These conditions contribute to a range of complications, including anaemia, hyperbilirubinaemia, respiratory issues, and intracranial haemorrhage, which can lead to long-term neurological and developmental challenges.[2] India, with the highest number of preterm births globally, is addressing this issue through the implementation of the World Health Organization-recommended guidelines, including antenatal corticosteroids, tocolytics, magnesium sulphate and Kangaroo Mother Care.[3] While survival rates have improved, preterm infants remain at high risk for conditions such as cerebral palsy, cognitive and motor impairments and sensory deficits.[3] Early identification and intervention, supported by structured follow-up programmes, are essential to mitigate these risks and improve outcomes for these vulnerable infants.[2]

MATERIAL AND METHODS

Methods of collection of data

Study design

Prospective observational study.

Study setting

Department of Paediatrics, Basaveshwar Teaching and General Hospital, Kalaburagi and Sangameshwar teaching and general hospital Kalaburagi. Attached to Mahadevappa Rampure Medical College, Kalaburagi.

Sample size: 30

Using the formula, $n = Z^2PQ/d^2$ where,

n = sample size, Z =confidence interval, P = Prevalence, Q = 1-P, d = error rate

P = 6.5% Q = 93.5

d^2 = permissible error was 10%

Sample size (n) = $Z^2{}_aPQ/d^2$

$= (1.96)^2 \times 6.5 \times 93.5/(10)^2$

= 23.34

Round figure sample size n =30

Study duration

August 01, 2022, to March 31, 2024 (20 months).

Inclusion criteria

1. Preterm babies <34 weeks
2. Both inborn and outborn babies are referred in the first 48 hours.

Table 1: Demographics and perinatal factors.

Parameter	Category	No. of patients	Percentage
Gender	Female	11	36.7
	Male	19	63.3
Birth weight (kg)	≤1.50	5	16.7
	>1.50	25	83.3
Gestational Age (weeks)	≤32	7	23.3
	>32	23	76.7
Mode of delivery	LSCS	12	40.0
	NVD	18	60.0
Place of delivery	BTGH	14	46.7
	PVT	3	10.0
	STGH	13	43.3
Antenatal risk factors	Abnormal NST	1	3.3
	DC twins	1	3.3
	Eclampsia	2	6.7
	MC twins	2	6.7
	Oligohydramnios	1	3.3
	Overt DM, G. HTN	1	3.3
	Pre-eclampsia	1	3.3
	Uteroplacental insufficiency	1	3.3
	Severe pre-eclampsia	2	6.7
	No risk factors	18	60.0
Steroid coverage	Completed	17	56.7
	Not given	7	23.3
	Partial	6	20.0
Need for resuscitation	Chest compression	1	3.3
	Intubation	2	6.6
	PPV	3	10.0
	No resuscitation	24	80.0
Need for ventilation	HFNC	1	3.3
	NIV	18	60.0
	Short ventilation	7	23.3
	Ventilation >7 days	2	6.7
	No ventilation	2	6.7

NVD: Normal vaginal delivery, PPV: Positive pressure ventilation, LSCS: Lower segment cesarean section, BTGH: Basaveshwar teaching and general hospital, STGH: Sangameshwar teaching and general hospital, PVT: Private hospital, NST: Non stress test, DC: Dichorionic, MC: Monochorionic, DM: Diabetes mellitus, G.HTN: Gestational hypertension, HFNC: High flow nasal cannula, NIV: Non invasive ventilation

Table 2: Risk stratification score.

	Mild risk	Moderate risk	Severe risk
Gestation	33–34 weeks	30–32 weeks	<30 weeks
Birth weight	>1501 g	1251–1500 g	<1250 g
Intrauterine insults		Maternal fever Abnormal non-stress test Premature rupture of membranes Dichorionic twins	Severe maternal pre-eclampsia Monochorionic Chorioamnionitis twins/triplets/higher order Abruption of placenta
Antenatal steroids	Complete	Incomplete course or <24 h from last dose	No antenatal steroids
Need for resuscitation at birth		Need for resuscitation-positive pressure ventilation	Extensive resuscitation -chest compressions, Adrenaline
Hypoglycaemia		Asymptomatic	Symptomatic
Shock	Nil	Saline bolus	Inotropes
Neonatal jaundice			Requiring exchange transfusion / Bilirubin induced neurological dysfunction

Exclusion criteria

1. Preterm >34 weeks of gestation
2. Preterm infants with congenital malformation requiring major surgeries, dysmorphism, intrauterine infections
3. Transferred to another hospital before completion of the care
4. Babies collapse during the first 48 hours of life.

Methodology

Following approval from the Institutional Ethical Committee and obtaining informed consent from the parents, 30 subjects were selected for the study based on inclusion criteria. A questionnaire was developed to gather participant information, including demographic data, birth details and associated risk factors [Table 1]. The infants were then categorised into mild, moderate, or severe risk groups according to the risk score [Table 2].

To account for prematurity, developmental follow-up assessments were age-corrected based on the expected date of delivery, using a full correction method. This adjustment ensured that developmental milestones were assessed relative to the infant's expected developmental timeline, considering their prematurity. Tone abnormalities were evaluated every 3 months using the Amiel-Tison angle (ATA) and scarf sign.[1] The Denver developmental screening test (DDST) was administered at 2, 4, 8 and 12 months to assess major milestone achievements [Table 3].[4]

At 12-month corrected gestational age, the Vineland social maturity scale (VSMS) was used to assess the infants' intelligence quotient (IQ).[5] In addition, visual assessments were conducted to screen for retinopathy of prematurity[6]

Table 3: Neurodevelopmental outcomes and risk factors.

Parameter	Category	No. of patients	Percentage
Neurodevelopmental outcome	Major NDD	5	16.6
	Minor NDD	9	30.0
	Normal	16	53.4
NEC	Stage 2	3	10.0
	No NEC	27	90.0
Shock	Inotropes	10	33.3
	Saline bolus	7	23.3
	No shock	13	43.3
Seizures/ encephalopathy	Yes	1	3.3
	No	29	96.7
IVH	Grade 4	1	3.3
	Grade 3	1	3.3
	Grade 1	1	3.3
	Normal	27	90.0
ROP	Early stage 2	5	16.7
	Stage 1	1	3.3
	Normal	24	80.0
BERA	Bilateral mild SNHL	1	3.3
	Left mild SNHL	1	3.3
	Normal	28	93.3
AT angle	Abnormal	8	26.6
	Normal	22	73.4

AT: Amiel-Tison, NEC: Necrotising Enterocolitis, ROP: Retinopathy of prematurity, BERA: Brainstem evoked response audiometry, SNHL: Sensorineural hearing loss, NDD: Neurodevelopmental delay, IVH: Intraventricular haemorrhage

and hearing assessments were performed to detect any hearing impairments.[7]

At the end of 1 year, the outcomes were categorised into primary and secondary outcomes. Primary outcomes were defined as death before 12 months post-discharge or major neurodevelopmental delays, such as cerebral palsy, mental impairment, blindness, or profound hearing loss.[8] Secondary outcomes included normal development or minor neurodevelopmental disabilities, such as refractive errors or squints, impaired hearing not requiring assistive devices, growth delays and delays in achieving milestones in two or fewer domains [Table 4].[7]

Table 4: Neurodevelopmental delay and IQ distribution.

Parameter	Category	No. of patients	Percentage
Developmental delay (DDST)	Fine motor delay	2	6.7
	GDD	6	20.0
	Gross motor delay	2	6.6
	Language delay	2	6.7
	No delay	18	60.0
IQ (VSMS)	Average	23	76.7
	Below average	4	13.3
	Borderline	2	6.7
	Mild intellectual disability	1	3.3
Clinical risk score for NDD	Low risk (0–1)	26	86.6
	High risk (≥2)	4	13.4

IQ: Intelligence quotient, VSMS: Vineland social maturity scale, DDST: Denver developmental screening test, GDD: Global developmental delay, NDD: Neurodevelopmental delays

RESULTS

This study includes neurodevelopmental outcomes of 30 early preterm babies followed up till 1 year of age with various assessments and investigations.

This study examined the neurodevelopmental outcomes of 30 early preterm infants followed until 1 year of age. It found that lower birth weight and earlier gestational age were significantly associated with higher rates of neurodevelopmental delays (NDD). Specifically, 80% of infants weighing <1.5 kg and 86% of those born at or before 32 weeks had abnormal developmental outcomes. The need for resuscitation at birth, particularly the use of positive pressure ventilation and intubation, was also significantly linked to major NDD. A clinical risk score based on gestational age, birth weight, need for resuscitation, and ventilation was developed, which successfully stratified infants into low- and high-risk groups for major NDD. The low-risk group had a 42.3% incidence of NDD, while the high-risk group had a 75% incidence.

DISCUSSION

In our study, amongst the 30 subjects, 63% were males and 37% were females, resulting in a male-to-female ratio of 1:0.5. This ratio is comparable to the findings of Serenius *et al.*[1] and Sujatha *et al.*[2] both reported a ratio of 1:0.8. The incidence of major NDD in our cohort was 16.6%, which aligns closely with the 20% reported by Jain *et al.*,[3] though it is higher than the 6.2% observed by Sujatha *et al.* [Table 5].[2]

The mean birth weight of preterm neonates in our study was 1.73 kg, which is higher than the values reported by

Table 5: Demographic and neonatal characteristics.

Study	Place	Sample size	Male/female ratio	Major NDD (%)	Mean GA (weeks)	Mean birth weight (kg)
Longo *et al.* (2019)[9]	Italy	502	1:1.04	10.7	29±2	1.11
Serenius *et al.* (2013[1]	Sweden	456	1:0.8	7.0	25±1	0.8
Sujatha *et al.* (2016)[2]	Kerala	225	1:0.8	6.2	30±2	1.42
Jain *et al.* (2020)[3]	Gujarat	62	1:1.2	20.9	-	-
Patel *et al.* (2017)[10]	-	-	-	-	31±2	1.45
Present Study (2024)	Kalaburagi	30	1:0.5	16.6	32±1	1.73

NDD: Neurodevelopmental delay, GA: Gestational Age

Table 6: Antenatal risk factors, delivery mode, resuscitation and ventilation.

Study	Antenatal risk factors	Steroids (%)	NVD	Resuscitation required	Ventilation (NIV+intubation)
Longo *et al.* (2019)[9]	-	88	19%	75%	51%
Serenius *et al.* (2013)[1]	-	90	-	-	-
Sujatha *et al.* (2016)[2]	70.5%	91	-	12.7%	59.2%
Present Study (2024)	40%	76.7	60%	20%	93%

NVD: Normal vaginal delivery, NIV: Non invasive ventilation

Longo *et al*.[9] and Serenius *et al*.[1] However, our findings are consistent with those of Patel *et al*.[10] and Sujatha *et al*.[2] reported similar mean birth weights around 1.4 kg. The mean gestational age in our study was 32 ± 1 weeks, which is consistent with the findings of Patel *et al*.[10] and Sujatha *et al*.[2] In contrast, Serenius *et al*.[1] reported a lower mean gestational age of 25 ± 1 weeks.

Antenatal risk factors were present in 40% of cases in our study, a lower proportion compared to the 70.5% reported by Sujatha *et al*.[2] Antenatal steroid coverage in our cohort was 76.7%, which was the lowest compared to the higher coverage rates reported by Sujatha *et al*.,[2] Serenius *et al*.,[1] and Longo *et al*.[9] Furthermore, 60% of the deliveries in our study were normal vaginal deliveries, a higher proportion compared to the 19% reported by Longo *et al*. [Table 6].[9]

In terms of neonatal interventions, 20% of the preterm neonates in our study required resuscitation at birth, which is lower than the 75% reported by Longo *et al*.[9] However, the requirement for ventilation was higher in our study at 93%, compared to the lower rates reported by Sujatha *et al*.[2] and Longo *et al*.[9]

Limitation of the study

Single centre study and relatively small sample size.
We did not assess the long-term impact on neurodevelopment or potential psychiatric or psychological disorders, including behavioural disorders.

CONCLUSION

Perinatal risk factors identified in the index study as poor neurodevelopmental outcome predictors were extreme prematurity that is, gestational age (≤32 weeks), birth weight, need for extensive resuscitation, and prolonged ventilation (>7 days). Babies were stratified based on these risk factors into low and high risk for major NDD at 1-year age. This will be helpful in planning the intensity of follow-up and early intervention. Parameters such as ATA, DDST, and VSMS can help in the early recognition of neuro-developmental disability. Early stratification of neonates with the possibility of abnormal outcomes can help in early intervention and moving towards an intact survival of high-risk neonates. Standardised follow-up programmes should be an integral part of every neonatal unit to improve the outcome of high-risk neonates.

Ethical approval: The research/study was approved by the Institutional Review Board at Mahadevappa Rampure Medical College Kalaburagi, number 20220796, dated 27th July 2020.
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Karnataka Paediatric Journal

Original Article

Incidence, risk factors, microbiological profile and outcome of ventilator-associated pneumonia in paediatric intensive care unit

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ABSTRACT

Objectives: This study aims to assess the incidence, risk factors and outcomes associated with ventilator-associated pneumonia (VAP) in PICU patients as well as analyse the microbiological characteristics of VAP.

Material and Methods: A 20-month prospective observational study was conducted in the PICU of a tertiary hospital. The study included all children requiring mechanical ventilation (MV) for more than 48 hrs, until 100 patients were enrolled. Information on demographics, clinical features, laboratory findings, imaging, treatment and outcomes was documented. VAP was diagnosed using centers of disease control/national nosocomial infections surveillance (CDC/NNIS) criteria and confirmed through endotracheal (ET) aspirate cultures (≥105 colony forming unit (CFU)/mL). Patients with VAP were compared to those without regarding risk factors, clinical details, treatment and outcomes, including length of stay and mortality. All participants were followed until discharge or death.

Results: VAP incidence was 51% based on CDC/NNIS criteria, with microbiological confirmation in 41% of cases. Nearly half of the cases were early-onset VAP, and the incidence density was 57.4 episodes/1000 ventilator days. Younger children (≤1 year) were disproportionately affected (60.8%). Gender had no significant impact on VAP development. Respiratory conditions were the most common predisposing factors, though primary diagnoses did not significantly affect VAP rates. Risk factors such as nasogastric feeding during MV, prior antibiotic use, proton pump inhibitors and uncuffed ET tubes were significantly associated with VAP ($P < 0.01$). The VAP-associated mortality rate was 33.3%, similar to the 18.4% mortality in non-VAP pneumonia. Most VAP-related deaths were linked to Gram-negative bacteria, primarily Acinetobacter, *Klebsiella* and *Escherichia coli*. The VAP group had significantly longer PICU and hospital stays compared to the non-VAP group.

Conclusions: VAP is a frequent and serious complication in mechanically ventilated PICU patients, significantly increasing the duration of hospitalisation and intensive care unit (ICU) stays. While it does not markedly raise mortality rates compared to non-VAP pneumonia, it emphasises the need for better prevention, early diagnosis and management strategies in the PICU setting.

Keywords: Endotracheal aspirate culture, Incidence, Mechanical ventilation, Risk factors, Ventilator-associated pneumonia

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a type of hospital-acquired pneumonia that develops in patients who have been mechanically ventilated for at least 48 h, either through an endotracheal

tube (ETT) or a tracheostomy tube. In paediatric intensive care units (PICUs), it ranks as the second most frequent nosocomial infection after bloodstream infections and is a significant contributor to morbidity and mortality amongst hospital-acquired infections.[1-3]

Despite advancements in managing patients reliant on mechanical ventilation (MV), VAP continues to affect 8–28% of those on ventilators.[4,5] In developed countries, the prevalence of VAP amongst ventilated PICU patients is estimated at 3–10%.[6] However, studies from India report much higher rates, ranging from 6% to 46%.[7] Understanding the primary bacterial pathogens causing VAP and their antibiotic resistance patterns is essential for guiding effective treatment strategies. In addition, identifying risk factors that influence VAP outcomes can help reduce the associated morbidity and mortality and contribute to the development of preventive measures.

MATERIAL AND METHODS

This prospective observational study was conducted in the PICU of a tertiary care hospital over 20 months. Ethical clearance was obtained from the Institutional Ethics Committee before commencing the research. The study included PICU patients aged 1 month–19 years who required conventional MV for more than 48 hrs. Patients who had been intubated and ventilated at other hospitals before being admitted to the PICU were excluded from the study.

The sample size was calculated using an online tool (Raosoft Sample Size Calculator) based on a previously reported VAP incidence of approximately 7% (range: 3–10%).[8] To achieve a 95% confidence level and a 5% margin of error, a minimum sample size of 92 was determined, which was rounded up to 100 participants. Eligible patients were enrolled consecutively after obtaining informed consent from their parents or guardians.

A structured data collection sheet was used to record demographic details such as age and sex, along with clinical information, including admission date, reason for admission (medical or surgical), comorbidities, nutritional and immunological status, socioeconomic status, primary diagnosis, PRISM III score, Glasgow Coma Scale (GCS) score, duration of MV, length of ICU stay, the occurrence of VAP, causative pathogens, prior antibiotic use (<48 hrs vs. >48 hrs before MV), patient positioning (supine or semi-recumbent), reintubation events, nasogastric feeding, use of medications (e.g., inotropes, sedatives, paralytics and peptic ulcer prophylaxis) and patient outcomes (discharge, improvement or death).

Broad-spectrum antibiotics, including amoxicillin-clavulanic acid, ceftriaxone, amikacin or piperacillin-tazobactam, were initiated based on PICU protocols and underlying conditions either before or immediately after initiating MV. Oral hygiene care was done with suction to remove excess fluid and saline swabs were used. Chlorhexidine mouthwashes were used twice daily. Reusable ventilator circuits were used. They were changed after 72 hrs or when it was visibly soiled. Reusable components that came in contact with the patient's mucous membranes or contaminated with their respiratory secretions were cleaned and disinfected. Wearing masks and gloves and washing hands before and after handling the circuit was practised.

A baseline chest X-ray was performed post-intubation, with additional imaging and blood cultures conducted for patients with suspected VAP. Endotracheal aspirates (ETAs) were collected aseptically using a mucus extractor connected to a suction machine. The collected samples were sent to the microbiology laboratory, where they were cultured using blood, chocolate and MacConkey agars, with fungal cultures conducted when indicated.

VAP was diagnosed using the centers of disease control/ national nosocomial infections surveillance (CDC/NNIS) criteria (2003)[2] and confirmed by a positive culture showing ≥105 colony forming unit (CFU)/mL. Samples yielding ≤105 CFU/mL or showing no growth that did not meet the criteria for nosocomial pneumonia were classified into the no-VAP group. Antibiotic regimens were adjusted based on the susceptibility patterns of the identified organisms.

Data were entered into Microsoft Excel and analysed using the Statistical Package for the Social Sciences. Descriptive statistics, such as percentages and medians with interquartile ranges, were used to summarise the data. Categorical variables were analysed with the Chi-square test, and continuous variables were compared using the Mann–Whitney *U*-test. A $P < 0.05$ was considered statistically significant. Variables significantly associated with VAP in univariate analysis were further analysed using multiple logistic regression to identify independent risk factors.

RESULTS

During the study, 1330 children were admitted to the PICU, of which 237 required MV. Of these, 100 patients met the study criteria and were analysed, contributing to a total of 889 ventilator days. Based on CDC/NNIS criteria, 51% of the patients developed VAP, while 49% did not [Table 1]. In the VAP group, 60.8% of the patients were ≤1 year old, and 21.6% were aged >1–5 years. Amongst non-VAP patients, 34.7% were >1–5 years old, followed by 32.7% aged ≤1 year. Overall, 69% of the study participants were male (male-to-female ratio: 2.2:1). In the VAP group, 72.5% were male, compared to 65.3% in the non-VAP group. Respiratory conditions were the leading cause of MV in both groups (23.5% in VAP vs. 28.6% in non-VAP patients). Sepsis was the second most

Table 1: Number of VAP cases diagnosed based on the CDC/NNIS criteria.

VAP	*n*=100	%
Yes	51	51
No	49	49

VAP: Ventilator-associated pneumonia, CDC: Centers of disease control, NNIS: National nosocomial infections surveillance

common diagnosis in the VAP group (15.7%), while sepsis and dengue fever were equally common in the non-VAP group (15.7% each). There was no statistically significant difference in primary diagnoses between the two groups [Table 2]. Positive ETAs cultures were obtained in 80.4% of clinically diagnosed VAP patients. Most isolates were Gram-negative bacteria (91.8%), with *Acinetobacter baumannii* being the most common, followed by *Klebsiella pneumoniae* and *Escherichia coli*. Early VAP was predominantly caused by Acinetobacter, *E. coli* and *Pseudomonas aeruginosa*, while late VAP was most associated with *K. pneumoniae*. A single case of early VAP involved *Candida tropicalis*. Univariate analysis revealed significant associations ($P < 0.05$) between VAP development and the following factors: Nasogastric feeding during MV, antibiotic use for more than 48 h before initiating MV, proton pump inhibitor (PPI) use (with a longer median duration in the VAP group, 10 days, compared to the non-VAP group, 6 days), the use of uncuffed ETT and reintubation during ventilation [Table 3].

27 cases in the VAP group and 8 cases in the non-VAP group had re-intubations, which was significant ($P < 0.0001$). The odds of developing VAP were 5.6 times higher with re-intubation compared to no re-intubation. The maximum number of cases (22 cases) had 1–2 re-intubations, with 14 (63.6%) in the VAP group and 8 (36.4%) in non-VAP cases. Ten patients in the VAP group had 3–4 and 3 patients had 5–6 re-intubations. With a higher number of re-intubations, there was a significant increase in the chances of developing VAP. None of them had spontaneous extubation.

Positive blood cultures were reported in 11 patients with VAP and 1 patient without VAP. Amongst the isolates in the VAP group were *Staphylococcus hominis* (2 cases), *Staphylococcus aureus* (1 case) and *Staphylococcus haemolyticus* (1 case). Methicillin-resistant *Staphylococcus aureus* was detected in a single patient in the non-VAP group. The mortality rate was higher in the VAP group (33.3%) compared to the non-VAP group (18.4%), but the difference was not statistically significant ($P = 0.3$). Amongst VAP cases, early VAP had a mortality rate of 39.3%, while late VAP had a rate of 26.1%. Improvement rates were 35.7% for early VAP and 55.1% for late VAP, but these differences were not statistically significant ($P = 0.3$). VAP patients had a significantly longer ICU stay, with a median duration of 10 days (range: 3–45 days) compared to 6 days (range: 3–16 days) for non-VAP patients ($P < 0.001$).

Table 2: Comparison of the primary diagnoses of VAP and non-VAP patients who received MV.

System involved	Total	VAP	No VAP
	n=100 (%)	*n*=51 (%)	*n*=49 (%)
RS	26 (26)	12 (23.5)	14 (28.6)
Sepsis	20 (20)	8 (15.7)	12 (24.5)
Dengue fever	19 (19)	7 (13.7)	12 (24.5)
CNS	14 (14)	9 (17.6)	5 (10.2)
Hydrocarbon poison	4 (4)	3 (5.9)	1 (2.0)
OP poisoning	3 (3)	0 (0)	3 (6.1)
Paraquat poisoning	1 (1)	1 (2.0)	0 (0)
CVS	6 (6)	6 (11.8)	0 (0)
Head injury	4 (4)	2 (3.9)	2 (4.1)
CVS	2 (2)	2 (3.9)	0 (0)
Tetanus	1 (1)	1 (2.0)	0 (0)

VAP: Ventilator-associated pneumonia, MV: Mechanical ventilation, CNS: Central nervous system, RS: Respiratory system, CVS: Cardiovascular system, OP: Organophosphate.

DISCUSSION

MV is a vital component of modern intensive care, but its use is associated with a significant risk of VAP. Identifying patients at high risk and recognising modifiable risk factors can aid in creating strategies to prevent infections and improve institutional protocols.

In the current study, the VAP incidence was 51%, higher than previous Indian studies reporting a range from 6.03% to 46.4%, and international studies[9-11] from developed nations, which show a range of 3–31%. These variations may be attributed to differences in diagnostic criteria, patient population and underlying conditions necessitating ventilator support. The higher incidence in this study may stem from the use of the CDC/NNIS criteria, as opposed to relying on clinical features combined with positive microbiological cultures from endotracheal (ET) aspirates, which other studies often use. When restricted to cases with significant microbiological growth in ET aspirates, the VAP incidence in this study was 41%, aligning with rates from other research, such as Awasthia *et al*. (36.2%)[10] and Payal *et al*. (46.4%).[12] In addition, most cases involved early-onset VAP.

The incidence density of VAP in this study was 57.4 episodes/1000 ventilator days. This figure surpasses the reported range of 1–63 episodes/1,000 ventilator days observed in both paediatric and neonatal populations. Factors influencing these rates include geographical location,

Table 3: Risk factors according to univariate analysis.

Risk factors	VAP	No VAP	*P*-value
	n (%)	*n* (%)	
Host factors			
GCS			
<7	20 (50.0)	20 (50.0)	0.6
>7	31 (51.8)	29 (48.2)	
Nutritional status			
PEM	5 (41.7)	7 (58.3)	0.3
Adequate	46 (52.3)	42 (47.7)	
Comorbidities			
Yes	21 (47.7)	23 (52.3)	0.9
No	30 (53.6)	26 (46.4)	
Treatment-related risk factors			
Requirement of paralytic agents			
Yes	8 (57.1)	6 (42.9)	0.6
No	43 (50.0)	43 (50.0)	
Sedation			
Yes	51 (51.0)	49 (49.0)	NA
Inotropic support			
Yes	45 (52.3)	41 (47.7)	0.3
No	6 (42.9)	8 (57.1)	
Aspiration of subglottic secretions			
Yes	51 (51.0)	49 (49.0)	NA
Antibiotics before MV			
Yes	43 (61.4)	27 (38.6)	0.001
No	8 (26.7)	22 (73.3)	
Antibiotic use <48 h before MV			
Yes	17 (44.7)	21 (55.3)	0.3
No	34 (54.8)	28 (45.2)	
Antibiotic use >48 h before MV			
Yes	26 (81.3)	6 (18.8)	<0.001
No	25 (36.8)	43 (63.2)	
Proton pump inhibitors			
Yes	51 (54.8)	42 (45.2)	0.005
No	0 (0.0)	7 (100.0)	
NG feeding			
Yes	17 (73.9)	6 (26.1)	0.01
No	34 (44.2)	43 (55.8)	
Type of ET tube			
Cuffed	13 (31)	29 (69)	<0.001
Uncuffed	38 (65.5)	20 (34.5)	
Reintubations			
Yes	27 (77.1)	8 (22.9)	<0.0001
No	24 (36.9)	41 (63.1)	

VAP: Ventilator-associated pneumonia, GCS: Glasgow coma scale, MV: Mechanical ventilation, ET: Endotracheal, PEM: Protein energy malnutrition, NG: Nasogastric feeding, NA: Not applicable

hospital type and the economic status of the country.[13] For instance, reported rates include 36.2% in Indian paediatric ICUs[10] and 31.8/1,000 ventilator days in Egypt.[14]

The study also analysed VAP risk factors by comparing patients with and without VAP. Amongst patients with VAP, 60.8% were under 1 year old, and a statistically significant difference in age was noted between the VAP and non-VAP groups ($P = 0.03$). Despite the predominance of male patients in both groups, the sex distribution was not significantly different ($P = 0.4$), with a male-to-female ratio of 2.6:1 in the VAP group, consistent with findings by Patra *et al.*[8] Most participants in both groups came from lower socioeconomic backgrounds, but socioeconomic status did not significantly affect VAP occurrence.

Other potential factors, such as the primary diagnosis, GCS score, nutritional status and comorbidities, showed no significant correlation with VAP in this study. These findings align with those of Vedhavathy and Sangamesh[11], who reported similar distributions of age, sex and MV indications between VAP and non-VAP groups. However, contrasting evidence from Galal *et al.*[15] suggests younger age (<1 year) and female sex as significant risk factors for VAP, along with specific diagnoses such as coma and multiple organ failure. Similarly, Amanti[16] identified immune status as a significant factor, whereas Patra *et al.*[8] found no link between age, malnutrition and VAP risk.

This study found no significant association between surgical procedures, including central line placement, bronchoscopy, tracheostomy, or thoracostomy, and the development of VAP. However, research by Vedhavathy and Sangamesh[11] reported that tracheostomy and the presence of central venous lines were significantly linked to VAP occurrence. Similarly, Elward *et al.*[6] observed that surgical interventions significantly contributed to VAP development.

Reintubation emerged as a critical risk factor for VAP. The study highlighted that the probability of developing VAP increased with a higher number of reintubations, particularly in cases of unplanned reintubation or multiple attempts. Prior studies, including those by Elward *et al.*,[6] Patra *et al.*,[8] Nemat B *et al.*[17] and Khalid Amro,[18] identified reintubation as an independent risk factor, with Patra *et al.*[8] reporting a strong statistical association ($P < 0.001$).

The use of cuffed ETT was associated with a significant reduction in VAP incidence in this study ($P < 0.001$). Conversely, findings from the Vedavathy S study[11] indicated no significant difference in VAP rates based on the type of ETT used.

In this study, factors such as the use of paralytic agents during intubation, sedatives and inotropes for haemodynamic stabilisation did not significantly contribute to VAP risk. However, prolonged use of antibiotics (beyond 48 h), PPIs and nasogastric (NG) feeding was significantly associated

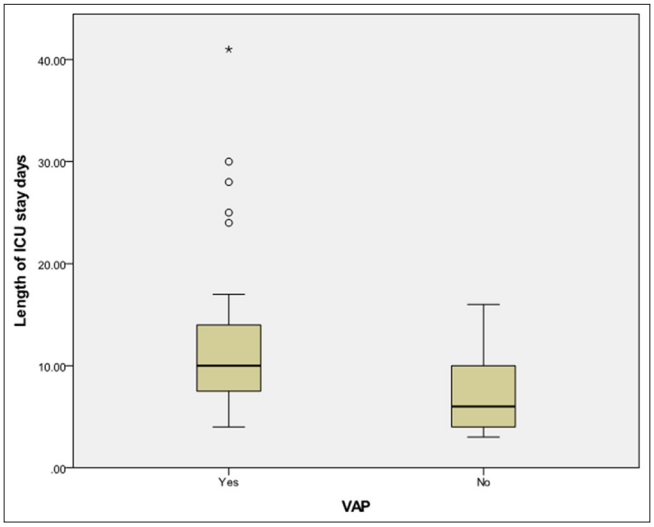

Figure 1: Box and whisker plot for the length of intensive care units stay (days) between ventilator-associated pneumonia (VAP) and non-VAP patients. ICU: Intensive care unit, Circle: Mild outliers, Star: Extreme outlier.

with an increased risk of VAP ($P < 0.05$). Previous studies by Vedavathy S[11] and Patra *et al*.[8] found that NG tubes and stress ulcer prophylaxis were not significant risk factors, while Elward *et al*.[6] reported H2 receptor blockers as contributing factors. In addition, early initiation of enteral feeding (on day 1 of MV) was linked to a higher risk of VAP compared to delayed feeding (starting on day 5).

Microbiological findings revealed that 80.4% of clinically diagnosed VAP cases had positive cultures from ETAs, with Gram-negative bacteria accounting for 91.8% of isolates. The predominant organisms were *A. baumannii*, *K. pneumoniae* and *E. coli*. These results align with studies by Balasubramanian and Tullu[7] and Patra *et al*.,[8], although their findings identified *Pseudomonas* as the second most common isolate. In contrast, *Staphylococcus aureus* was more prevalent in studies from Europe and North America. Many pathogens in this study exhibited multidrug resistance, presenting significant treatment challenges. Polymicrobial infections were detected in some cases, with frequent co-isolation of *Acinetobacter* and *E. coli*.

The mortality rate amongst VAP patients in this study was 33.3%, comparable to rates reported in other studies, including those by Mahantesh *et al.* (28.38%),[19] Patra *et al.* (31.8%),[8] Balasubramanian and Tullu (42.8%)[7] and Amanati *et al.* (47%).[16] No significant difference in mortality was observed between early-onset VAP (39.3%) and late-onset VAP (26.1%). In addition, the mortality rate in VAP patients was not significantly higher than in non-VAP patients (18.4%, $P = 0.3$).

The median duration of PICU stay (10 vs. 7.5 days) [Figure 1] and overall hospital stay (14 vs. 12 days) in the VAP group were significantly longer compared to the non-VAP group, consistent with findings from prior studies.[6,8,20,21] In contrast, the study by Galal *et al*.[15] reported shorter PICU stays (11 vs. 17 days) and shorter MV durations (8 vs. 12 days) in patients with VAP, attributed to reduced median survival time leading to earlier mortality.

Amongst the 17 VAP-related deaths in the current study, 94% were due to Gram-negative bacterial infections. *Acinetobacter* was responsible for nearly half of these fatalities, followed by *Klebsiella* (29.4%), *E. coli* (11.7%) and *Stenotrophomonas maltophilia* (5.9%). Similarly, in the study conducted by Patra *et al*.,[8] all deaths in patients with nosocomial pneumonia were caused by Gram-negative bacteria, with *Pseudomonas* accounting for 57.1% of fatalities.

CONCLUSION

Although VAP was associated with adverse outcomes, it did not significantly contribute to overall mortality. Increased awareness of these risk factors is essential for reducing the morbidity and mortality associated with VAP.

Further research is warranted to understand better the risk factors and diagnostic criteria for VAP in paediatric intensive care settings.

Ethical approval: The research/study was approved by the Institutional Review Board at Jagadguru Sri Shivarathreeswara Medical College Institutional Ethics Committee, number JSSMC/PG/130/2016-17, dated 24th November 2016.
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Original Article

Establishing normative data on anterior fontanelle size: Associations with gender, mode of delivery, weight at birth, head circumference and gestational maturity

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ABSTRACT

Objectives: The anterior fontanelle (AF) is a fibrous gap between skull bones and is most important among all fontanelles in clinical examination of neonates and children in the first 2 years of life. There is a lack of normative data on AF size in our region, and hence, establishing normative data and understanding its associations with various perinatal factors can facilitate clinical evaluations and early diagnosis of potential abnormalities. The study aims to generate normative data on AF size in neonates and investigate its associations with gender, mode of delivery, weight at birth, head circumference and gestational maturity.

Material and Methods: This study was conducted over 3 months in the outpatient department section of the Special Care Newborn unit in an associated hospital of medical college in North India, including normal term neonates born between 37 and 42 weeks. The study excluded pregnancies with antenatal risk factors and neonates with certain defined conditions and measured AF size using the Keisler and Ricer method.

Results: In a study of 217 neonates (114 males and 103 females), the mean AF size was 2.43 ± 0.60, with 97.70% having an AF size between 0.6 and 3.6 cm. No significant gender differences were found in AF size. Neonates born through lower-segment caesarean sections had significantly larger head circumferences compared to those born through normal vaginal delivery. Weak positive correlations were observed between AF size and gestational maturity.

Conclusion: The study shows that AF size is influenced significantly by gestational maturity only and not by weight at birth, head circumference, gender or mode of delivery. These results could help paediatricians in assessments of normal and abnormal fontanelle size in neonates. The high percentage of neonates with good-sized fontanelles between 0.6 and 3.6 cm warrants further investigation to determine if this is due to rampant Vitamin D deficiency of mothers in this part of India or influenced by measurement methods.

Keywords: Anterior fontanelle, Neonate, Gestational maturity, Size, Head circumference

INTRODUCTION

The fontanelles are windows in the bony skull where multiple bones meet and are covered by soft, fibrous, membranous tissues.[1] The word fontanelle is borrowed from the French word 'fontenele', which is a contraction of Fontaine, meaning little spring.[2-4] At birth, there are six fontanelles, including one anterior, one posterior, two mastoids and two sphenoids.[5-7] The

largest and easiest to identify is anterior fontanelle (AF), a rhomboid-shaped opening between frontal and parietal bones.[7] AF facilitates faster brain growth relative to calvaria growth.[2,4,8] Clinical examination of AF size as a part of a comprehensive examination in neonates and infants is followed across world in best centres of Neonatology and Paediatrics. Size of AF can be used to follow the development and nutrition of children in the early years of life as it is considered a good index of cranial growth and development in prenatal and postnatal periods.[2,3,5,9] The flat bones of the skull are membranous bones with ossification centres at the centre and are continuously remodelled by a delicate balance between osteoblastic and osteoclastic activity. These bones grow by central resorption and accretion of bone at edges during antenatal and postnatal periods. With the exception of metopic suture, they stay open till brain growth recedes towards end of 2nd year[10] as with fusion of sutures, growth perpendicular to that suture is limited. Therefore, the size of fontanelles is determined by neural growth, dural factors, suture characteristics and osteogenesis.[11,12]

The extremes of fontanelle size may be a hallmark of both diseases within the bony skull or outside.[13-15] A very small fontanelle may be due to slowed brain growth, craniostenosis[16] or hyperthyroidism.[13] A large fontanel with normal intracranial pressure is seen in variety of disorders[17] such as bone dysplasias,[14] developmental disorders of clavicles,[18] osteogenesis imperfecta,[19] chromosomal aneuploidy,[17] hypothyroidism[15] or intrauterine malnutrition.[20] In view of these associations, AF dimensions are vitally important for the early identification of these disorders indicating the importance of measurements of AF. The size of AF may be defined as the average of the anteroposterior and transverse dimensions or by surface area.[14,21] The fontanelle size at birth varies from 0.6 cm to 3.6 cm.[14]

The development of fontanel is determined by brain growth, attachments of dura, suture development and osteogenesis.[15] Like other parameters of neonatal anatomy, AF size is affected by gestational maturity, gender, birth weight and may be other environmental, genetic and racial factors. The present study was undertaken to study the dimensions of AF in selected neonates born at our hospital over a period of 3 months to find normal size range due to scarcity of same in our area and to compare it with results from various studies and find correlation with various demographic characteristics.

MATERIAL AND METHODS

A cross-sectional study over a period of 3 months was conducted from March 2024 to May 2024 in the neonatal outpatient section of the Special Care Newborn unit in the department of paediatrics in an associated hospital of a medical college in north India after proper ethical clearance. A total of 217 normal-term neonates born between 37 weeks and 42 weeks and 0 days were included in our study after consent from one of the parents. The sample size was calculated using the following formula $N= Z^2\ SD^2/d^2$ where:

N= sample size required

Z= standard normal variate set at 1.96 corresponding to confidence interval of 95% and 0.05% level of significance.

SD = Standard deviation from previous studies which are equal to 2.

d= precision level taken as 0.3 cm above and below the expected mean.

Taking the attrition rate of 15% as many females with healthy babies asked for discharge within 24 h, the final sample size came around 200.

Pregnancies with any associated antenatal risk factors like gestational diabetes, pregnancy induced hypertension, infections affecting foetal growth, maternal smoking, drug abuse, use of teratogenic drugs or postnatal complications such as excessive moulding, cephalhematoma, subgaleal bleed, caput succedaneum, and head injuries were excluded from the study. Similarly, neonates with facial dysmorphism, obvious congenital anomalies, intrauterine growth retardation, macrocephaly or microcephaly and babies with weight which is too large for their gestational age were also excluded from the study. Gestational age was determined from earliest antenatal ultrasonography supplemented by taking meticulous menstrual history and confirmed by new Ballard's score done at the time of measurements. The AF was measured by the Keisler and Ricer method by two examiners between 12 and 24 hrs. One examiner palpated for bony edges of AF and moved ahead to find the meeting point called the anterior vertex of the fontanelle which was marked with washable ink by the second examiner. Similarly, all other vertices were marked. The anteroposterior and transverse diameter were measured by measuring tape to an accuracy of ±0.1 cm and size of AF was calculated as under:

Size of AF = (AP) diameter + Transverse diameter (TD)/2.

The weight of the neonate was taken by digital beam balance in grams with an accuracy of ±100 g. The head circumference was taken by non-stretchable tape just above the supraorbital ridges anteriorly and the most prominent point on occiput posteriorly and recorded to accuracy of 1 mm. The procedure of measurements and data collection was done by one 2nd year national board of examinations (NBEMS) diploma candidate, one senior medical officer and a junior resident working in special newborn unit after the principal investigator trained them and their ability to take measurements was assessed by taking a pilot study before the main study.

The data were recorded in predesigned pro forma, which included gestational age, mode of delivery, gender, weight at birth, head size, AP diameter of AF, transverse diameter of

AF and AF size and data were subjected to standard statistical analysis.

As per previous studies, the size of AF varies from 0.6 to 3.6 with a mean of 2.1.[14] The anterior fontanel is classified as small if <0.6 cm; normal if it is 0.6–3.6 cm and large fontanelle if >3.6 cm.[1]

RESULTS

Out of 217 neonates enrolled in our study, 114 were male and 103 were female. The extreme and mean values of gestational age, weight at birth and head size are shown in Table 1.

The mean anteroposterior diameter was 2.79 ± 0.61 cm, and the mean transverse diameter was 2.08 ± 0.89 cm. The mean AF size was 2.43 ± 0.60, indicating that on average, the AF size was in the range as per the classification criteria used as in Table 2.

About 97.70% of neonates have an AF size between 0.6 and 3.6 cm. About 2.3% of neonates have an AF size >3.6 cm, suggesting that a significant portion of the population studied has AF size within the range of 0.6–3.6 cm. This high percentage of neonates with good-sized AFs may be due to several factors such as genetic, racial, ethnic, measurement technique, or sample characteristics or due nutritional status of mothers with rampant Vitamin D deficiency. The AF size in males (2.38 ± 0.61 cm) is slightly smaller than in females (2.49 ± 0.59), but this difference is not statistically significant ($P = 0.161$), as shown in Table 3.

Neonates born through lower segment caesarean section have significantly larger head circumferences (33.41 ± 1.77 cm) compared to those born through normal vaginal delivery (32.75 ± 1.32 cm), with $P = 0.015$, making this a statistically significant finding, as shown in Table 4. This could be because babies born through vaginal delivery may experience some head moulding during birth.

No significant difference is observed between the AF size of neonates born through normal vaginal delivery (2.35 ± 0.53 cm) and those born through lower segment caesarean section (2.46 ± 0.62 cm) with ($P = 0.254$), as shown in Table 4. A positive and statistically significant correlation (r = 0.255, $P = 0.001$) is observed between gestational age and AF size, as shown in Table 5. This suggests that as gestational age increases, the AF size tends to increase slightly. A weak non-significant positive correlation (r = 0.081 $P = 0.233$) is found between weight at birth and AF size, indicating that babies with higher birth weights tend to have slightly larger fontanelles. No significant correlation is found between head and AF sizes (r = 0.068, $P = 0.316$), suggesting that head size does not strongly influence the size of the AF.

Table 1: Descriptive statistics for various neonatal measurements.

Parameter	Minimum	Maximum	Mean ± SD
Gestational age	37	40	38.73±1.16
Birth weight	2.5	4.5	3.15±0.45
Head circumference	25.0	38.9	33.26±1.70
Anteroposterior diameter	1.1	5.0	2.79±0.61
Transverse diameter	0.9	8.0	2.08±0.89
Anterior fontanelle size	1.0	5.3	2.43±0.60

SD: Standard deviation

Table 2: Distribution of neonates according to anterior fontanelle size.

Anterior fontanelle size	No.	%
Small (<0.6 cm)	0	0
Normal (0.6–3.6 cm)	212	97.70
Large (>3.6)	5	2.30
Total	217	100

Table 3: Association of various neonatal measurements with gender.

Parameter	Male (*n*=114)	Female (*n*=103)	*P*-value
Gestational age	38.61±1.15	38.86±1.17	0.114
Birth weight	3.14±0.48	3.16±0.43	0.779
Head circumference	33.31±1.71	33.2±1.69	0.632
Anteroposterior diameter	2.75±0.65	2.83±0.55	0.349
Transverse diameter	2.01±0.87	2.16±0.92	0.208
Anterior fontanelle size	2.38±0.61	2.49±0.59	0.161

Table 4: Association of various neonatal measurements with mode of delivery.

Parameter	NVD (*n*=50)	LSCS (*n*=167)	*P*-value
Gestational age	38.68±1.15	38.75±1.17	0.716
Birth weight	3.07±0.45	3.18±0.45	0.162
Head circumference	32.75±1.32	33.41±1.77	**0.015***
Anteroposterior diameter	2.76±0.64	2.80±0.60	0.704
Transverse diameter	1.94±0.68	2.12±0.95	0.199
Anterior fontanelle size	2.35±0.53	2.46±0.62	0.254

*Statistically significant, NVD: Normal vaginal delivery, LSCS: Lower segment cesarean section. Bold value: Meaning that there is very low probability of observing data you did if the null hypothesis (no effect) is true ,concluding that there is significant effect present from this data.

DISCUSSION

As AF is the most relevant in the clinical evaluation of young children and considering that cranial bones are membranous, the borders of AF, being the edges of cranial bones, serve as

Table 5: Correlation of anterior fontanelle size with gestational age, birth weight and head circumference among neonates.

	Pearson correlation coefficient (r)	*P*-value
Gestational age	0.255	0.001*
Birth weight	0.081	0.233
Head circumference	0.068	0.316

*Statistically significant

important indicators of bone growth determined by their time of closure.[14]

The mean AF size in our study was 2.43 ± 0.60 cm with maximum and minimum of 1.00 cm and 5.30 cm, similar to studies done by Perera *et al.*[22] in Sri Lankan neonates (2.55 cm), Shajari *et al.*[5] (2011) in Iranian neonates (2.54 ± 1.33), Esmaeili *et al.*[7] (2015) in Iranian neonates (2.55 ± 1.92) and Chang and Hung[23] in Chinese neonates (2.67). The mean AF size in our study was smaller than reported by Chakrabarti[24] from India, who found AF size of 3.80 ± 1.95 cm in 130 neonates from hilly region and 3.35 ± 1.07 cm in 110 neonates from non-hilly areas, by Mathur *et al.*[25] from East India (3.37 ± 0.06 cm), by Adeyemo *et al.*[26] from Nigerian Ibadan (4.0 ± 1.0) and by Tirpude *et al.*[4] from Indian Nagpur (4.24 ± 2.2). Smaller mean AF sizes were reported in studies by Srugo and Berger[27] from Israel (2.06 cm), Jackson *et al.*[28] (2.25 cm) from Hispanic neonates, Duc and Largo[29] (2.01) from Switzerland, El-Mougi *et al.*[30] (2.20) from Egypt and Brandt *et al.*[31] from Germany (2.00 cm). The possible reason for such varying AF in different studies may be due genetic, ethnic, geographical and possibly climatic factors which demands more studies.

The AF size was 2.38 ± 0.61 cm and 2.49 ± 0.59 cm in male and female neonates, which were not statistically significant ($P = 0.161$), which agrees with studies done by Faix [32] Lyall *et al.*[33] and although some studies have found significant differences between genders, like Mir and Weislaw[34] The insignificant difference in AF size between genders in our study may be due racial, ethnic and geographical factors nullifying effect of gender on AF size.

The AF size in neonates born through normal vaginal delivery and lower segment caesarean section in our study is 2.35 ± 0.53 cm and 2.46 ± 0.62, respectively, with $P = 0.254$, which is not statistically significant such as studies done by Esmaeili *et al.*,[7] Pedroso *et al.*[21] and Shajari *et al.*[5]

Direct correlation (weak positive) was found between gestational maturity and AF size with Pearson correlation coefficient of r = 0.255 and $P = 0.001$. Direct correlation (very weak positive) was also found between AF size and weight at birth with a Pearson correlation coefficient of 0.081 and $P = 0.233$. This was in agreement with studies done by Shajari *et al.*,[5] Oumer *et al.*,[35] G/meskel *et al.*,[3] Jackson *et al.*[28] and Lyall *et al.*[33] Our study is probably one of few studies which reported a direct correlation between gestational maturity and AF size like the one reported by Volpe JJ *et al.*[36] Only Shajari *et al.*[5] found a significant negative correlation between AF size and infant's weight (r = 0.10, $P = 0.04$). No important correlation was reported between AF size and infant's weight by similar studies in Nigeria and Turkey by Malas and Sulak[9] and Adeyemo *et al.*[26] No notable association was found between head circumference and AF size in studies done by Malas and Sulak[9] Shajari *et al.*[5] and Jackson *et al.*[28]

A very strong association was found between the mode of delivery and head circumference (32.75 ± 1.32 cm in neonates born through normal vaginal delivery and 33.41 ± 1.77 cm in neonates born through lower segment caesarean section) with $P = 0.015$. This may be due to excessive moulding during normal delivery and higher chances of caesarean section in mothers with larger head sizes.

CONCLUSION

The study shows that AF size is influenced by gestational age and birth weight but not by head circumference, gender or mode of delivery. These results could help guide paediatricians in assessments of normal and abnormal fontanelle size in neonates. The high percentage of neonates with large fontanelles may warrant further investigation to determine if this is population-specific or influenced by measurement methods. The main limitation of our study was that measurements were obtained within the first 24 hrs of life as most babies are discharged after 24 hrs from the hospital and moulding sustained during the birth process might have affected our results.

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Original Article

Spectrum of congenital heart diseases in infants of diabetic mothers

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ABSTRACT

Objectives: The objectives of this study were as follows: To find out if babies born to diabetes mothers have congenital cardiac disease. To ascertain the congenital heart disease pattern that affects babies whose mothers have diabetes. To determine the relationship between the mother's type of diabetes and the newborn's congenital heart condition.

Material and Methods: The study, which involved 49 newborns with diabetic mothers, was carried out at Yenepoya Medical College. These babies had clinical examinations of the cardiovascular system. SpO_2 was measured, and an echocardiogram was obtained. Demographic profiles and relevant information from medical records were collected using a structured Pro forma.

Results: Out of 49 babies,8 babies were detected with congenital heart disease. Among them 4 were having Atrial septal defect(ASD) and 4 were having ventriculoseptal defect.The spectrum of congenital heart diseases mentioned are moderate atrial septal defect and ventricular septal defect.

Conclusion: Among babies whose mothers have diabetes, congenital cardiac disease is prevalent. Acyanotic heart disease was predominant, and ASD was the most common in our study. Neonatal heart disease is more commonly seen in infants of maternal diabetes mellitus than that of gestational diabetes mellitus.

Keywords: Congenital heart disease, Echocardiography, Gestational diabetes mellitus, Infant of diabetic mother

INTRODUCTION

Diabetes mellitus is a multifactorial disease with genetic, environmental and pathogenic origins that is typified by elevated blood sugar levels due to insufficient or ineffective insulin secretion.[1] Pregnancy is the initial indicator of glucose intolerance with varying degrees of severity at the beginning, known as gestational diabetic mellitus (GDM).[2]

GDM was more common in urban women in southern India (17%), semi-urban women (13.8%) and rural women (9.8%).[3,4] Compared to the general population, infants of diabetes mothers (IDM) are 3 to 5 times more likely to be born with congenital abnormalities.[5] Neural tube defects, congenital heart disease, renal malformations and Caudal regression syndrome are some of these anomalies. Significant correlations have been shown between IDM and foetal cardiac anomalies, such as atrial septal defect (ASD), ventricular septal defect (VSD), transposition of the great vessels, truncus arteriosus, coarctation of the aorta and hypertrophic cardiomyopathy.[6]

Compared to women without diabetes, mothers with overt diabetes had a 17-fold higher incidence of transposition of great arteries.[7] When compared to a normal newborn, kids of diabetic mothers experienced delayed ductal closure and a drop in pulmonary pressure.[8,9] Sustaining appropriate blood

sugar levels did not affect the incidence of asymmetrical septal hypertrophy, but it did enhance outcomes and lower the risk of foetal heart illness.[10] During the first few months of life, diabetic cardiomyopathy was frequently a transient ailment that went away. It had no clinical ramifications and was also self-limiting.[7] Septal hypertrophy happens regardless of the type of diabetes, even in mothers with adequate glycaemic control.[11] Compared to type 2 and GDM, type 1 diabetes had a higher prevalence of septal hypertrophy. Congenital malformations were 3 to 4 times more likely in mothers with diabetes than in mothers without the disease. The hyperglycaemia and hyperinsulinemia of these infants made them more likely to grow larger.[12]

MATERIAL AND METHODS

This prospective cross-sectional investigation was carried out from 1 March to 31 August 2023 at the Yenepoya Medical College Hospital in Mangalore. Before beginning the study, ethical clearance was acquired from the Ethics Committee. The study covered all diabetic mothers' babies born at Yenepoya Medical College Hospital in Mangalore. The study excluded all diabetic mothers who also had systemic lupus erythematosus, toxoplasmosis, rubella, cytomegalovirus, herpes and other agents (TORCH) infections, usage of teratogenic cardiotoxic medications, or newborns with syndromic anomalies as additional risk factors for the development of congenital heart problems. This study included 49 infants born to diabetic mothers. With knowledge, the parents gave their approval. Each baby born to a diabetic mother underwent a clinical assessment. Both pre-ductal and post-ductal oxygen saturation were measured. 48 h after the baby was born, an echocardiography was conducted. A structured proforma was used to collect data relevant to the demographic profile. The required information was provided by the mother's and the neonate's case sheets. The association between the study parameter and the Chi-square test was assessed.

RESULTS

1. Gender out of 49 neonates, 25 were male and 24 were female [Figure 1].

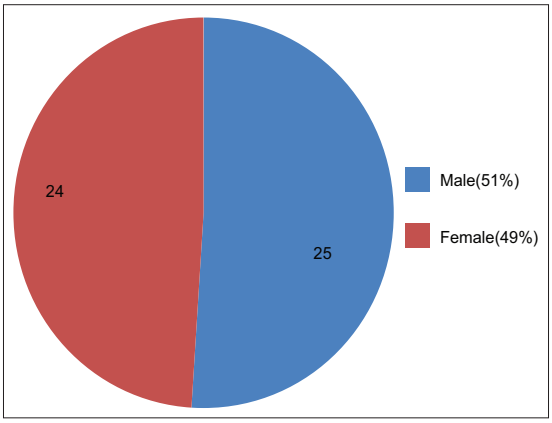

Figure 1: Gender.

2. Type of maternal diabetes 40 were having gestational diabetes and nine were having pregestational diabetes [Figure 2].

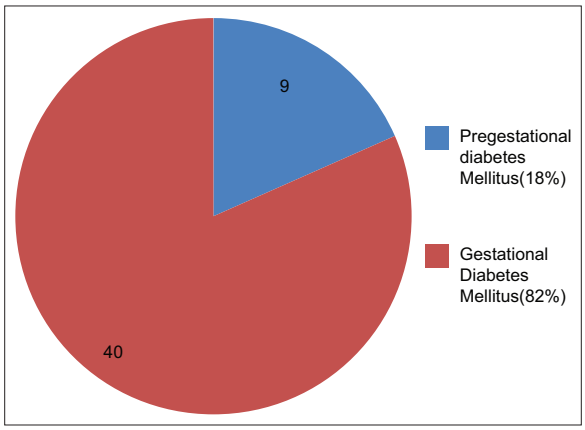

Figure 2: Type of maternal diabetes.

3. Maternal treatment regimen – Twelve were on oral glycaemic agents, 18 were on insulin and 19 were receiving nutritional therapy [Figure 3].

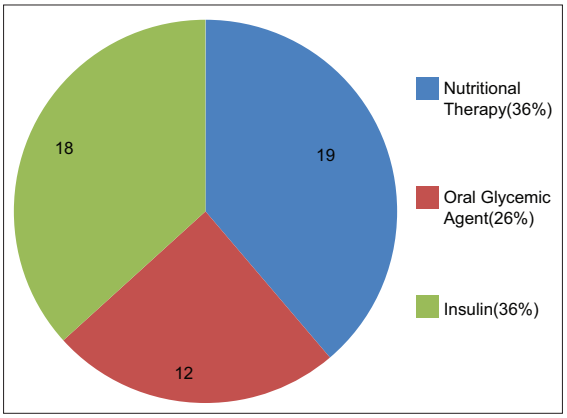

Figure 3: Maternal treatment regimen.

4. Mode of delivery – 17 were vaginal delivery and 32 were caesarean sections [Figure 4].

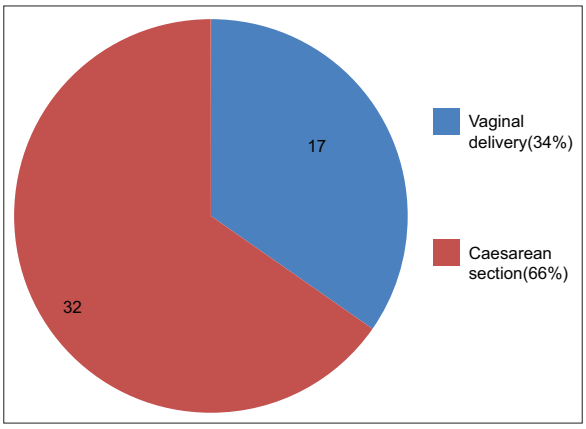

Figure 4: Mode of delivery.

5. Gestational – age 37 were terms, 12 were preterms [Figure 5].

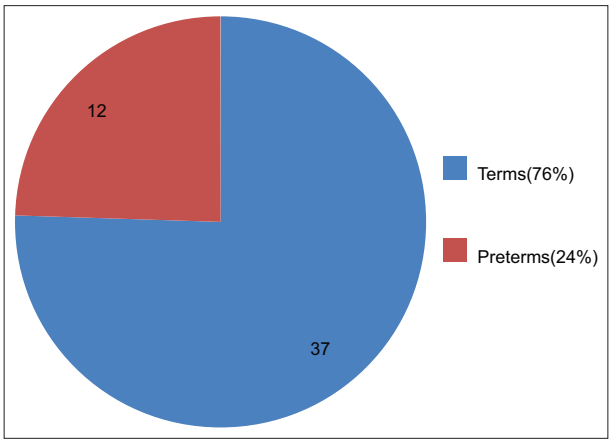

Figure 5: Gestational age.

6. Birth weight 11 were <2.5 kg, 34 were between 2.5 and 4 kg and 4 were more than 4 kg [Figure 6].

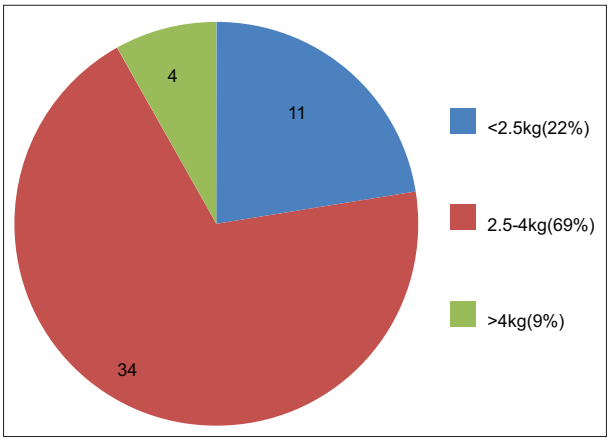

Figure 6: Birth weight.

7. Out of 49 babies, eight babies were detected with congenital heart disease. Among them four were having atrial septal defect (ASD) and four were having ventriculoseptal defect. The spectrum of congenital heart diseases mentioned are moderate ASD and ventricular septal defect [Figure 7].

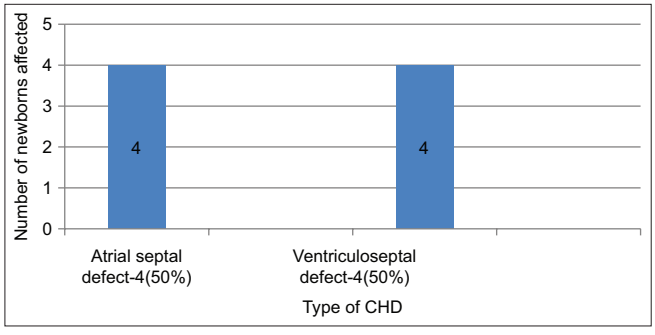

Figure 7: Congenital heart diseases (CHD)-8/49(16%).

8. It has been noted that there is no statistically significant correlation between congenital cardiac disease and the type of maternal diabetes (Pearson Chi-square test statistic value=0.060 [*P*=0.806]) [Table 1].

Table 1: Association of type of maternal diabetes and congenital heart disease.

Maternal diabetes type * congenital heart disease			
	Congenital heart disease		Total
	CHD	Normal	
Maternal diabetes type			
Gestational	6	34	40
Pregestational	2	7	9
Total	8	41	49

CHD: Congenital heart disease, * means indicates

9. It has been noted that there is no statistically significant correlation between maternal treatment regimen and congenital cardiac disease (Pearson Chi-square test statistic value=1.793 [*P*=0.408]) [Table 2].

Table 2: Association of maternal treatment regimen and congenital heart disease.

Maternal treatment regimen * Congenital heart disease			
	Congenital heart disease		Total
	CHD	Normal	
Maternal treatment regimen			
Meal plan	3	16	19
OHA	2	10	12
Insulin	3	15	18
Total	8	41	49

Pearson's Chi-square test *P*=0.408. CHD: Congenital heart disease, OHA: Oral hypoglycemic agents, * means indicates

DISCUSSION

The incidence of congenital heart disease (CHD) (16%) in this study is comparable to other studies which is comparable to other studies, i.e., 15%.[13] All congenital heart diseases detected were acyanotic which is common with other previous studies.[13-15] In our study, the echocardiography findings of the neonates were 50% ASD and 50% VSD which is not consistent with other studies[13-15] Since all newborns with CHD were asymptomatic, it is preferable to perform a two-dimensional echocardiogram on every child whose mother has diabetes. A prior study concluded that foetal echocardiography should be performed in IDM due to their elevated risk of cardiovascular malformation.[15]

Although it has been noted that mothers using insulin therapy (used to treat uncontrolled diabetes) and newborns with overt diabetes have higher rates of congenital cardiac disease, this association is not statistically significant,

possibly due to the smaller sample size. Maternal insulin-dependent diabetes is a substantial risk factor for CHD. For this patient population, timely diagnosis and treatment are critical.

Limitation

Due to the small sample size, the relationship between the type of maternal diabetes, the treatment plan for the mother and congenital heart disease is not statistically significant. An adult cardiologist did an echocardiogram.

CONCLUSION

An echocardiography aids in the early diagnosis of congenital heart disease in asymptomatic newborns. Maternal diabetes is a substantial risk factor for congenital heart disease. The congenital cardiac conditions in this study are ASD and ventricular septal defect. All the congenital heart disorders found are acyanotic heart diseases. Compared to gestational diabetes mellitus, neonatal cardiac damage is more prevalent in newborns with overt diabetes mellitus.

Ethical approval: The research/study approved by the Institutional Review Board at Yenepoya Ethics Committee-1, number YEC-1/2023/051, dated 31st March 2023.
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Karnataka Paediatric Journal

Case Report

Meckel's diverticulum perforated by swallowed chicken bone in infant: A very rare finding

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ABSTRACT

A male infant with 1-year-old suddenly developed abdominal cramps, greenish vomitus, with constipation for 10 days' duration. The vomiting is green after each feeding. His past medical and surgical history was otherwise unremarkable. There is no previous history of foreign body ingestion. On physical examination, the child was ill, dehydrated, in pain, with tachycardia (H.R. 155 B/M); normal respiratory rate and temperature was 38.8 C with 100% oxygen saturation. His abdomen was moderately distended and tender on palpation. Erect abdominal X-ray with dilatation of loops of bowel and multiple air-fluid levels. Ultrasound of the abdomen with free fluid in the pelvic cavity. Laboratory workup revealed a high leucocyte count (19.000), hyponatremia, and hypokalaemia. The first diagnosis was of bowel obstruction. The infant was kept nil per oral. He received an intravenous fluid and electrolytes for resuscitation. A nasogastric tube was inserted. Surgical exploration was done in the operating theatre through a supraumbilical transverse incision; we found a swallowed chicken bone that impacted Meckel's diverticulum and caused perforation.The surgery was done under general anesthesia by resection of diverticulum, removal of impacted bone, and appendectomy. The perforated chicken bone has been removed. A drain was left in the pelvic cavity.

Keywords: Chicken bone, Meckel's diverticulum, Perforation

INTRODUCTION

Meckel's diverticulum was an unrare anomaly remnant of the omphalomesenteric duct. Meckel's is composed of whole intestinal wall layers and, therefore, is a true diverticulum of the ileum. The main aetiology of the diverticulum is remnant of omphalomesenteric duct fails to regress in the 5^{th}–7^{th} week of gestation.

CASE REPORT

A male infant with 1-year-old suddenly developed abdominal cramps, greenish vomitus, with constipation for 10 days' duration. The vomiting is green after each feeding. His past medical and surgical history was otherwise unremarkable. There is no previous history of foreign body ingestion. On physical examination, the child was ill, dehydrated, in pain, with tachycardia (H.R. 155 B/M); normal respiratory rate and temperature was 38.8 C with 100% oxygen saturation.

His abdomen was moderately distended and tender on palpation. Abdominal x-ray has been done that shows dilated bowel loops and air fluid level. Abdominal ultrasound shows free fluid in pelvic cavity. Laboratory workup revealed a high leucocyte count (19.000),

hyponatremia, and hypokalaemia. The first diagnosis was of bowel obstruction. The infant was kept nil per oral. He received an intravenous fluid and electrolytes for resuscitation. A nasogastric tube was inserted. Surgical exploration was done in the operating theatre, and through a supraumbilical transverse incision, we found a swallowed chicken bone impacted in Meckel's diverticulum and caused perforation [Figures 1-3]. The surgery was done under general anesthesia by resection of diverticulum, removal of impacted bone, and appendectomy. The perforated chicken bone has been removed [Figure 3]. A drain was left in the pelvic cavity. Our infant kept nil per oral and electrolytes/intravenous fluid and antibiotics postoperatively. He started to pass stool on the 3rd post-operative day and started to drink clear fluid on the 5th post-operative day.

The child was discharged home in good condition. Now, the infant is on frequent follow-up visits and we check him in the out patient clinic.

DISCUSSION

Meckel's diverticulum was an unrare anomaly remnant of the omphalomesenteric duct. Meckel's is composed of whole intestinal wall layers and, therefore, is a true diverticulum of the ileum.[1] The main aetiology of the diverticulum is vitellointestinal duct fails to regress in the 5th–7th week of gestation.[2]

Frederick Meckel (in 1809) was the first one to describe Meckel's diverticulum.[3,4]

Normally, the diverticulum is asymptomatic but if symptoms occur, the age of 2 years is the most common age of presentation. Meckel's was unlikely to be diagnosed clinically or imagistically, and it is often mistaken for other abdominal pathologies.[3] The frequent complication of the diverticula is bleeding; a rare and unusual complication of foreign body ingestion (chicken/fish bones) was perforation of the Meckel's diverticulum, leading to an intestinal perforation that requires surgical exploration.[5]

A recent review by Alghamdi and Raboei.[1] found that seventy-nine cases of Meckel's diverticulum were impacted and perforated by foreign bodies (only 24 cases were among paediatrics). About 45% of cases were by swallowed fish bone but only seven cases of perforation due to chicken bone. Swallowed chicken bone with impact in Meckel's diverticulum was very rarely reported in English literature.[1]

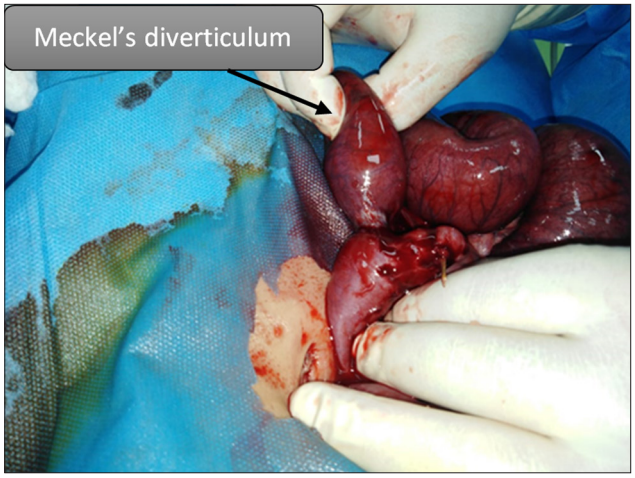

Figure 1: Intraoperative finding of Meckel's diverticulum.

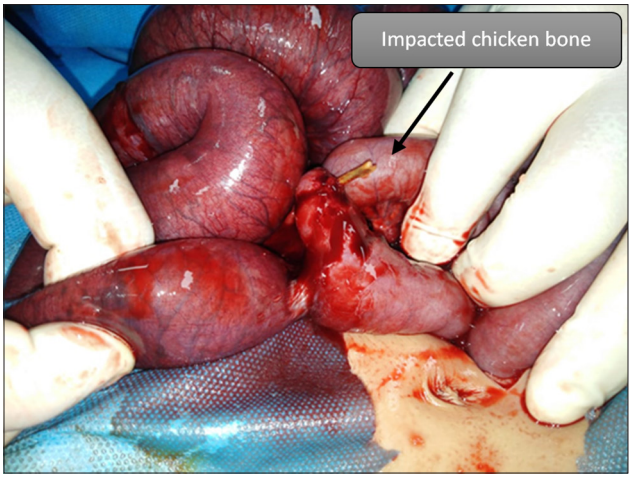

Figure 2: Intraoperative finding of dilated ileum with chicken bone impacted into Meckel's diverticulum.

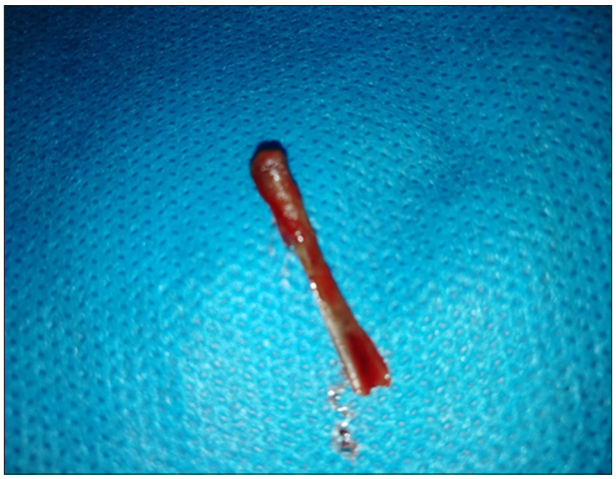

Figure 3: Chicken bone after removal from the Meckel's diverticulum.

CONCLUSION

To the best of the authors' knowledge, this is the first reported case of swallowed chicken bone impacted in Meckel's diverticulum in an infant of 1 year old. Perforated Meckel's diverticulum by swallowing chicken bone should be suspected in a child of intestinal obstruction.

Ethical approval: The report was approved by the Ethical Approval Committee in Anbar Medical College, approval number 134, dated 7th March 2023.
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Karnataka Paediatric Journal

Case Report

Traumatic brain injury unmasking Vitamin B12 deficiency in an infant with long-term follow-up

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ABSTRACT

Falls are very common in infancy and toddler age groups. We are presenting a case of insignificant fall from the cot causing severe neurological problems in an infant due to previous underlying relatively asymptomatic vitamin B12 deficiency. A six-month-old female infant presented with a fall from a cot followed by altered sensorium, vomiting, right focal seizures, and right sided weakness. On examination, a low Glasgow coma scale (8/15), right sided weakness (MRC power of 3/5 in the right upper and lower limbs), with anaemia were noted. Investigations revealed left frontal contusion with haemorrhage, megaloblastic anaemia, and thrombocytopenia with low vitamin B12 level. The child improved with symptomatic management of raised intracranial pressure and injectable vitamin B12 supplements. Prompt intervention and appropriate treatment led to favourable outcomes in the infant, highlighting the importance of recognizing and addressing concomitant deficiencies in infants with TBI.

Keywords: Traumatic brain injury, Vitamin B12 deficiency, Infancy, Neurological manifestations, Haematological manifestations

INTRODUCTION

Traumatic brain injury (TBI) is a significant concern in infants, requiring prompt evaluation and management to prevent potential complications. In the Indian scenario, 20–30% of head injuries are seen in the paediatric population between ages 1 and 16 years.[1,2] Vitamin B12 deficiency is very common in infancy and can lead to both haematological and neurological manifestations. Neurological manifestations include global developmental delay, neuroregression, irritability, lethargy, excessive crying, involuntary movements such as tremors and changes in behaviour such as agitation or withdrawal.[3-5] Haematological manifestations of Vitamin B12 deficiency include megaloblastic anaemia and pancytopenia. We report a case of a 6-month-old female infant who suffered an insignificant fall from a cot, resulting in intracranial haemorrhage due to previously unrecognised thrombocytopenia secondary to Vitamin B12 deficiency.

CASE REPORT

A 6-month-old female infant was brought to the emergency room after an alleged history of falling from a cot with onset of vomiting and right focal seizures after three hours. On examination, her weight was 8 kg (0 to +1 Z score), and her head circumference was 42 cm (0 to −1 Z score). There was severe pallor and hypopigmented spar hair with knuckle hyperpigmentation. No external injuries

were noted. Glasgow Coma Scale: 9/15, with equal and reactive pupils with a power of 3/5 (Medical Research Council [MRC] grade), was observed on the right side.

Laboratory investigations revealed anaemia-haemoglobin of 6.1 g/dL with mean corpuscular volume (MCV) of 106.7, thrombocytopenia (13 × 10^3/uL) and low levels of serum Vitamin B12 121.2 pg/mL (normal 211–911 pg/mL) and increased levels of serum homocysteine of 89.83 µmoL/L (normal 3–50 µmoL/L). Peripheral smear examination indicated microcytic hypochromic cells, elongated cells, a few macro ovalocytes and hypersegmented neutrophils. Serum iron was 59.04 ug/dL (35–145 ug/dL), Unsaturated iron binding capacity (UIBC) was 321.10 ug/dL (135–392 ug/dL), total iron-binding capacity (TIBC) was 380.14 ug/dL (250–400 ug/dL), transferrin was 310.2 mg/dL (200–360 mg/dL), transferrin saturation was 15.53% (20–50%) and serum ferritin of 173.2 ng/Ml (20–110 ng/mL). Liver and renal function tests, serum electrolytes and metabolic workup done were normal. An initial computed tomography scan brain showed a haemorrhage in the left frontal region measuring 12 × 15 mm. Electroencephalogram showed focal epileptiform discharges arising from the left frontal region. A follow-up magnetic resonance imaging (MRI) of the brain after one month of trauma revealed volume loss and altered signal intensity in the left frontal lobe [Figure 1a-c], suggestive of gliosis due to injury.

Given the clinical findings of TBI and concurrent Vitamin B12 deficiency, she received intravenous levetiracetam and 3% sodium chloride and supportive care. To address her anaemia, she received packed red blood cells and IV Vitamin B12 (cyanocobalamin) at 1000 mcg/day for seven days followed by oral supplements continued for three months post-discharge. Due to persistent bicytopenia (severe anaemia and thrombocytopenia) during the prolonged hospital stay of 30 days, bone marrow aspiration was done, suggestive of megaloblastic anaemia.

Laboratory values post-treatment were Vitamin B12 of 11850 pg/mL (normal 211–911 pg/mL) and normalised levels of homocysteine of 16.68 µmoL/L (normal 3–50 µmoL/L). Her last follow-up at three years of age was found to have mild residual right upper and lower limb weakness [Figure 1d].

DISCUSSION

This case report highlights the unmasking of Vitamin B12 deficiency in an infant following TBI. The fall from the cot resulted in TBI, leading to symptoms such as vomiting and seizures. Despite the seemingly insignificant nature of the fall, the presence of hemiparesis, brain haemorrhage observed on MRI, as well as the co-occurrence of anaemia and thrombocytopenia, raised concerns of underlying Vitamin B12 deficiency. Initially, anaemia was attributed to being secondary to brain haemorrhage by trauma, but the cause of thrombocytopenia could not be explained, which prompted further investigation into Vitamin B12 deficiency along with clinical manifestations. Other causes of anaemia and thrombocytopenia, such as leukaemia, were ruled out after a bone marrow examination. Identification of low Vitamin B12 levels in the patient led to the recognition of an underlying deficiency, which has implications for neurological functioning.

Vitamin B12 deficiency is known to have neurological manifestations, including developmental delay/neuro regression, cognitive impairment in children, peripheral neuropathy and neuropsychiatric manifestations in the older age groups.[6] In addition to these effects, Vitamin B12 deficiency has also been associated with ischaemic stroke.[7] Studies have shown that Vitamin B12 deficiency can result in increased levels of homocysteine, an amino acid associated with an increased risk of vascular diseases, including stroke.[7] However, the exact mechanisms underlying the association between Vitamin B12 deficiency and worse outcomes in ischaemic stroke are still unknown.[7]

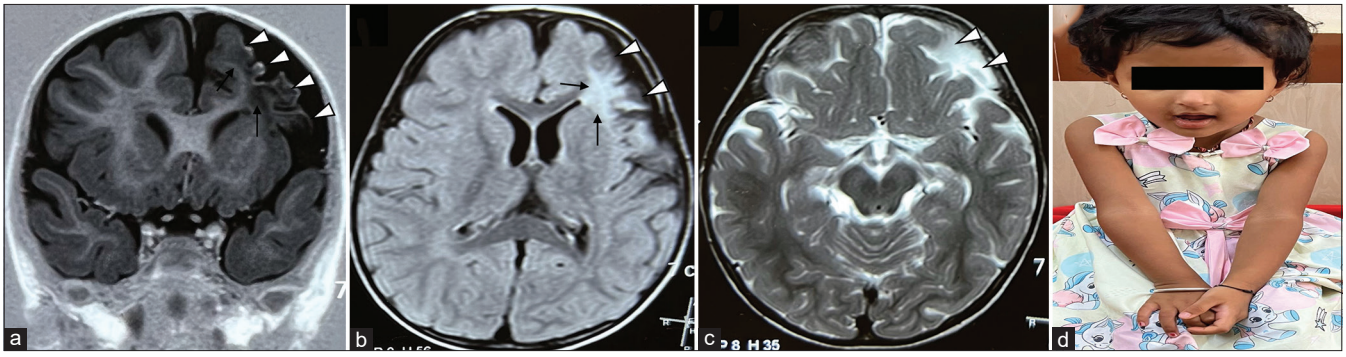

Figure 1: (a) Magnetic resonance imaging brain with T1-weighted coronal (white arrow heads), (b) T2-weighted axial (white arrow heads) and (c) short tau inversion recovery axial sequences show loss of left frontal lobe volume (white arrow heads) with gliotic ischaemic areas (thin black arrows [in a-c]) in cortex and subcortical white matter regions, (d) clinical photograph of the child during the last follow-up at three years showing mild residual weakness of the right upper limb.

While this case report focuses on detailed clinical examination and analysis of investigations influencing the outcome, prompt intervention and appropriate treatment played crucial roles in achieving favourable outcomes. The findings from this case report underscore the importance of considering concomitant nutritional deficiencies in infants with TBI, as they can contribute to the clinical presentation and influence management strategies. The child is currently three years old, with regular follow-up and achieving age-appropriate milestones, weight of 10.6 kg (−2 to −3 Z score), head circumference of 46 cm (at −3 Z score) and mild paucity of movements on the right side. The limitation of the report is we do not have clinical and radiological images during initial admission.

CONCLUSION

TBI in infants can be complicated by underlying nutritional deficiencies, such as Vitamin B12 deficiency. This case report emphasises the significance of recognising and addressing concomitant deficiencies in infants with TBI, as they can impact clinical presentation and management strategies.

Ethical approval: The Institutional Review Board has waived the ethical approval for this study
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Karnataka Paediatric Journal

Case Report

Hereditary spherocytosis with preserved eosin-5-maleimide binding

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ABSTRACT

Hereditary spherocytosis (HS) is a common congenital hemolytic anemia caused by genetic mutations affecting red blood cell (RBC) membrane proteins and is usually inherited in an autosomal dominant manner. The diagnosis of HS is based on clinical and laboratory features, but traditional diagnostic methods have limitations in sensitivity and specificity. This study presents the clinical course and diagnostic challenges of a 16-year-old girl with HS complicated by vitamin B12 deficiency. She presented with a one-month history of dyspnea, pallor, jaundice, and hepatosplenomegaly, with signs of cardiac failure. Initial investigations revealed severe anemia with a few spherocytes and macro-ovalocytes on a peripheral smear. Despite a negative eosin-5-maleimide (EMA) binding test, due to the presence of spherocytes, an elevated mean corpuscular hemoglobin concentration (MCHC), and a strong family history, raised the suspicion of HS. Genetic mutation analysis confirmed Ankyrin 1 (ANK-1) gene mutation, consistent with HS. The patient was concurrently diagnosed with vitamin B12 deficiency, which had exacerbated the anemia. This case highlights the diagnostic challenges in hereditary spherocytosis, particularly when associated with nutritional deficiencies. Early diagnosis and appropriate management, including genetic testing and nutritional supplementation, are critical for optimal patient outcomes.

Keywords: Eosin-5-maleimide-negative hereditary spherocytosis, Phenotype genotype difference in hereditary spherocytosis, Splenectomy, *ANK 1* mutation

INTRODUCTION

Hereditary spherocytosis (HS) is a common haemolytic anaemia resulting from gene mutations encoding red blood cell (RBC) membrane proteins. This disorder is predominantly inherited in an autosomal-dominant manner. The diagnosis is based on a clinical history of anaemia (easy fatigability and dyspnoea), jaundice, hepatosplenomegaly in the background of strong family history, the presence of spherocytes on a peripheral blood smear, elevated mean corpuscular haemoglobin concentration (MCHC), increased osmotic fragility and decreased eosin-5-maleimide (EMA) binding. However, these diagnostic methods have variable sensitivity and specificity.[1]

Recent studies have improved the diagnostic accuracy for HS by employing methods based on the principle of flow cytometry, which is considered the gold standard for confirming HS. While the EMA binding test has a high specificity of 98%, its sensitivity is 93%, and there is a possibility of false-negative results.[2]

CASE REPORT

A 16-year-old girl, previously normal, well grown, weight - 44 kg (between 25th and 50th centile) and height 167 cm (between 90 and 97th centile), presented with a 1-month history of

dyspnoea. Clinical examination revealed pallor, icterus, hepatosplenomegaly (liver span 8 cm and spleen size 3 cm below left costal margin) and signs of cardiac failure. Initial laboratory investigations showed low haemoglobin levels of 2.9 g/dL, total counts of 7640/mm^3, with differential counts - neutrophils - 58.9%, lymphocytes 32.5%, eosinophils - 2.5%, monocytes - 6.1%, platelet count - 1.08 lakh, reticulocyte count of 0.21% and a peripheral blood smear which was negative for atypical cells but demonstrated few spherocytes and predominant macro-ovalocytes. Direct Coombs test was negative. Total bilirubin was 2.42 mg/dL, with direct bilirubin being 0.44 mg/dL. Further evaluation revealed that the patient was a picky eater; subsequent testing confirmed low vitamin B12 levels <159 pg/mL (160–950 pg/mL). The patient was initiated on vitamin B12 and folic acid supplementation. The child received a packed RBC transfusion for her acutely decompensated state and was started with Vitamin B12 supplements. Initially, IV B 12 of 1000 mcg/day later switched over to oral after 1 week. Platelet counts improved to more than 1.5 lakh after 72 h of B12 supplementation.

Osmotic fragility test results showed a normal pattern with haemolysis that began at 0.4% and ended at 0.1%, with median corpuscular fragility being 4.1% (normal range 4–4.5%).

Flow cytometric analysis using EMA showed a mean fluorescence intensity (MFI) of 8609 versus a control of 8429. The patient's MFI (8609) is slightly higher than the control (8429), with only a 2.13% increase in MFI percentage difference (MFI Patient − MFI Control/MFI control) × 100, which is not consistent with HS.

However, due to the elevated mean corpuscular hemoglobin concentration of 34.5 g/dl (MCHC>33 g/dL), the presence of spherocytes, and the family history of the mother undergoing splenectomy at 12 years of age due to a blood disorder (details not available), diagnosis of hereditary spherocytosis was considered.

Whole exome sequencing was performed, which identified an ANK1 gene mutation (*ANK1* (NM_000037.4), Intron 20, c.2296-2A>G,) which was a heterozygous pathogenic autosomal dominant mutation confirming the diagnosis of hereditary spherocytosis type 1.

The patient is currently under follow-up, continuing oral vitamin B12 supplementation with a good clinical response. Haemoglobin levels improved following a single transfusion and Vitamin B12 and folic acid supplementation, now stabilised between 10 and 11 g/dL, with a healthy reticulocyte count (6–7.3%) and she is doing well in the 3-month follow-up.

Further management of the child will include immediate family screening and close follow-up. As the child is currently thriving and responding well to oral treatment, splenectomy is not indicated. However, if the need for repeated blood transfusions arises or if growth retardation occurs, splenectomy may be considered.[3]

DISCUSSION

HS is a common cause of congenital haemolytic anaemia, characterised by clinical features such as anaemia, jaundice and splenomegaly. The pathophysiology of HS involves defects in the RBC membrane cytoskeleton, leading to reduced membrane stability and the formation of spherocytes, which are prone to premature destruction in the spleen.

HS can be diagnosed at any age, from the neonatal period to adulthood.[4] In mild cases of HS, patients typically exhibit compensated haemolysis without anaemia. However, in moderate–to-severe cases, patients experience incompletely compensated haemolysis, leading to anaemia. These more severe cases are also characterised by mild-to-moderate splenomegaly, haemoglobin levels ranging from 7 to 9 g/dL and reticulocytosis of 10% or higher.[5]

HS can clinically manifest as mild, moderate and severe clinical forms. This patient exhibited a mild phenotype, probably explaining her being asymptomatic till this presentation. However, the concomitant Vitamin B12 and probably folic acid deficiency led to clinical decompensation. The patient's mother, who is presumed to have the same condition, underwent a splenectomy at approximately 12 years of age. In contrast, our index case was not diagnosed until 14 years of age and presented with symptoms primarily due to associated nutritional deficiencies. This highlights the variability in genotype and phenotype expression, even with the likely same genetic mutation in both mother and child. The father has been clinically evaluated, remains asymptomatic and shows no evidence of splenomegaly.

Conventionally, the diagnosis of HS has relied on osmotic fragility testing using NaCl or glycerol, which assesses the vulnerability of RBCs to lysis in hypotonic solutions. However, these tests have limited sensitivity and specificity, particularly in mild cases of HS. Advances in diagnostic techniques have led to the development of more specific assays, such as the EMA binding test, which directly targets the molecular defect in HS. EMA is a fluorescent probe that binds to transmembrane proteins, including band 3, Rh protein, Rh glycoprotein and CD47.[6] These proteins are reduced in RBCs from patients with HS, resulting in decreased fluorescence intensity. In addition, defects in cytoskeletal proteins such as spectrin and protein 4.2 can indirectly reduce EMA binding, likely due to alterations in the conformation of the band 3 protein.

The EMA binding test has become a valuable diagnostic tool due to its high specificity and relative ease of use. A significant decrease in MFI (often >10–15% reduction compared to control) is seen in HS due to reduced binding of EMA to band 3 and other proteins. Our patient MFI showed a 2.13% increase which is not consistent with HS. Patients with mild forms of HS may have near-normal EMA binding due to minimal reduction in membrane protein defects (such as spectrin, ankyrin or band 3 protein). The fluorescence reduction may fall within the normal range, leading to a false-negative result.[3] Conditions such as iron deficiency anaemia, vitamin B12 deficiency or folate deficiency can alter red cell membrane characteristics, potentially masking the reduced EMA binding in HS.[7] Other occasions where false-negative results have been seen include in conditions with co-existent thalassemia and other haemoglobinopathies which can modify red cell membrane properties,[7] mutations in less common genes, such as those associated with stomatin-deficient HS or other membrane protein abnormalities, may not significantly affect band 3 protein,[5] which is the target of the EMA test, delayed shipment in which tests are performed on stored samples >48 h and analytical errors of laboratory.[3]

Therefore, when clinical suspicion is high but EMA results are negative, additional testing such as genetic analysis may be warranted to confirm the diagnosis.[8]

Overall, the integration of clinical, laboratory and genetic data is essential for the accurate diagnosis and management of HS, especially in cases complicated by overlapping conditions such as Vitamin B12 deficiency or iron deficiency, which can exacerbate the anaemia and complicate the clinical picture as in our patient. A repeat EMA test done after correction of nutritional deficiencies with an appropriate reticulocyte response may likely give a correct EMA result.

Lessons learned

Diagnosis of haemolytic anaemia like hereditary spherocytosis can be challenging due to various factors such as the type of mutations involved, genotype-phenotype discrepancy, and compounding nutritional deficiencies. Hence, a thorough clinical workup and, if required, genetic workup is essential to manage a child with such disorders. Eosin-5-maleimide, though has high specificity, can still miss certain kinds of hereditary spherocytosis which can be diagnosed with other methods, such as mutational analysis.

CONCLUSION

This case highlights the diagnostic challenges in HS, particularly when complicated by nutritional deficiencies, despite the limitations of standard diagnostic tests such as EMA binding, a comprehensive clinical and genetic approach led to the diagnosis. The patient's mild HS phenotype, compounded by Vitamin B12 deficiency, underscores the importance of considering compounding aetiologies in patients presenting with haemolytic anaemia. Early diagnosis and appropriate management, including genetic testing and nutritional supplementation, are critical for optimal patient outcomes.

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Karnataka Paediatric Journal

Case Report

New-onset discoid lupus erythematosus after Oxford-AstraZeneca adenoviral (Covishield™) vaccination in a paediatric patient

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ABSTRACT

Oxford Astra-Zeneca adenoviral vaccine (Covishield™) is a viral vector vaccine that uses an attenuated, non-replicating strain of Chimpanzee adenovirus as a vector to carry the spike glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into human cells. Although highly effective against SARS-CoV-2 infection coronavirus disease 19 (COVID-19), COVID-19 vaccines have been implicated in triggering and exacerbating various autoimmune diseases due to their role in inciting antigen-specific immune responses. There have been various reports of the development or exacerbation of dermatomyositis and systemic lupus erythematosus (LE) following COVID-19 vaccine. Here, we present the rare case of the development of discoid LE (DLE) in a 14-year-old female patient 3 weeks following the administration of the first dose of Covishield™ (ChAdOx1 nCoV-19 vaccine). The patient also had positive anti-nuclear antibody titres. The temporal relationship of her symptoms after vaccine administration could suggest a possible association between the vaccine and the development of DLE, as this is the time interval for antibody formation post-vaccine.

Keywords: Discoid lupus erythematosus, Paediatric discoid lupus erythematosus, Covishield™, Vaccine-induced lupus

INTRODUCTION

The term lupus erythematosus (LE) refers to a broad range of clinical conditions that are related to the development of an autoimmune response, primarily directed against the molecular components of nucleosomes and ribonucleoproteins. The cutaneous manifestations of LE can be roughly divided among lesions that exhibit the distinctive histologic alterations associated with LE, such as interface dermatitis (LE-specific skin disease), and those that do not (LE non-specific skin disease).[1] Acute cutaneous LE, subacute cutaneous LE, and chronic cutaneous LE (CCLE) are the three main subtypes of LE-specific skin diseases. Discoid LE (DLE) is a subtype of CCLE that includes classic DLE, hypertrophic DLE, and mucosal DLE, among its many morphological variants.

According to the literature, systemic lupus erythematosus (SLE) patients are more likely to experience adverse outcomes with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection coronavirus disease 19 (COVID-19), and immunisation is recommended for SLE patients, particularly those receiving strong immunosuppressive medications.[2,3] However, given their role in eliciting antigen-specific immune responses and the fact that

multiple cases of SLE have been documented following SARS-CoV2-vaccination,[2,4-8] vaccines have been considered a potential trigger for the development of SLE. Various cases of SLE exacerbations following SARS-CoV2 vaccination have been reported, including the relapse of class V (membranous) lupus nephritis.[8-10] However, we could not identify any reports describing the development of DLE after SARS-CoV2-vaccination. We report the case of a 14-year-old female who developed clinical symptoms of DLE 3 weeks after administration of the first dose of the recombinant Oxford-AstraZeneca adenoviral vaccine (Covishield™).

CASE REPORT

A 14-year-old Indian female without any history of autoimmune disorders presented to the dermatology outpatient department of a tertiary care hospital with well-defined, scaly and erythematous to violaceous plaques on the dorsal as well as palmar aspect of bilateral hands for 1.5 months. The lesions showed characteristic surrounding hyperpigmentation [Figure 1]. This was followed by the appearance of hyperpigmented plaques on the concha of bilateral ears [Figure 2]. The patient had received the first dose of Covishield™ (ChAdOx1 nCoV-19 vaccine) 3 weeks before the onset of lesions. There was no history of preceding trauma before the onset of lesions. The rest of the cutaneous examination was grossly unremarkable. There was no prior history of joint pains, malar rash or photosensitivity. No significant family history of autoimmune illnesses was noted. A dermoscopy of the lesion on the right hand revealed cicatricial milky red areas, structureless white patches and a peripheral pigmented network [Figure 3]. Disease activity was assessed using the cutaneous LE disease area and severity index (CLASI) score. The CLASI-A (activity score) was 6, indicating a mild disease activity at presentation.

Laboratory investigations revealed an elevated anti-nuclear antibody titre (1:160). Based on the above findings, a formal diagnosis of DLE was made. Other serological investigations such as anti-Sjögren's-syndrome-related antigen A (anti-SSA), anti-Sjögren's-syndrome-related antigen B(anti-SSB), Anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-Smith (anti-Sm), and anti-ribonucleoprotein (anti-RNP) could not be done due to the financial constraints of the patient. The patient was counselled to undergo a skin biopsy, but did not consent. The patient was lost to follow-up after the initial investigations.

DISCUSSION

DLE is a subtype of CCLE that is frequently characterised by lesions on the photo-exposed parts of the body. It is more common in the second to fourth decade of life, and the female-to-male ratio ranges between 3:2 and 3:1, which is considerably lower than that of SLE.[11] Pathogenesis of this disease is multi factorial and involves an interplay of various host and environmental factors. In genetically predisposed individuals, environmental factors such as ultraviolet radiation, certain drugs, and infections can cause cell damage, thereby activating the immune response. Autoantibodies and immune complexes are formed and deposited as a result of an inflammatory cascade of cytokine activation, specifically the type I and type II interferons.[12] Comprehensive research has been done on the role of viral infections, such as cytomegalovirus, hepatitis A, and coronaviruses, in initiating or aggravating autoimmune disorders. Molecular mimicry, bystander inflammation, epitope spreading, and the exposure

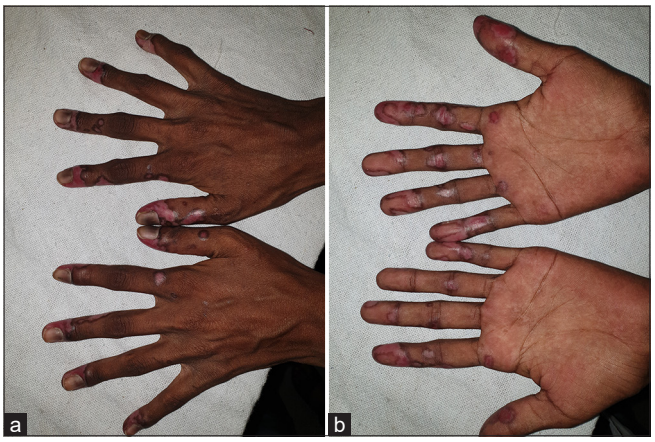

Figure 1: (a) Well-defined, erythematous to violaceous scaly plaques with surrounding hyperpigmentation on the dorsal and (b) ventral surface of bilateral hands.

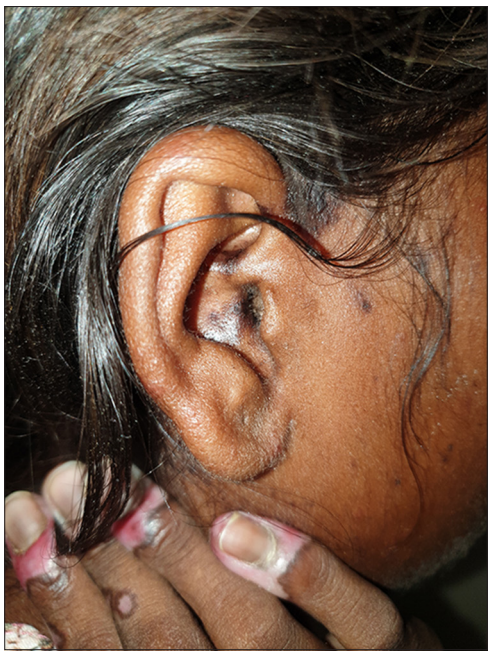

Figure 2: Hyperpigmented plaque with follicular plugging involving the concha of the ear.

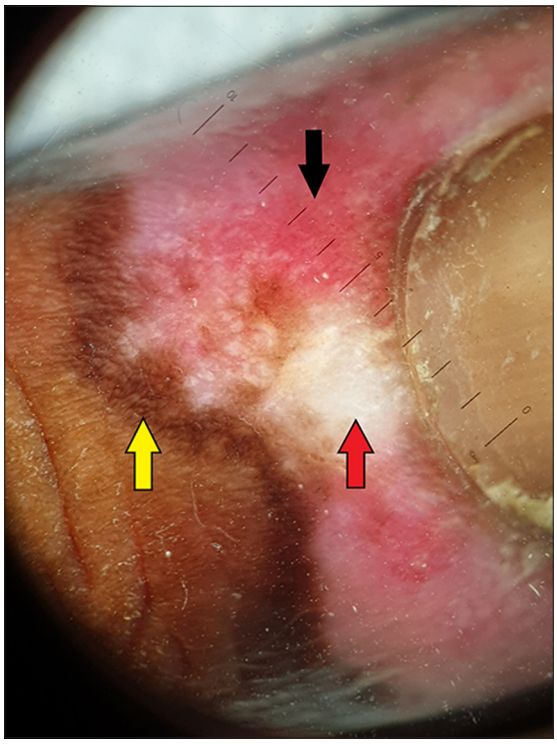

Figure 3: Dermoscopy of the lesion on the right hand showing cicatricial milky red areas (black arrows), structureless white patches (red arrow) and a peripheral pigmented network (yellow arrow) (Heine Delta 20T dermatoscope, non-polarised contact mode, ×10).

of cryptic antigens are some of the potential mechanisms at play.[13]

It is a well-known fact that the COVID-19 virus can trigger or exacerbate autoimmune disorders; however, it is noteworthy that in certain cases, these disorders are triggered or exacerbated by the vaccine itself. Covishield™ is a viral vector vaccine that uses an attenuated, non-replicating strain of chimpanzee adenovirus as a vector to carry the spike glycoprotein of SARS-CoV-2 into human cells.[14] On the administration of the Covishield™ vaccine, T-cells are activated, which initiates an immune response. A rise in CD8 T-cell count triggers the activation of B-cells, which synthesize virus-neutralising antibodies. It takes around 2–3 weeks for antibodies to develop, and these are of immunoglobulin G type, which stays for an extended period.

Sprow *et al*. reported the exacerbation of symptoms in pre-existing cases of dermatomyositis and SLE following the COVID-19 vaccine, although these exacerbations were significantly more common in dermatomyositis than in SLE.[15] A case series published by Garg *et al*. in 2022 reported six cases of new-onset cutaneous autoimmune disorders and four cases of aggravation of pre-existing disorders following Covishield™ vaccine. According to this case series, Covishield™ has also been reported to trigger alopecia areata, lichen planus, vitiligo with leukotrichia and exacerbate previously diagnosed cases of vitiligo and lichen planus.[13]

Autoimmunity induced by inactivated vector vaccines is currently being rigorously studied. Other vaccines with inactivated viral vector delivery, such as influenza vaccine, have also been linked to the flaring of autoimmune diseases in recipients,[16] thereby implicating a role of viral vector in eliciting host immune response. However, in a study done by Kanduc *et al*., significant peptide sharing was seen between SARS-CoV-2 spike protein and human proteins at the heptapeptide level, suggesting that antibodies produced in response to the spike protein may cross-react with the host and induce autoimmune responses.[16]

In patients with cutaneous LE, increased levels of Th1 cells and Th 1- Th1-associated cytokines have been reported in lesional skin following SARS-CoV-2 vaccination.

Although exacerbation of pre-existing cutaneous autoimmune disorders has been reported following the COVID-19 vaccine, reports of the development of cutaneous autoimmune disorders following the COVID-19 vaccine in previously healthy patients are rare. We report herein a case of a 14-year-old female who developed DLE-like lesions on bilateral hands and concha of bilateral ears 3 weeks following the administration of the first dose of the Covishield™ vaccine.

The period between vaccine administration and the development of lesions is consistent with the time interval for antibody formation to occur following vaccination, thereby indicating the possible role of vaccine-triggered autoimmunity. The CLASI, a tool designed to score the disease activity (the presence of erythema, scale and hypertrophy) and damage (dyspigmentation, scarring and atrophy), can be used by healthcare providers to assess the skin lesions and a thorough systemic examination should also be done to look for signs and symptoms of systemic LE.

However, the possibility that the development of these lesions was merely a coincidence and not associated with vaccine administration cannot be completely ruled out. In a study done by Mok *et al*. to determine the hesitancy for SARS-CoV-2 vaccines and post-vaccination flares in patients with SLE, it was observed that 8.2% of the vaccinated patients with SLE experienced flares, which was not statistically significant compared with the 6.2% flare rate in unvaccinated SLE controls. Identification of flare associated risk factors such as positive lupus serology and a history of arthritis or discoid lesions before vaccination can help us in predicting post-vaccination flare risk and in selecting the right candidates for vaccination.[17]

It is also possible that the patient had a positive lupus serology (anti-nuclear antibodies [ANA] titres) before receiving the vaccine and therefore was already at risk of developing DLE, which was triggered upon vaccine administration. Since the

pre-vaccination serology of the patient is not known, this possibility cannot be completely ruled out.

The existing literature suggests that the severity of signs and symptoms of autoimmune conditions is further exacerbated after receiving the second dose of the COVID-19 vaccination or with prior COVID-19 infection.[12] This suggests that the enhanced immune response brought on by repeated exposure to either the vaccine or the virus itself corresponds to an enhanced autoimmune response and raises the prospect that booster doses may also increase the risk of autoimmune exacerbations. However, disease activity following subsequent doses of the vaccine could not be evaluated in this patient due to loss of follow-up.

However, vaccine-induced autoimmune illnesses are extremely rare and should not overshadow the advantages of immunisation, especially in those who are vulnerable.

CONCLUSION

COVID-19 vaccines can trigger new-onset autoimmune diseases and exacerbate pre-existing autoimmune diseases in recipients. This case report defines the rare case of new-onset DLE in a paediatric patient following Covishield™ (ChAdOx1 nCoV-19 vaccine). However, these side effects are rare and should not outweigh the benefits of these vaccines, especially in vulnerable individuals.

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Karnataka Paediatric Journal

Letter to the Editor

Perception and knowledge of nursing professionals on screening of congenital heart disease in newborns

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Dear Editor,

Pulse oximetry (PO) combined with clinical examination is a cost-effective and sensitive screening tool for congenital heart diseases (CHDs) in the newborn period. CHD screening with PO, along with clinical examination, is not universally implemented in India. There are few studies on the role of combined screening of CHD in term newborns, but there are no studies on the perceptions of nursing professionals of the same. For developing a national recommendation on screening and implementation by integration into the mainstream, the perception and knowledge of nursing professionals about the basics of screening and its limitations is important as they are responsible for performing, interpreting, and documenting screening as well as educating and counselling parents to ensure follow-up.[1-3] This study was done with the objective of assessing the knowledge and perception of nursing professionals on CHD screening of term newborns.

A total of 1009 term newborns underwent combined screening for CHD in a tertiary care hospital. To assess the knowledge and perception of nurses on CHD screening, a survey was done by the investigator administered a questionnaire to nurses working in the paediatric ward, post-natal ward and neonatal intensive care unit (NICU). Informed consent was obtained from parents before initial screening. The Institutional Ethical Committee approval was taken for the study.

Forty-four nurses working in the paediatric ward, post-natal ward, paediatric intensive care unit and NICU participated in the study. About 93.2% felt that it was easy to convince parents of PO screening. About 95.4% knew that PO screening could not detect all forms of CHD, 88.6% knew optimal timing, 97.7% knew about the correct sites for screening, 100% of them knew about factors that affect pulse ox reading, and 95.4% were aware of interpretation of pulse ox readings to consider as screen positive and report. About 100% of them agreed that combined screening with clinical examination and PO is the best screening method for CHD, and PO screening is worth doing, cost-effective, non-invasive and easy.

Ethical approval: The research/study approved by Institutional ethical committee ref no JSS/MC/IEC/21/5047/2015-16 dated 9th November 2015.
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Karnataka Paediatric Journal

Letter to the Editor

Focal areas of signal intensity in neurofibromatosis type 1(NF1)

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Dear Editor,

A 5-year-old girl presented with developmental delay and skin lesion with a history of similar skin lesions in her paternal grandmother. On examination, a child was hyperactive; multiple

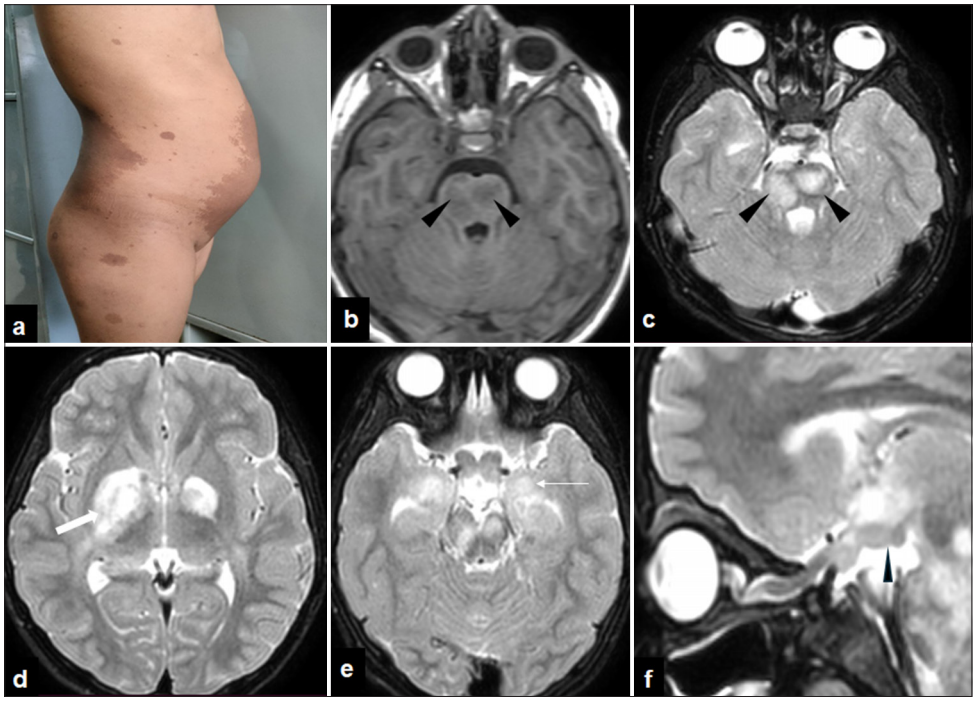

Figure 1: (a) Clinical photograph of child showing multiple café-au lait macules, well circumscribed, dark brown pigmented skin lesions with sizes ranging from sub centimetric to largest one encircling back, left side of trunk and abdomen measuring about 20 cm. (b) Magnetic resonance imaging of axial T1-weighted images of the brain showing multiple hypointense areas in the midbrain (black arrow heads). (c) Axial T2-weighted (T2W) images of brain show multiple focal hyperintense lesions at brain stem (black arrow heads), (d) bilateral lentiform nucleus (thick white arrow) and (e) medial temporal lobes (thin white arrow). (f) Sagittal T2W images of brain and orbit shows thickened optic nerves, chiasma, and proximal optic tracts (black arrowhead) arrowhead iso- to hypointense to brain parenchyma.

café-au lait macules with sizes ranging from subcentimetric to the largest one encircling the back, the left side of the trunk, and the abdomen measuring about 20 cm are shown [Figure 1a]. Lisch nodules in the iris of the right eye were noted. Magnetic resonance imaging of the brain showed multiple hypointense areas on T1-weighted images [Figure 1b] and hyperintensities on T2-weighted (T2W) images [Figure 1c-e] in the midbrain, bilateral lentiform nucleus, and medial temporal lobes. Sagittal T2W images of the brain and orbit [Figure 1f] showed thickened bilateral optic nerves, chiasma, and proximal optic tracts iso- to hypointense to brain parenchyma. An autosomal dominant, pathogenic frameshift deletion mutation of neurofibromatosis type 1 (*NF1) gene at exon 12* was detected, confirming the diagnosis of NF1.

The common neuroimaging feature noted in NF1 includes focal areas of signal intensity (FASI). The FASIs include T2 WI and fluid-attenuated inversion recovery hyperintensities with T1 iso/mild hyperintensities with no mass effect/ enhancements.[1] The differential diagnosis considered was demyelinating disorder and brain tumours. The demyelinating lesions are smaller than FASIs and show mass effect/surrounding oedema.[2] Tumours may be considered if the lesions show both clinical and radiological progression, mass effect, and magnetic resonance spectroscopy shows choline peak.[3] To differentiate FASI from optic glioma following points are to be considered: in FASI, no mass effect and contrast enhancement are seen compared to optic glioma. FASI is more commonly seen in optic chiasma and optic tract, and gliomas can be seen in the intraorbital part of the optic nerve as well as the optic chiasma and tracts.

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Journal Summary

Current advances in paediatric healthcare

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1. Immunological markers in kids with recurrent respiratory infections

Source: Machura E, Krakowczyk H, Kleszyk M, Swiętochowska E, Grzywna-Rozenek E, Rusek M, Góra A, Chrobak E, Pukas-Bochenek A, & Szczepanska M. (2024). Serum levels of selected cytokines and chemokines and immunoglobulin G4 in children with recurrent respiratory tract infections. *J Immunol Res,* 5170588. doi: 10.1155/2024/5170588.

The study provides valuable insights into the immunological profile of children with recurrent respiratory infections (RRIs), particularly with a focus on pro-inflammatory cytokines such as regulated upon activation, normal T cell expressed and secreted (RANTES), interleukin (IL)-18 and IL-23 as potential biomarkers. There are several strengths to highlight, but also areas where some further clarity or context could enhance the overall interpretation.

First, the finding that RANTES shows such high sensitivity and specificity as a biomarker for RRI is notable and adds a solid clinical implication to the study. However, while the significance of this result is clear, some additional discussion on how this could be applied in practice would be beneficial. For instance, could RANTES levels be used in routine clinical settings to predict RRIs? Exploring any potential limitations of using it as a diagnostic tool would add depth to the conclusion.

The study's focus on pro-inflammatory cytokines is relevant to understanding the pathophysiology of RRIs, but the authors do mention the limitation of not looking at anti-inflammatory markers. Since a balance between pro- and anti-inflammatory responses is critical in regulating immune function, considering both sides of the inflammatory spectrum would provide a more comprehensive view. A brief mention of future work that could explore this could help acknowledge this gap without detracting from the current findings.

The elevated immunoglobulin G4 (IgG4) levels observed are intriguing, and while this is noted as possibly reflecting chronic antigen exposure, the implications could be explored more fully. Does this suggest a specific immune adaptation in these children? In addition, IgG4's role in non-allergic immune responses is touched on, but some more elaboration on its function in recurrent infections would help round out this aspect of the study.

The correlation between IL-18 and other cytokines is well presented, but some further explanation of its clinical significance in the context of RRI would strengthen the discussion. For example, IL-18's involvement in Th1/Th2 responses and its role in respiratory infections is important, but understanding how this influences disease progression or outcomes in children with RRIs would be helpful.

In summary, the study presents solid data on the immune profiles of children with RRIs and highlights important biomarkers that could have diagnostic value. Some additional context

regarding the clinical applications of these findings, particularly for RANTES and IgG4, and acknowledgement of the broader immune balance could add to the depth of the analysis. While the immunological insights from this study are highly relevant to understanding RRIs in children globally, including in India, local epidemiological, environmental and socioeconomic factors would need to be considered. Further research in the Indian context would help validate and adapt these findings to the local population and healthcare system.

However, overall, the research adds to the understanding of immune responses in paediatric RRIs and opens avenues for future work to build on these findings.

2. Acquired demyelination syndromes in Indian paediatric cohorts

Source: Chakrabarty B, Gulati S, Madaan P, Kumar A, Sondhi V, Dubey R, Gupta J, & Pandey RM. (2024). Acquired demyelination syndrome in children and adolescents: 10 years experience from a tertiary care centre in North India. *Neurol India,* 72(5):997-1002. doi: 10.4103/neurol-india.NI_1141_20. Epub 2024 Oct 19.

This study provides valuable insights into paediatric acquired demyelination syndrome (ADS) in India, emphasising the unique challenges faced in resource-constrained settings. The study offers a comprehensive analysis of demographic, clinical, radiological and immunological features, comparing monophasic and recurrent cases. Such an exploration is critical for identifying predictors of recurrence, particularly in a paediatric cohort, and is relevant for clinical practice in similar low-resource environments.

The study provides a detailed characterisation of paediatric ADS subtypes: Clinically isolated syndrome (CIS) (48.4%), acute disseminated encephalomyelitis (ADEM) (23.2%), multiple sclerosis (MS) (18.9%) and neuromyelitis optica spectrum disorder (9.5%), emphasising regional variations and the influence of genetic and environmental factors.

The gender distribution, showing male predilection, contrasts with findings from Western cohorts, where female preponderance is more common, especially in MS. This variation, however, aligns with some studies from East Asia, indicating possible regional or ethnic influences. The study's comparison of various cohorts from France, Italy and Japan strengthens the discussion on how age, gender and genetic/environmental factors shape ADS manifestations. The observation that MS is common in the first decade, contrary to some literature, adds to the growing body of evidence that early-onset MS needs greater attention in paediatric populations.

The detailed radiological findings are consistent with established literature on ADS, but the study's focus on polyfocal presentations in CIS is particularly notable, given the younger age group. The subtle but important observation that ADEM-like initial presentations do not rule out MS is crucial for early and accurate diagnosis, which can be challenging in young children.

The findings on cerebrospinal fluid inflammation and the role of pleocytosis and raised protein levels in predicting recurrence are significant, especially given that these are easily accessible bedside tests. While interferon-β, glatiramer acetate and fingolimod are the Food and Drug Administration-approved first-line therapies for paediatric MS, their high cost and the need for repeated injections limit their feasibility in this setting. The study offers compelling evidence that azathioprine and rituximab could serve as practical long-term therapies in resource-poor settings where traditional first-line agents may not be feasible. The use of azathioprine as a long-term immunomodulatory treatment due to its affordability and tolerability is practical in low-resource settings. However, it would be beneficial to explore the long-term efficacy and potential side effects of such treatment in larger cohorts alongside more expensive options like rituximab.

A notable strength of this study is its attempt to delineate early predictors of recurrence in a paediatric population, which can guide early therapeutic interventions. However, the study's retrospective design and limited sample size are constraints. Prospective studies with larger cohorts are essential to validate these findings.

In conclusion, the study highlights the importance of recognising paediatric ADS in resource-poor settings, where diagnostic and therapeutic options may be limited. Early immunotherapy is critical, and studies like this provide a foundation for optimising treatment protocols. The exploration of cost-effective treatments like azathioprine is particularly relevant for countries like India, where healthcare resources are limited. However, further research, particularly prospective studies, is needed to fine-tune the management of paediatric ADS and ensure better outcomes for these patients.

3. Exploring the global burden and mechanisms of vaccine-associated Guillain-Barré syndrome

Source: Jeong YD, Park S, Lee S, Jang W, Park J, Lee K, Lee J, Kang J, Udeh R, Rahmati M, Yeo SG, Smith L, Lee H, & Yon DK. (2024). Global burden of vaccine-associated Guillain-Barré syndrome over 170 countries from 1967 to 2023. *Sci Rep*, 14(1):24561. doi: 10.1038/s41598-024-74729-2. PMID: 39427003; PMCID: PMC11490553.

This study addresses a critical gap in the literature concerning Guillain-Barré syndrome (GBS) as a potential adverse neurological effect of vaccines, particularly during the COVID-19 pandemic. While the investigation utilises data from the World Health Organization pharmacovigilance

database, its conclusions about the association between vaccines and GBS warrant cautious interpretation.

The study identifies a notable increase in GBS reports associated with COVID-19 vaccines during the pandemic, emphasising the need for comprehensive data on vaccine-related adverse events globally. Specifically, the analysis reveals a 5.47-day mean time to onset of GBS symptoms post-vaccination, indicating that most cases manifest within 1 week of receiving the vaccine.

Reports associated with COVID-19 vaccines showed a marked increase, particularly with Ad5-vectored vaccines, compared to mRNA vaccines, which had the highest incidence of GBS. Some studies suggest that vaccination against varicella zoster might reduce the risk of GBS compared to natural infection. While GBS has been associated with vaccines like the tetanus-diphtheria-pertussis and rotavirus vaccines, the overall incidence remains low.

Notably, despite the surge in reports, the relative risk of GBS from COVID-19 vaccines appears low compared to the incidence associated with infections. The analysis reveals age-related risks, with a more significant association in older populations. Interestingly, a gender imbalance was noted in the 45–64 age group, contrasting with traditional GBS epidemiology, which typically shows a male predominance.

The study discusses the plausible mechanisms for vaccine-associated GBS, notably the molecular mimicry hypothesis. However, it also points out that the patterns observed with the Ad5-vectored COVID-19 vaccine differ from those seen with traditional vaccines, highlighting a need for further research into specific antigens responsible for this association.

The authors stress the importance of considering vaccination history in GBS cases, particularly in older patients, and the potential for delayed treatment in low-income countries to affect patient outcomes adversely.

The findings align with the natural epidemiological patterns of GBS, wherein incidence rises with age. This context enriches our understanding of the interplay between vaccines and GBS and emphasises the necessity for continued surveillance. Before the COVID-19 pandemic, three mechanisms contributing to immune system activation were implicated in explaining vaccine-associated GBS. The molecular mimicry hypothesis has garnered significant attention.

The study's strengths lie in its comprehensive approach, and the extensive database utilised, allowing for an analysis that transcends geographical boundaries. However, limitations include potential underreporting from lower-income countries, biases in reporting and challenges in establishing causation due to the nature of GBS onset following infections and vaccinations. The lack of detailed age stratification may further obscure the relationship between age and GBS risk.

In conclusion, while this study provides valuable insights into the relationship between vaccines and GBS, it underscores the necessity for ongoing research and vigilant monitoring of vaccine safety, especially in high-risk groups. The findings can guide future vaccination protocols, contributing to improved public health strategies and patient safety.

4. Parental arsenic exposure and their infants born with spina bifida

Source: Tindula G, Mukherjee SK, Ekramullah SM, Arman DM, Islam J, Biswas SK, Warf BC, Christiani DC, Lemos B, Liang L, Cardenas A, & Mazumdar M. (2024) Parental arsenic exposure and tissue-specific DNA methylation in Bangladeshi infants with spina bifida. *Epigenetics*, 19(1):2416345. doi: 10.1080/15592294.2024.2416345. Epub 2024 Oct 19. PMID: 39425535; PMCID: PMC11492674

The hypothesis connecting arsenic toxicity to disrupted epigenetic mechanisms, particularly DNA methylation, is gaining traction. This study explores the correlation between parental arsenic exposure and DNA methylation patterns in tissue samples (in infant dural tissue collected during spina bifida surgery) from 28 infants diagnosed with spina bifida in Bangladesh. This approach may provide valuable insights into the potential epigenetic impacts of arsenic exposure.

A significant link was identified between arsenic levels in fathers' toenails and DNA methylation at the CpG site methylation (CpG) site cg24039697 (located on chromosome 10 within the gene body of *FLJ45983)* in dural tissue ($P = 7.6 \times 10^{-9}$), even after adjusting for multiple hypotheses and relevant covariates. Gene ontology analysis revealed biological pathways connected to neural tube defects, particularly Wnt signalling pathways linked to paternal arsenic exposure and infant whole blood. Furthermore, regional analyses identified 3–19 differentially methylated regions (DMRs) associated with parental arsenic exposure and infant DNA methylation, covering diverse metabolic pathways. These findings highlight the critical relationship between parental arsenic exposure – a pressing public health issue – and tissue-specific DNA methylation in infants, including in the underexplored nervous system tissue.

In the regional analysis, significant associations were observed between parental arsenic exposure and infant DNA methylation in dural tissue, with fathers linked to three DMRs and mothers to nine. Gene ontology analysis highlighted various biological pathways, with 'Wnt' signalling pathways being particularly relevant. These pathways are crucial for embryonic development processes, including neurulation and neural tube closure, with this study revealing connections to regulation and cell signalling within the 'Wnt' pathway.

The current study's limitations include a small sample size, which restricted the power to detect significant associations

between parental arsenic exposure and infant DNA methylation, leading to predominantly null findings in individual CpG analyses. Furthermore, tissue collection was confined to infants undergoing surgery for neural tube defect closure, and as controls were not included, it was impossible to compare epigenetic differences between affected and unaffected individuals.

Conversely, the study's strengths lie in the thorough characterisation of arsenic exposure through toenail samples from both parents, which reflect exposures over the past 3–18 months. Given the pervasive arsenic contamination in Bangladesh's water supply, exposure levels are presumed to be relatively stable over time. By including paternal exposure data, this study contributes to the existing literature linking parental exposure to child DNA methylation outcomes. Findings indicated associations at both CpG and regional levels related to parental arsenic exposure, underscoring the relevance of this understudied tissue in understanding epigenetic impacts.

In summary, this study assessed arsenic levels, a chemical prevalent due to contaminated drinking water, in toenail samples from parents of infants with spina bifida, a significant congenital disability associated with long-term health challenges. This research is particularly relevant to India, where similar issues of arsenic contamination in water sources pose substantial public health risks. The findings highlight the urgent need for addressing environmental health factors linked to developmental disorders in vulnerable populations.

5. Endoscopic injection versus ureteral reimplantation in high-grade vesicoureteral reflux

Source: Nascimben F, Molinaro F, Maffi M, Nino F, Lachkar A, Zislin M, Ogunleye M, Becmeur F, Messina M, Cobellis G, Lima M, Angotti R, & Talon I. (2024). Endoscopic injection versus anti-reflux surgery for moderate- and high-grade vesicoureteral reflux in children: A cost-effectiveness international study. *J Robot Surg*, 18(1):371. doi: 10.1007/s11701-024-02103-5.

This study offers a comparative analysis of endoscopic injection (EI) and ureteral reimplantation (UR) for treating vesicoureteral reflux (VUR) in paediatric patients, specifically those with grades III, IV and V of the condition. VUR, though common, lacks standardised treatment guidelines, especially for moderate-to-severe cases. The findings emphasise the strengths and limitations of both procedures, with EI emerging as a promising option for grade III VUR due to its lower complication rate, shorter hospital stays, reduced pain and lower overall costs. On the other hand, for higher-grade VUR (IV and V), UR – whether performed open, laparoscopically or robotically – offers better long-term outcomes and fewer redo surgeries, although it involves higher costs and longer recovery times.

Despite the general advantages of EI, such as reduced post-operative pain and quicker recovery, the higher risk of recurrences and redo surgeries limits its efficacy in more severe cases. The study also highlights that while minimally invasive surgeries such as laparoscopic and robotic-assisted approaches provide better cosmetic outcomes and post-operative comfort, they come with a higher financial burden, especially in contexts with limited resources and robotic expertise. In particular, robotic-assisted ureteral reimplantation should be cautiously implemented, especially in centres with limited paediatric robotic experience, as the higher costs may not be offset by significant benefits in terms of success rate or reduced complication rates compared to open or laparoscopic UR.

This study's retrospective nature and the inclusion of patients from three different institutions introduce some variability in the results, which could affect the reliability of the findings. The lack of multivariable adjustment for factors such as age, gender, comorbidities and hospital differences adds another layer of complexity to the data interpretation.

The study also touches on an important concern regarding radiation exposure in paediatric urology, specifically from procedures like voiding cystourethrogram, which may increase the long-term risk of gonadal tumours, leukaemia and other malignancies. Non-ionising technologies, such as colour-flow Doppler ultrasonography, are proposed as safer alternatives for monitoring VUR, especially in India, where large-scale population screening is often essential and the risks associated with radiation need to be minimised.

In the Indian context, the findings of this study are particularly relevant. Given the country's resource constraints, the cost-effectiveness of treatments is a key consideration. EI, with its lower cost and reduced hospital stay, may be a viable option for treating low-to-moderate grades of VUR in resource-limited settings. However, the higher rates of recurrence and redo surgeries suggest that a more cautious approach is required for severe cases, where UR may offer better long-term outcomes despite its higher initial costs. Robotic-assisted surgery, although gaining popularity globally, may still be out of reach for most Indian paediatric centres due to financial and technical limitations.

In summary, while EI proves to be an excellent first-line treatment for lower grades of VUR, particularly in terms of cost-effectiveness, UR remains superior for managing higher-grade cases. Future prospective studies and standardised treatment protocols will be essential in determining whether minimally invasive techniques can become the gold standard for managing severe VUR. The study's limitations underscore the need for more controlled, multivariable analyses to account for various patient and institutional factors.

6. Non-invasive neurally adjusted ventilatory assist in preterm infants

Source: Minamitani Y, Miyahara N, Saito K, Kanai M, Namba F, & Ota E. (2024). Non-invasive neurally-adjusted ventilatory assist in preterm infants: A systematic review and meta-analysis. *J Matern Fetal Neonatal Med*, 37(1):2415373. doi: 10.1080/14767058.2024.2415373. Epub 2024 Oct 15. PMID: 39406682.

This study systematically reviews and analyses the effects of non-invasive neurally adjusted ventilatory assist (NIV-NAVA) compared to conventional non-invasive respiratory support (nasal continuous positive airway pressure [NCPAP]/ nasal intermittent positive pressure ventilation [NIPPV]) in preterm infants with respiratory distress. The evidence gathered from five randomised controlled trials (RCTs) involving 279 preterm infants suggests that NIV-NAVA may improve patient-ventilator synchrony and reduce the incidence of extubation failure in post-extubation respiratory support.

The primary finding, indicating a significant reduction in treatment failure with NIV-NAVA in comparison to NCPAP/ NIPPV, holds potential clinical relevance, particularly in reducing reintubation rates, which are associated with severe complications like bronchopulmonary dysplasia (BPD). This improved synchrony, specific to NIV-NAVA, helps preterm infants match their respiratory efforts more effectively with the ventilatory support, reducing work of breathing and fatigue and potentially minimising apnoea-related reintubation.

However, the evidence is tempered by several limitations. The included RCTs were small, with high risks of performance, detection and attrition biases, largely due to the challenge of blinding in ventilation studies. The limited sample sizes and broad confidence intervals also reduce the certainty of the findings. Importantly, while NIV-NAVA showed benefits in preventing extubation failure, it did not significantly impact secondary outcomes such as BPD, severe BPD or mortality. This discrepancy suggests that while NIV-NAVA may provide short-term benefits in preventing immediate extubation failure, its influence on long-term respiratory outcomes remains unclear.

One notable limitation of the review is the heterogeneity in study protocols, including differences in patient populations, ventilation settings and outcome definitions. The lack of gestational age subgroup analyses, as well as non-uniform criteria for diagnosing outcomes like BPD, further complicates the interpretation. While the systematic review demonstrates promising short-term results for NIV-NAVA, further research, particularly large, well-designed trials, is required to confirm these findings and explore the potential for broader clinical impact.

In the Indian context, where neonatal care units face significant resource constraints and high preterm birth rates, the findings suggest that adopting NIV-NAVA could reduce the need for more invasive interventions like reintubation, which is associated with longer hospital stays and higher healthcare costs. However, the applicability of these findings in Indian neonatal intensive care units, where access to advanced ventilatory support technologies like NIV-NAVA may be limited, warrants further exploration. Future research should consider cost-effectiveness, resource availability and the practicalities of integrating such technologies into lower-resource settings.

7. Waning immunity of single-dose typhoid conjugate vaccine

Source: Qadri F, Khanam F, Zhang Y, Biswas PK, Voysey M, Mujadidi YF, Kelly S, Bhuiyan AI, Rajib NH, Hossen I, Rahman N, Islam S, Pitzer VE, Kim YC, Clemens JD, Pollard AJ, & Liu X. (2024). 5-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Bangladeshi children (TyVOID): A cluster randomised trial. *Lancet,* 404(10461):1419-1429. doi: 10.1016/S0140-6736(24)01494-6.

The study follows an important trajectory in typhoid prevention, particularly in high-burden regions such as Bangladesh and India. It extends the findings of the original TyVAC trial to assess the long-term protection offered by a single-dose typhoid conjugate vaccine (TCV), tracking its effectiveness up to 5 years post-vaccination. A notable decline in vaccine efficacy between the 3rd and 5th years raises significant questions about the durability of TCV-induced immunity, particularly in younger children. This age group (<7 years at fever visits) exhibited a sharp reduction in vaccine protection, from 85% to 24%, hinting at a worrying vulnerability in the years most critical for maintaining immunity.

The age-related waning observed adds to the complexity of TCV administration. It is unclear why younger children experience this more pronounced decline in immunity. Some possible explanations are that younger children may have underdeveloped bone marrow, impairing their ability to sustain long-lived plasma cells or that older children may have had more exposure to *Salmonella typhi*, which could boost their immune response over time. This leaves a gap in protection at school entry age (around 4–5 years), which the study hints may be a period of increased vulnerability to typhoid fever. The discussion around waning protection, tied to the decay of anti-Vi immunoglobulin G concentrations, urges us to rethink the current single-dose regimen, especially for younger children in high-burden settings.

The findings diverge from those of the Malawi trial, which reported no significant waning of immunity up to 4.3-year

post-vaccination. The difference might stem from the higher natural exposure to *S. typhi* in Bangladesh, which is about 3 times that of Malawi. This higher exposure could mean that Bangladeshi children require a stronger or more sustained immune response to achieve the same level of protection. Essentially, the study argues that regions with higher bacterial exposure, like Bangladesh (and, by extension, India), may require more robust vaccination strategies than those with lower exposure, suggesting that a single dose may not be enough in these contexts.

Despite the methodological limitations, particularly the lack of blinding and the differences in follow-up durations amongst groups, the study remains robust in its primary finding of waning immunity. The use of test-negative design and sensitivity analyses strengthens the argument for a decline in vaccine effectiveness, especially when compared to unvaccinated children. While these limitations do not seem to induce significant bias, they do call for more rigorous research, particularly large-scale RCTs, that can capture the full extent of TCV's medium- and long-term efficacy.

In terms of relevance to India, the implications are clear. India, like Bangladesh, has a high typhoid burden, and the introduction of TCV in routine immunisation programmes is underway. The findings suggest that a booster dose around school entry age may be necessary to maintain immunity, especially for children vaccinated at younger ages. This could have a substantial public health impact, as maintaining high levels of immunity during the school years – when exposure risk is highest – might prevent a resurgence of typhoid cases.

Policywise, the World Health Organization's current recommendation of a single dose might need to be revisited. If the data from Bangladesh hold true in other high-burden regions like India, a booster dose strategy would be essential to sustaining immunity. While this presents logistical challenges, especially in resource-limited settings where routine preschool visits may not be standard, there is growing momentum for introducing such a visit globally. The idea of using TCV as a catalyst to push for broader preschool vaccination could be a game-changer in countries like India.

Ultimately, this study highlights the need for ongoing vigilance in typhoid vaccine programmes. While the short-term protection offered by TCV is substantial, the medium-term decline suggests that without adjustments to the current vaccine schedule, we risk leaving a large cohort of children vulnerable just as they enter their peak exposure years. This calls for more research, better data and, perhaps most urgently, a policy shift towards booster doses for sustained protection.

8. Non-invasive continuous positive airway pressure and extubation failure in preterm infants

Source: Ho JJ, Kidman AM, Chua B, Chang G, Fiander M, & Davis PG. (2024). Nasal continuous positive airway pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev*, 10(10): CD000143. doi: 10.1002/14651858.CD000143.pub2.

This updated Cochrane (this is an update of a review first published in 1997 and last updated in 2003) review addresses the ongoing challenge of respiratory failure in preterm infants following extubation from invasive mechanical ventilation. Historically, interventions such as head box oxygen or low-flow nasal cannulae were used, but non-invasive pressure support, specifically non-invasive continuous positive airway pressure (NCPAP), has emerged as a potentially more effective method in stabilising the upper airway, reducing apnoea and improving lung function post-extubation. The review includes data from nine trials with a total of 726 infants, with most studies conducted in high-income countries and one from Chile, classified as upper-middle income at the time.

The key outcomes of the review suggest that NCPAP may reduce the risk of extubation failure (relative risk [RR]: 0.62, 95% confidence interval [CI] 0.51–0.76) and subsequent endotracheal reintubation (RR: 0.79, 95% CI 0.64–0.98), although the evidence supporting the latter is highly uncertain due to heterogeneity across studies and variability in results. A notable strength of the review is its low risk of detection bias in most trials, as objective criteria were used to define primary outcomes. However, there remains a high risk of performance bias, as the nature of the intervention precluded the blinding of clinical staff. This is a crucial limitation to acknowledge.

The review also touches on the potential impact of NCPAP on bronchopulmonary dysplasia, although the evidence here is equally uncertain, with little difference observed between intervention and control groups (RR: 0.89, 95% CI: 0.47–1.68). Neurodevelopmental outcomes were not assessed in any of the included trials, representing a significant gap in the evidence base.

In the Indian context, where neonatal intensive care units often face constraints in resources and staff, the findings of this review are particularly relevant. While NCPAP has become standard practice in many high-resource settings, its application in resource-constrained environments like India needs careful consideration. India has a large burden of preterm births, and ensuring access to and the correct application of NCPAP could significantly impact outcomes in these vulnerable infants. Given the low-certainty evidence but widespread adoption of the intervention, there may be less need for further large-scale studies on its efficacy. However, more research on long-term neurodevelopmental outcomes, especially in lower-income countries, would be of considerable value.

Important points:

- NCPAP may significantly reduce extubation failure post-invasive ventilation in preterm infants

- Evidence supporting reduced reintubation and its impact on bronchopulmonary dysplasia is highly uncertain
- The absence of neurodevelopmental outcome data highlights a key gap in the research
- High risk of performance bias in all trials due to a lack of blinding
- Relevance to India includes the potential for NCPAP to improve outcomes in resource-limited neonatal units, but long-term outcome studies are needed.

While NCPAP is a promising intervention for immediate respiratory support post-extubation, the long-term impact, especially in low- and middle-income settings like India, remains to be fully understood. The study underscores the need for further research focusing on the specific challenges and resource limitations in these environments, particularly regarding long-term developmental outcomes.

9. Pharmacological Interventions in paediatric migraine prophylaxis

Source: Kohandel Gargari O, Aghajanian S, Togha M, Mohammadifard F, Abyaneh R, Mobader Sani S, Samiee R, Kermanpour A, Seighali N, & Haghdoost F. (2024). Preventive Medications in Paediatric Migraine: A Network Meta-Analysis. *JAMA Netw Open*, 7(10):e2438666. doi: 10.1001/jamanetworkopen.2024.38666.

This comprehensive review attempts to address a critical gap in the management of paediatric migraine – effective prophylactic pharmacological interventions. Paediatric migraine, which significantly impacts quality of life and academic performance, demands a focused approach, particularly in developing safe and effective preventive treatments. This NMA, the largest conducted to date, evaluated a variety of pharmacological agents across a substantial number of paediatric patients. While the findings affirm the effectiveness of certain drugs in reducing migraine frequency, they also expose limitations in the current therapeutic strategies, particularly in terms of improving quality of life and reducing migraine duration.

Several key points emerge from the review. First, migraine frequency, a central metric in assessing treatment efficacy, was significantly reduced with agents such as pregabalin, topiramate (with and without vitamin D3), flunarizine, levetiracetam, cinnarizine and amitriptyline compared to placebo. Interestingly, combinations such as cinnarizine and propranolol showed a synergistic effect, further amplifying cinnarizine's efficacy in reducing headache intensity by up to 55%. However, propranolol alone failed to show significant impact, challenging earlier findings.

Second, while these drugs reduced both migraine frequency and intensity, no treatment improved quality of life (measured by PedMIDAS) or headache duration. This points to an essential but overlooked aspect of paediatric migraine care: Even if medications reduce the burden of attacks, their failure to improve daily functioning calls for a broader therapeutic perspective. Clinically, this is significant, as parents and clinicians often measure treatment success by improvements in life quality, not just attack reduction.

This study acknowledges several limitations that warrant attention. Heterogeneity in dosing, treatment formats and reporting methods across trials may influence both statistical outcomes and their real-world applicability. In addition, a substantial proportion of participants were from Iran (44.8%), potentially skewing the generalisability of the results. Moreover, some of the included medications, such as levetiracetam, cinnarizine and flunarizine, were tested in fewer than 100 patients, raising concerns about small-study effects and the robustness of the findings.

A major confounder in paediatric migraine research is the high placebo effect, a well-documented challenge in this population. Many included studies showed a placebo response that diminished the apparent effectiveness of active treatments. This effect was particularly evident with propranolol, where despite showing some efficacy, it was not statistically significant when compared to placebo, highlighting the need for more nuanced clinical trials.

In terms of methodology, this NMA stands out for its sophisticated approach. Unlike prior reviews that merged categorical and continuous variables into singular metrics, this analysis provided discrete evaluations for each outcome – migraine frequency, intensity, quality of life and duration – offering a more granular understanding of drug efficacy. The meta-regression analysis further solidifies the findings by showing that baseline characteristics had minimal influence on the treatment outcomes, enhancing the study's reliability.

In the Indian context, where paediatric migraine is often underdiagnosed and undertreated, these findings have significant clinical relevance. First-line treatments such as topiramate, pregabalin and flunarizine, particularly when combined with vitamin supplements, may be more effective in reducing migraine frequency than previously thought. The idea of combination therapies, especially with cost-effective supplements such as vitamin D3 and riboflavin, could be particularly valuable in India, where access to expensive treatments may be limited. However, caution is necessary when interpreting these results, given the high placebo response in paediatric populations and the potential for over-reliance on pharmacological interventions without corresponding improvements in quality of life.

This review rightly calls for more randomised, placebo-controlled trials on under-researched drugs such as levetiracetam, cinnarizine and flunarizine, with an emphasis on combination therapies and real-world efficacy beyond

placebo effects. Given the lack of improvement in quality of life and duration outcomes, future research should also explore non-pharmacological interventions, behavioural therapies and comprehensive care models that may better address the multifaceted needs of paediatric migraine patients.

To conclude, while this study strengthens the evidence base for several pharmacological agents in reducing migraine frequency and intensity, it underscores the persistent gap in improving life quality and functional outcomes in paediatric patients. This calls for a broader, more integrated approach to migraine management that goes beyond mere attack frequency and focuses on long-term well-being. As paediatric migraine becomes an increasingly recognised burden, especially in under-resourced settings such as India, there is a clear imperative for targeted research that addresses both the biological and social dimensions of this condition.

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