ISSN: 2349-6592
E-ISSN: 2455-7099

Vol. No. 7 Issue No. 2
MARCH-APRIL 2020

Journal of Pediatric Critical Care

Official Journal of IAP Intensive Care Chapter

CONTENTS

Wolters Kluwer

www.jpcc.org.in

Medknow

Print ISSN: 2349-6592, E-ISSN: 2455-7099

Journal of Pediatric Critical Care

Official Journal of IAP Intensive Care Chapter

Editorial Board

Indian Academy Of Pediatrics

Intensive Care Chapter

Excecutive Board 2020

Dr. Basavaraja GV
Chairperson

Dr. Dhiren Gupta
Chairperson Elect

Dr. Bakul Parekh
Past Chairperson

Dr. Dayanand Nakate
Vice Chairperson

Dr. Arun Bansal
Secretary

Dr. Manish Sharma
Joint Secretary

Dr. Vinod Ratagiri
Treasurer

Dr. Praveen Khilnani
Vice Chancellor, IAP-ICC College of Pediatric Critical Care

Dr. Kundan Mittal
Editor, Journal of Pediatric Critical care

South Zone
Dr. K. Rajendran
Dr. Raghunath CN

North Zone
Dr. Punit Pooni
Dr. Manindar Dhaliwal

West Zone
Dr. Vinayak Patki
Dr. Sameer Sadawarte

Central Zone
Dr. Satyen Gyani
Dr. Kasi Bandaru

East Zone
Dr. Mihir Sarkar
Dr. Sibabratta Patnaik

Office: Secretary, IAPICC, R No 3112, Level 3-A,
Advanced Pediatric Centre, Post Graduate Institute of Medical
Education & Research, Sector 12, Chandigarh – 160 012.

Journal of Pediatric Critical Care
Official Journal of IAP Intensive Care Chapter

General Information

The journal

Journal of Pediatric Critical Care (ISSN: Print - 2349-6592, Online - 2455-7099) is peer-reviewed journal published on behalf of the Intensive Care Chapter of Indian Academy of Pediatrics. Main aim of the journal is to publish research articles,case reports,review articles,editorials related to the field of Pediatric critical care and related issues to spread the knowledge amongst pediatricians, intensive care fellows, pediatric intensivists, academicians and allied health care personnel in the field of Pediatric critical care. Articles related to various subspecialities including (but not limited to) pediatric cardiology, pulmonology, nephrology, neurology, infectious diseases, life threatening Pediatric emergencies as well as latest and emerging technology in diagnosis and therapy of critically ill children. The Journal is published Bimonthly in the month of January, March, May, July, September and November.

Information for Authors

There are no page charges for submissions to the journals. Please check http://www.jpcc.org.in/contributors.asp for details.

All manuscripts must be submitted online at www.journalonweb.com/jpcc.

Subscription Information

Copies of the journal are provided free of cost to the members of IAPICC. A subscription to Journal of Pediatric Critical Care comprises 6 issues. Prices include postage. *Annual Subscription Rate for non-members-*

Individual in India (INR): Rs.2000/-
Institutional in India (INR): Rs.15000/-

For mode of payment and other details, please visit https://www.piccindia.com/pre-application-form-for-jpcc-subscription.php.

Claims for missing issues will be serviced at no charge if received within 60 days of the cover date for domestic subscribers, and 3 months for subscribers outside India. Duplicate copies cannot be sent to replace issues not delivered because of failure to notify publisher of change of address.

Nonmembers: Please send change of address information to jpccjournal@gmail.com

Advertising policies

The journal accepts display and classified advertising. Frequency discounts and special positions are available. Inquiries about advertising should be sent to Wolters Kluwer India Private Limited, advertise@medknow.com.

The journal reserves the right to reject any advertisement considered unsuitable according to the set policies of the journal.

The appearance of advertising or product information in the various sections in the journal does not constitute an endorsement or approval by the journal and/or its publisher of the quality or value of the said product or of claims made for it by its manufacturer.

Addresses

Editorial Office
Journal of Pediatric Critical Care,
Dr. Vinayak Patki,
Chief Pediatric Intensivist and Head,
Dept of Pediatrics Wanless Hospital,
Miraj, 416410, Maharashtra, India
Email ID: jpccjournal@gmail.com,
Phone: 9822119314

Published by
Wolters Kluwer India Private Limited
A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2
Village Marol, Andheri (East),
Mumbai - 400 059, India.
Phone: 91-22-66491818
Website: www.medknow.com

Printed at
Kundan Press, Jaysingpur,
Dist. Kolhapur, 416101, Maharashtra

Journal of Pediatric Critical Care
Official Journal of IAP Intensive Care Chapter

CONTENTS

Volume 7, Issue 2, March-April 2020

Hypocalcemia and Vitamin D3 deficiency in critically ill children: Does it matter?

Metabolic derangements are very common in critically ill patients, especially children. Identification and appropriate correction are crucial for the disease management and decreasing mortality and morbidity. Data on the abnormalities of calcium, phosphorus, and Vitamin D in critically ill children admitted to a pediatric intensive care unit (PICU) are scarce, especially from developing countries.

Hypocalcemia has been reported in 12%–90% of critically ill adults and children.[1,2]

Hypophosphatemia is known to develop during the ICU stay, and the studies have shown that 60%–75% children developed hypophosphatemia during the PICU stay.[3] With Vitamin D deficiency being very common in healthy individuals, studies have reported the incidence of Vitamin D in critically ill children to be 17%–79%.[4,5]

Abnormality of serum Ca can be due to a variety of causes, e.g., altered Ca binding due to a change in the blood pH, elevation of fatty acids, sepsis, hypoalbuminemia, blood transfusion, renal failure, and hypomagnesemia.[6] Hypophosphatemia is influenced by long-term low intake, decreased absorptive state, intracellular redistribution, and increased renal tubular losses.[7] The frequency and predisposing factors in children are not yet fully understood.

Singhi *et al.* studied calcium profile in 100 children admitted to a PICU and concluded that hypocalcemia is common in critically ill children admitted to a PICU and is associated with higher mortality.[8] They found hypocalcemia in 35% of the patients at admission and in another 13% during hospital stay. In their study cohort, mortality was significantly higher in hypocalcemic (28.3%) group.

Lodha *et al.* studied a cohort of 162 children and identified that hypophosphatemia was common in critically ill children and was associated with prolonged length of stay and increased duration of mechanical ventilation.[9] In their study, serum phosphate <2.5 mg/dL was associated with increased mortality.

McNally *et al.* conducted a systematic review on Vitamin D deficiency in the PICU and found it to be highly prevalent and associated with severity and disease outcome.[10] Sankar *et al.* studied the prevalence of Vitamin D deficiency and its association to clinical outcome in 196 children admitted to a PICU and found high prevalence of Vitamin D deficiency in critically ill children with increased length of ICU stay.[11]

In this issue, Agarwal *et al.*[12] reported the findings from a prospective cross-sectional study done in the PICU of a tertiary care hospital. In the study, calcium, phosphorus, and Vitamin D levels of children admitted to PICU were analyzed. Of the 135 children included in the study, 24.4% had hypocalcemia. The study showed a very high incidence of Vitamin D deficiency (85.9%). Their study showed that total and ionized hypocalcemia were significantly more among the nonsurvivors ($P = 0.012$ and 0.047, respectively). Hypophosphatemia and hyperphosphatemia were also significantly more in the nonsurvivor group ($P = 0.048$ and 0.018, respectively). They found that mortality was higher in the children with total hypocalcemia ($P = 0.006$) and ionized hypocalcemia ($P = 0.03$). They concluded that calcium, phosphate, and Vitamin D abnormalities are common in critically ill children in a developing country and that these abnormalities are associated with poor outcome.

These results are consistent with many studies that emphasize the importance of identifying the metabolic derangements. They analyzed the calcium, phosphorus, and Vitamin D levels together to find a correlation. However, the study population was small and they could not find a relation to Vitamin D levels, probably due to the high incidence of Vitamin D deficiency in the study group. It is difficult to conclude that the low Vitamin D levels are due to the critical illness considering that studies have shown high incidence of Vitamin D deficiency in healthy subjects from the same geographic area.[13]

This study emphasizes the importance of identifying metabolic derangements in a critically ill child. It reinforces that timely recognition and appropriate management are crucial for a favorable outcome in a sick child.

Overall, this study is a welcome addition to the available scant data on calcium, phosphate, and Vitamin D levels

in critically ill children. However, further systematic multicenter studies are required to confirm these findings.

Rakshay Shetty

Department of Pediatric Critical Care and Emergency Medicine, Rainbow Children's Hospital, Marathahalli, Bengaluru, Karnataka, India

Address for correspondence: Dr. Rakshay Shetty, Department of Pediatric Critical Care and Emergency Medicine, Rainbow Children's Hospital, Marathahalli, Bengaluru, Karnataka, India.
E-mail: rakshayshetty@gmail.com

REFERENCES

1. Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia: A pervasive metabolic abnormality in the critically ill. Am J Kidney Dis 2001;37:689-98.
2. Cardenas-Rivero N, Chernow B, Stoiko MA, Nussbaum SR, Todres ID. Hypocalcemia in critically ill children. J Pediatr 1989;114:946-51.
3. de Menezes FS, Leite HP, Fernandez J, Benzecry SG, de Carvalho WB. Hypophosphatemia in critically ill children. Rev Hosp Clin Fac Med Sao Paulo 2004;59:306-11.
4. Marwaha RK, Sripathy G. Vitamin D and bone mineral density of healthy school children in Northern India. Indian J Med Res 2008;127:239-44.
5. Lucidarme O, Messai E, Mazzoni T, Arcade M, du Cheyron D. Incidence and risk factors of Vitamin D deficiency in critically ill patients: Results from a prospective observational study. Intensive Care Med 2010;36:1609-11.
6. Chernow B, Zaloga G, McFadden E, Clapper M, Kotler M, Barton M, *et al*. Hypocalcemia in critically ill patients. Crit Care Med 1982;10:848-51.
7. Miller DW, Slovis CM. Hypophosphatemia in the emergency department therapeutics. Am J Emerg Med 2000;18:457-61.
8. Singhi SC, Singh J, Prasad R. Hypocalcaemia in a paediatric intensive care unit. J Trop Pediatr 2003;49:298-302.
9. Lodha R, Shah S, Irshad M, Gupta N, Kabra S. Hypophosphatemia in critically ill children. Pediatr Crit Care Med 2014;15:60.
10. McNally JD, Nama N, O'Hearn K, Sampson M, Amrein K, Iliriani K, *et al*. Vitamin D deficiency in critically ill children: A systematic review and meta-analysis. Crit Care 2017;21:287.
11. Sankar J, Lotha W, Ismail J, Anubhuti C, Meena RS, Sankar MJ. Vitamin D deficiency and length of pediatric intensive care unit stay: A prospective observational study. Ann Intensive Care 2016;6:3.
12. Agarwal S, Jhamb U, Kaushik S. Calcium, phosphate, and Vitamin D abnormalities in critically ill children. J Pediatr Crit Care 2020;7:61-8.
13. Puri S, Marwaha RK, Agarwal N, Tandon N, Agarwal R, Grewal K, *et al*. Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: Relation to nutrition and lifestyle. Br J Nutr 2008;99:876-82.

Received: 26-02-2020 **Accepted:** 08-03-2020
Published: 10-04-2020

Access this article online

Quick Response Code:

Website: www.jpcc.org.in

DOI: 10.4103/JPCC.JPCC_36_20

How to cite this article: Shetty R. Hypocalcemia and Vitamin D3 deficiency in critically ill children: Does it matter? J Pediatr Crit Care 2020;7:53-4.

The role of Vitamin D in asthma management: Myth or reality?

Asthma is a chronic respiratory disease characterized by increased airway inflammation and hyperresponsiveness and is a major public health issue. It is one of the most common diseases affecting millions of population globally. Association between asthma pathogenesis and Vitamin D has become a matter of great interest for many researchers worldwide in the past two decades.

Vitamin D is a fat-soluble nutrient which is a modulator of calcium absorption and bone health. It also plays an important role in immune regulation and respiratory infections.[1] Studies have concluded that decreased level of serum 25 (OH) D is correlated with an increased prevalence, hospitalization, and increased emergency visits along with declined lung function and increased airway hyperresponsiveness in asthmatic children.[2]

Gupta *et al.* was one of the pioneer researches to point out the role of Vitamin D in the asthma pathogenesis at the molecular level. They found that children with both moderate and severe asthma had significantly diminished levels of anti-inflammatory interleukin (IL)-10 in airway lavage samples when compared with nonasthmatic controls. The addition of Vitamin D3 enhanced IL-10 secretion without increasing IL13 or IL17 levels. Thus, this study also demonstrated the steroid-sparing properties of Vitamin D which may have additional benefits in the management of severe asthma.[3]

A cross-sectional survey on 75 Italian asthmatic children found that the prevalence of Vitamin D-deficiency was 53.3%.[4] In another survey from North America, 17% of asthmatics had Vitamin D deficiency, and a positive correlation was observed between Vitamin D levels and lung function.[5]

Kaaviyaa *et al.* demonstrated that Vitamin D deficiency is associated with inadequate asthma control in children with moderate persistent asthma, on inhaled corticosteroids, in their small observational studies of Indian Children.[6]

However, a study conducted by Thuesen *et al.* on 4999 Danish adults reported contrasting results and concluded that 25 (OH) D levels do not have any effect on the development of asthma and allergic symptoms.[7]

Esfandiar *et al.* in their study stated that though the presence of Vitamin D deficiency effectively predicts increased risk for childhood asthma, the severity or control status of this event may not be predicted by confirming Vitamin D deficiency.[8]

In this present issue, Sharma *et al.*, in their prospective observational study of 75 children, demonstrated that 66.66% of the patients admitted with asthma had Vitamin D3 insufficiency and 9.33% had deficiency. Among Vitamin D3 deficient patients, 71.4% had moderate persistent asthma. However, the correlation between the level of asthma control and Vitamin D3 sufficiency levels could not be demonstrated.[9]

There is no evidence to suggest that asthmatic patients should be screened for Vitamin D deficiency or insufficiency. However, the high-risk group (obese patients and who have limited sun exposure) must be screened for this deficiency.

Several clinical trials of Vitamin D to prevent asthma exacerbation and improve asthma control have been conducted in children and adults. Jolliffe *et al.* in their meta-analysis of seven studies with 955 participants found that Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (adjusted incidence rate ratio 0·74, 95% confidence interval 0·56–0·97; $P = 0·03$; 955 participants in seven studies). There were no significant differences between the use of Vitamin D and placebo in the proportion of participants with at least one exacerbation or time of first exacerbation.[10]

Martineau *et al.*, in their meta-analysis which included seven trials involving a total of 435 children and two trials involving a total of 658 adults, found that people who were given Vitamin D experienced fewer asthma attacks needing treatment with oral steroids. The average number of attacks per person per year went down from 0.44 to 0.28 with Vitamin D (high-quality evidence). Vitamin D reduced the risk of attending hospital with an acute asthma attack from 6/100 to around 3/100 (high-quality evidence). Vitamin D had little or no effect on lung function or day-to-day asthma symptoms (high-quality evidence).[11]

Trials with larger sample sizes are needed to provide the evidence of causality between Vitamin D and asthma. These trials will also be helpful in establishing the appropriate route, dose, and safety of Vitamin D supplementation for the prevention and treatment of asthma. Further researches are needed on the molecular level of Vitamin D receptor to explain the role of dietary Vitamin D in the prevention and management of asthma.

Vinayak Patki

Department of Pediatrics, Wanless Hospital, Miraj, Maharashtra, India

Address for correspondence: Dr. Vinayak Patki, Department of Pediatrics, Wanless Hospital, Miraj, Maharashtra, India.
E-mail: patkivinayak@gmail.com

REFERENCES

1. Chambers ES, Hawrylowicz CM. The impact of Vitamin D on regulatory T cells. Curr Allergy Asthma Rep 2011;11:29-36.
2. Ali NS, Nanji K. A review on the role of Vitamin D in asthma. Cureus 2017;9:e1288.
3. Gupta A, Dimeloe S, Richards DF, Chambers ES, Black C, Urry Z, *et al.* Defective IL-10 expression and *in vitro* steroid-induced IL-17A in paediatric severe therapy-resistant asthma. Thorax 2014;69:508-15.
4. Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL. Vitamin D serum levels and markers of asthma control in Italian children. J Pediatr 2011;158:437-41.
5. Devereux G, Wilson A, Avenell A, McNeill G, Fraser WD. A case-control study of Vitamin D status and asthma in adults. Allergy 2010;65:666-7.
6. Kaaviyaa AT, Krishna V, Arunprasath TS, Ramanan PV. Vitamin D deficiency as a factor influencing asthma control in children. Indian Pediatr 2018;55:969-71.
7. Thuesen BH, Skaaby T, Husemoen LL, Fenger M, Jørgensen T, Linneberg A. The association of serum 25-OH Vitamin D with atopy, asthma, and lung function in a prospective study of Danish adults. Clin Exp Allergy 2015;45:265-72.
8. Esfandiar N, Alaei F, Fallah S, Babaie D, Sedghi N. Vitamin D deficiency and its impact on asthma severity in asthmatic children. Ital J Pediatr 2016;42:108.
9. Sharma P, Alok K, Mittal K. Correlation of severity of asthma with serum Vitamin D3 and serum magnesium level in children aged 5-14 years. J Ped Crit Care 2020;7:69-72.
10. Jolliffe DA, Greenberg L, HooperRL, Griffiths CJ, Camargo CA Jr, Kerley CP, *et al.* Vitamin D supplementation to prevent asthma exacerbations: A systematic review and meta-analysis of individual participant data. Lancet Respir Med 2017;5:881-90.
11. Martineau AR, Cates CJ, Urashima M, Jensen M, Griffiths AP, Nurmatov U, *et al.* Vitamin D for the management of asthma. Cochrane Database Syst Rev 2016;9:CD011511. doi:10.1002/14651858.CD011511.pub2

Received: 29-02-2020 **Accepted:** 07-03-2020
Published: 10-04-2020

Access this article online

Quick Response Code:

Website: www.jpcc.org.in

DOI: 10.4103/JPCC.JPCC_37_20

How to cite this article: Patki V. The role of Vitamin D in asthma management: Myth or reality? J Pediatr Crit Care 2020;7:55-6.

Risk factors for bronchiolitis - Can we really predict?

Acute bronchiolitis (AB) is one of the most common respiratory infection in infant and toddler <2 years of age with significant morbidity and huge economic burden to the society. The incidence peaks in winter and may require hospital admission in around 1.8% of such children.[1] Typically, AB is characterized by generalized peripheral small airway obstruction and manifests with tachypnea, increased work of breathing and low hemidiaphragms on chest radiographs. Respiratory syncytial virus (RSV) is the most common virus in 50%–80% cases; however, adenovirus, influenza, parainfluenza, metapneumovirus, coronavirus, enterovirus, and rhinovirus are other viral etiological agents.[2] Pathologically, infection by RSV is characterized by sloughed necrotic respiratory epithelium, excessive mucus secretions, bronchial mucosal edema, and peribronchial inflammation. Most of the symptomatic children are managed with oxygen therapy and generalized supportive therapy.[3] None of the pharmacological agents including nebulization has been effective in the management of AB.[2] Lately, the use of continuous positive pressure and heated humidified high-flow nasal cannula have been used with good results. The main predictor of severity and poor outcome appears to be young age, prematurity, low birth weight, previous history of pulmonary or cardiac diseases, immunodeficiency, malnutrion, lack of breast feeding, presence of apnea, and pulmonary consolidation on admission chest radiograph.[4] There is paucity of clinical data from India on risk factors for the development of AB.

In this issue, J of Peds Crit care by Kulhalli. *et al.*, a retrospective study from south India has been published to determine risk factors in the development of AB.[5] All demographic data, immunization status, socioeconomic status, malnutrition, overcrowding, exposure to pets, and allergies were studied. A total of 85 cases and 91 controls were studied. On multiple logistic regression, low socioeconomic status, unimmunized status, exposure to pets, and birth by cesarean section were found to have significant risk factor for development of AB. The present study found increased incidence in younger infant which has been attributed to reduced immunity to viral infection in this vulnerable age group. Low socio economic condition has been attributed in studies from China, Spain, and other countries too and has been hypothesized to result from enhanced risk of nutritional deficiency, increased risk of pollution, low immunization status, environmental hazards contributing to this risk factor.[5,6] Cesarean section as modality of delivery has been found to a have conflicting results. In the present study, exposure to pets have been found a predictor, similar to another study from this subcontinent by Malla *et al.* has found, however, such predisposition is mired with controversy due to inconsistent results.[7] In another similar study by Das *et al.*, this study also found heightened risk of AB in unvaccinated children which might have been due to either other co-risk factors or due to lack of cross protection from other infection in such deprived children.[8] Since very few prospective study exists for predictor of risk factors of AB in small infant and children, it is considered prudent to do such multicentric clinic-epidemiological study to understand risk factors for development and severity of AB in children from our region. Till we have such studies, it is difficult to predict both development and severity of AB.

Bal Mukund, Ahmed Zaid Jamal

Departments of Pediatrics and Intensive Care, INHS Kalyani, Visakhapatnam, Andhra Pradesh, India

Address for correspondence: Dr. Bal Mukund, Department of Pediatrics and Intensive Care, INHS Kalyani, Visakhapatnam, Andhra Pradesh, India.
E-mail: bmdoc2002@rediffmail.com

REFERENCES

1. Brooks AM, McBride JT, McConnochie KM, Aviram M, Long C, Hall CB. Predicting deterioration in previously healthy infants hospitalized with respiratory syncytial virus infection. Pediatr 1999;104:463-7.
2. Meissner HC. Viral bronchiolitis in children. N Engl J Med 2016;374:62-72.

3. Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. Lancet 2017;389:211-24.
4. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, *et al*. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. Pediatr 2014;134:e1474-502.
5. Kulhalli P, Dakshayini JN, Ratageri VH, Shivanand I, Kari PK. Risk factors for bronchiolitis. J Ped Crit Care 2020;7:79-83.
6. Leem JH, Kim HC, Lee JY, Sohn JR. Interaction between bronchiolitis diagnosed before 2 years of age and socio-economic status for bronchial hyperreactivity. Environ Health Toxicol 2011;26:e2011012.
7. Malla T, Poudyal P, Malla KK. Modifiable demographic factors that differentiate bronchiolitis from pneumonia in Nepalese children less than two years-a hospital based study. Kathmandu Univ Med J(KUMJ) 2014;12:175-80.
8. Das PK, Saha JB, Basu K, Lahiri S, Sarkar GN. Some clinico-epidemiological aspect of bronchiolitis among infants and young children – A hospital based study. Indian J Public Health 2003;47:66-71.

Received: 01-03-2020 **Accepted:** 09-03-2020
Published: 10-04-2020

Access this article online

Quick Response Code:

Website: www.jpcc.org.in

DOI: 10.4103/JPCC.JPCC_39_20

How to cite this article: Mukund B, Jamal AZ. Risk factors for bronchiolitis - Can we really predict? J Pediatr Crit Care 2020;7:57-8.

Microalbuminuria as a sensitive predictor of early glomerular injury in children with sickle cell anemia

Microalbuminuria (MA) defined as minute elevation in the urine albumin (30–300 mg/24 h in an adult or an albumin: creatinine ratio >20–30 mg/g creatinine in a random sample) in the absence overt proteinuria that is not detectable by conventional dipstick methods. It is a nonspecific but sensitive indicator of preclinical renal and cardiovascular morbidity and mortality. Its role as a sensitive marker in diagnosing nephropathy of varied ethology (glomerular damage caused by hyperfiltration, hyperperfusion, etc.) and as a predictor of progression to overt renal failure is not something new, for example, diabetic nephropathy (DN) where it is widely used to predict and prognosticate. Other areas of its use are hypertensive nephropathy, cardiovascular disease (CVD) risk, etc.

Similar renal damage is known to occur in sickle cell anemia (SCA). Therefore, similar phenomenon of microproteinuria is reported to occur long before it progresses to overt proteinuria or renal failure.[1-3] Renal damage (sickle cell nephropathy [SCN]) results from recurrent vaso-occlusive crisis, ischemia–reperfusion injury, loss of renal mass, glomerular hyperfiltration, and sclerosis.[4] Evidence of kidney changes has been observed as early as infancy, and MA has been detected in as early as 3–4 years.[5] Identification of MA and risk factors may allow early interventions such as ACE inhibitors (ACEI) and hydroxyurea, which have been shown to retard the progression to overt renal failure. In this issue of *Journal of Pediatric Critical Care*, Meher *et al.* have tried to address the role of MA in SCN similar to DN.[6] Given the limited data, screening the children with SCA at an early age and follow-ups for the development of MA would have been more apt to address the objectives of the study. Enrolling a known, in fact, those in quite, advanced nephropathy takes away the whole idea of finding out MA as an early indicator. Therefore, one can wonder that the study adds any value in differentiating those with SCN versus not. According to authors' enrolment strategy, those with the "disease" (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2 body surface area [BSA]) categorized into Stage-III chronic kidney disease (CKD);[7] understandably, this is quite advanced kidney disease rather than preclinical nephropathy. Again, the estimation of GFR based on single creatinine value is a crude method that often poorly correlates with measured GFR. McKie *et al.*[8] analyzed longitudinal data of 191 sickle cell children aged 3–20 years with a mean follow-up of 2.19 ± 2.05 years. ACEI and hydroxyurea showed to reverse MA in half (44% hydroxyurea and 56% ACEI) of the patients. Therefore, longitudinal studies further in earlier age groups with follow-ups will address the primary concern of how early these children at risk can be identified and appropriate (preventive) measures could be applied.

In nutshell, improved standards of care have reflected in the longer survival of children with SCA. SCN is an important risk factor for long-term morbidity and mortality. Longitudinal studies involving earlier age groups are needed to address the optimum age for early identification and then early interventions. Interventions such as ACEI and hydroxyurea have been shown to retard the progression to overt renal failure or CKD in these children.

Govind Benakatti

Department of Pediatric Intensive Care, NMC Royal Hospital, AD, UAE

Address for correspondence: Dr. Govind Benakatti, NMC Royal Hospital, AD, UAE.
E-mail: govind.pgi@gmail.com

REFERENCES

1. McBurney PG, Hanevold CD, Hernandez CM, Waller JL, McKie KM. Risk factors for microalbuminuria in children with sickle cell anemia. J Pediatr Hematol Oncol 2002;24:473-7.
2. King L, MooSang M, Miller M, Reid M. Prevalence and predictors of microalbuminuria in Jamaican children with sickle cell disease. Arch Dis Child 2011;96:1135-9.
3. Abhulimhen-Iyoha IB, Ibadin MO, Ofovwe EG. Comparative usefulness of serum creatinine and microalbuminuria in detecting early renal changes in children with sickle cell anaemia in Benin city. Niger J Paediatr 2009;36:1-2.
4. Pham PT, Pham PC, Wilkinson AH, Lew SQ. Renal abnormalities in

sickle cell disease. Kidney Int 2000;57:1-8.
5. Marsenic O, Couloures KG, Wiley JM. Proteinuria in children with sickle cell disease. Nephrol Dial Transplant 2008;23:715-20.
6. Meher SK, Mishra NR, Khamari DK, Nayak BK. Diagnostic accuracy of microalbuminuria among sickle cell children with nephropathy. J Ped Crit Care 2020;7:73-8.
7. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.
8. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. J Pediatr Hematol Oncol 2007;29:140-4.

Received: 03-03-2020 **Accepted:** 10-03-2020
Published: 10-04-2020

Access this article online

Quick Response Code:

Website: www.jpcc.org.in

DOI: 10.4103/JPCC.JPCC_41_20

How to cite this article: Benakatti G. Microalbuminuria as a sensitive predictor of early glomerular injury in children with sickle cell anemia. J Pediatr Crit Care 2020;7:59-60.

Original Article

Calcium, phosphate, and Vitamin D abnormalities in critically ill children

Shipra Agrwal, Urmila Jhamb, Smita Kaushik[1]

Department of Pediatrics and [1]Biochemistry, Maulana Azad Medical College, New Delhi, India

Abstract

Background and Aims: Calcium, phosphate, and Vitamin D abnormalities are common in critically ill children, which may affect their outcome. However, data regarding the prevalence of these abnormalities are scarce from developing countries. This study assessed the prevalence of calcium, phosphate, and Vitamin D abnormalities in critically ill children and their association with the outcome.

Materials and Methods: This was a prospective, cross-sectional study of children aged 1 month to 12 years admitted to the pediatric intensive care unit of a tertiary care public hospital. Relevant clinical information and PRISM III score were recorded, and blood sample for the estimation of serum calcium, phosphate, Vitamin D, and other relevant parameters were collected at admission. Children were followed up till final outcome.

Results: A total of 135 children were included with a median age of 36 months. Total and ionized hypocalcemia were present in 9.6% and 22.9%, respectively, and both were associated with higher mortality ($P = 0.006$ and 0.03, respectively). Children with total hypocalcemia more often had sepsis and required significantly more fluid boluses and inotropes. Hypophosphatemia and hyperphosphatemia were present in 28.8% and 10.3%, respectively, and were also associated with significantly higher mortality. 85.6% of the children were Vitamin D deficient, but no significant association with severity and outcome was found.

Conclusion: Calcium, phosphate, and Vitamin D abnormalities were common in critically ill children. Higher mortality was associated with hypocalcemia and abnormal phosphate levels but not with Vitamin D deficiency. There was significant association of hypocalcemia with sepsis, fluid bolus, and inotrope requirement.

Keywords: Critically ill children, hypocalcemia, mortality, pediatric intensive care unit stay, Vitamin D level

Address for correspondence: Dr. Urmila Jhamb, Department of Pediatrics, Maulana Azad Medical College, New Delhi - 110 002, India.
E-mail: ujhamb@hotmail.com

INTRODUCTION

Abnormalities of calcium, phosphate, and Vitamin D are common in critically ill children admitted to the pediatric intensive care unit (PICU), but data are scarce from developing countries. Critically ill children have various metabolic derangements which predispose them for hypocalcemia, e.g., hypoalbuminemia, renal failure, Vitamin D deficiency, and hypoparathyroidism.[1] Some studies have shown association of hypocalcemia with the duration of stay, ventilation, severity of illness, and mortality.[2-5] Critically ill children also have various risk factors for developing hypophosphatemia, e.g. malnutrition, sepsis, diuretics, and steroid use, and this has been shown to be associated with increased duration of stay and sepsis

Received: 22-01-2020 **Revised:** 22-02-2020
Accepted: 29-02-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_9_20

How to cite this article: Agrwal S, Jhamb U, Kaushik S. Calcium, phosphate, and Vitamin D abnormalities in critically ill children. J Pediatr Crit Care 2020;7:61-8.

in some studies, while others have failed to find any such association.[6-8] Occurrence of hypercalcemia and hyperphosphatemia is less in critically ill children, and the association of these abnormalities with the outcome has not been studied in detail. Studies have shown that Vitamin D deficiency is common among critically ill children, and there are variable results of studies regarding its association with severity of illness, sepsis, duration of ventilation, and PICU stay.[9-15] High incidence of Vitamin D deficiency has been found even in healthy Indian children.[16,17]

The present study aims to analyze the prevalence of abnormalities in serum calcium, phosphate, and 25-hydroxyvitamin D levels in the children admitted to the PICU and to study the association of these abnormalities with the outcome.

MATERIALS AND METHODS

This prospective, cross-sectional study was conducted in the seven-bedded PICU of a tertiary care hospital in Delhi. Children aged 1 month to 12 years admitted to the PICU were consecutively enrolled. Children with known renal or parathyroid dysfunction or those taking Vitamin D were excluded. Taking prevalence of 40%, precision of 10%, and 95% confidence interval, using the formula for sample size calculation for qualitative, cross-sectional study, a sample size of minimal 96 was calculated.

Demographic data, history including drug intake, anthropometry, examination findings, primary diagnosis at admission, PRISM III score, requirement of mechanical ventilation, and its duration, fluid boluses or inotropic support, outcome, and duration of stay were recorded. Blood sample for the estimation of serum calcium (total and ionized), phosphate, sodium, potassium, alkaline phosphatase, blood urea, serum creatinine, serum albumin, and Vitamin D was collected within 24 h of admission (first morning). Methods used for analysis were O-cresolphthalein complexone for serum calcium, phosphomolybdate for serum phosphate, and electrochemiluminescence immunoassay method for Vitamin D.

Cutoff values were taken as follows:

- Hypocalcemia – Total serum calcium <8.5 mg/dL and ionized calcium level <1 mmol/L[3]
- Hypercalcemia – Total serum calcium >11 mg/dL and ionized serum calcium >1.25 mmol/L[18]
- Hypophosphatemia – Serum phosphate <3.7 mg/dL[19]
- Hyperphosphatemia – >6.5 mg/dL[19]
- Vitamin D deficiency – serum 25 hydroxyvitamin D <20 ng/mL[20]
- Hypervitaminosis D – 25 hydroxyvitamin D >100 ng/mL.

Serum calcium value was corrected for serum albumin.

Data were analyzed using SPSS 16.0 software (Copyright 2007, SPSS Inc, Chicago, IL, USA). A $P < 0.05$ was considered statistically significant. For comparison of categorical variables, Chi-square/Fisher's exact test was applied. Mann–Whitney/Student's *t*-test was applied for comparison of categorical with quantitative variables. Pearson and Spearman correlation coefficients were used to determine the correlation of the quantitative variables.

The study was approved by the institutional ethical committee. Informed written consent was taken from the parents.

RESULTS

A total of 226 children were admitted in the PICU during the study period (March–September 2014), and 135 were included in the study. Ninety-one were excluded for various reasons, e.g. death or transfer out of PICU before the sample was drawn, consent not given, previous kidney disease, age <1 month, and readmission. Ninety-three (68.1%) were males and 42 (31.9%) were females. Median age of the study population was 36 months. 33.3% of the children were <1 year of age, 29.7% were between 1 and 5 years of age, and 37% were more than 5 years of age. Sixty-five (48.1%) children required ventilator support, and mortality in the study population was 22.2%. Primary system involved was central nervous system in 24%, respiratory system in 17%, cardiovascular system in 15.5%, and gastrointestinal system in 10.5%. Fourteen percent were postoperative patients, and the remaining 7.4% had other miscellaneous diagnosis.

Table 1 shows the prevalence of various serum abnormalities in the study population. 17 (12.6%) children had history of prior calcium supplementation. There was no significant difference in the occurrence of hypocalcemia among those who had received prior calcium supplementation ($P = 0.93$). The study showed a very high incidence of Vitamin D deficiency (85.9%). 74% of children had levels Vitamin D <10 ng/mL. None of them had hypervitaminosis D.

Association of calcium abnormalities with demography, PICU morbidities, and outcome is shown in Table 2. Median age of the children with total hypocalcemia

Table 1: Prevalence of metabolic abnormalities in the study population

Parameter	Value		
	Calcium		
	Total (mg/dL)	Corrected for albumin (mg/dL)	Ionized (mmol/L)
Mean (SD)	8.9 (1.2)	9.86 (1.3)	1.08 (0.18)
Males, mean (SD)	9.0 (1.28)	9.9 (1.25)	1.08 (0.19)
Females, mean (SD)	8.8 (1.18)	9.8 (1.29)	1.09 (0.16)
Hypocalcemia, *n* (%), mild, moderate, severe	33 (24.4)	13 (9.6)	31 (22.9) (1.1, 7.4, 4.4)
Hypercalcemia, *n* (%), mild, moderate, severe	3 (2.2)	9 (6.6)	17 (12.6) (4.4, 5.9, 2. 2)
Phosphate			
Serum phosphate (mg/dL), mean (SD)		4.5 (1.5)	
Male, mean (SD)		4.7 (1.5)	
Female, mean (SD)		4.0 (1.3)	
Hypophosphatemia, *n* (%)		39 (28.8)	
Hyperphosphatemia, *n* (%)		14 (10.3)	
Vitamin D			
Serum level (ng/mL), mean (SD)		11.4 (13.2)	
Male, mean (SD)		9.7 (12.7)	
Female, mean (SD)		9.5 (11.2)	
Deficiency (<20 ng/mL), *n* (%)		116 (85.9)	
Insufficiency (20-30 ng/mL), *n* (%)		10 (7.4)	
Sufficiency (>30 ng/mL), *n* (%)		9 (6.7)	

SD: Standard deviation

was significantly lower ($P = 0.006$). They were more likely to have sepsis ($P < 0.001$) and required more fluid boluses ($P = 0.007$) and inotropes support ($P = 0.012$). Mean calcium was significantly lower among the children with sepsis ($P = 0.004$). Mortality was higher in the children with total hypocalcemia ($P = 0.006$) and ionized hypocalcemia ($P = 0.03$), but no association was found with hypercalcemia. There was no statistically significant difference in gender distribution, need for mechanical ventilation, duration of PICU stay, and duration of ventilation between the normal and abnormal calcium levels.

We did not find any significant association of abnormal serum phosphate levels with various morbidities, such as sepsis, fluid bolus, inotrope, and ventilation requirement. PRISM III score and mortality were significantly higher among the children with abnormal serum phosphate levels. The study did not find any significant association of Vitamin D deficiency with requirement and duration of mechanical ventilation, duration of PICU stay, biochemical abnormalities of calcium or phosphate, sepsis, requirement of fluid bolus or inotropes, and mortality as shown in Tables 3 and 4.

Comparison of the biochemical abnormalities between survivors and nonsurvivors is shown in Figure 1. Total and ionized hypocalcemia were significantly more among the nonsurvivors (*P* value 0.012 and 0.047, respectively). Hypophosphatemia and hyperphosphatemia were also significantly more in the nonsurvivor group ($P = 0.048$ and 0.018, respectively). There was no significant difference in the rate of Vitamin D deficiency (not shown in figure).

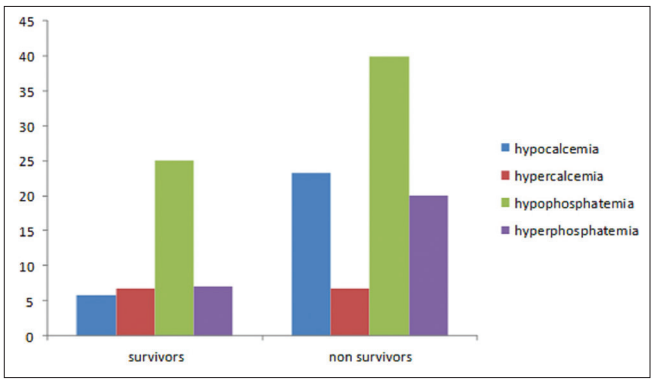


Figure 1: Biochemical abnormalities among survivors and nonsurvivors

DISCUSSION

Hypocalcemia has been reported in 18%–65% of the critically ill children and adults.[2-5,21] We found hypocalcemia at admission in 24.4%; however, when corrected for albumin, it was 9.6%. One gram per deciliter decrease in serum albumin decreases the total calcium by 0.8 mg/day, and we considered serum albumin levels of <4 mg/dL as hypoalbuminemia. In our study, 122 (90%) children had serum albumin <4 mg/dL. Occurrence of total hypocalcemia at admission in our study was lower than the study by Singhi *et al*.[3] (35%) and Cardenas-Rivero *et al*.[5] (49%). Singhi *et al*.[3] found that an additional 13% of the patients developed hypocalcemia during PICU stay. Ionized hypocalcemia at admission in our study was higher than the study by Broner *et al*.[4] (12.5%) and Cardenas-Rivero *et al*.[5] (17.9%), while it was lower than the study by Naik and Dandge[21] (47.5%). We did not check calcium levels again during the PICU stay. Children with hypocalcemia had

Table 2: Correlation of calcium abnormalities with patient characteristics, severity of illness, sepsis, and biochemical parameters

Parameter	Total Ca^{++}			Ionized Ca^{++}		
	Normocalcemia (113)	Hypocalcemia (13)	Hypercalcemia (9)	Normocalcemia (87)	Hypocalcemia (31)	Hypercalcemia (17)
Age (months), median (IQR)	36 (8-96)	8 (3 21) *P*=0.006	18 (6-56) *P*=0.346	36 (8-96)	30 (5-96) *P*=0.363	24 (5-69) *P*=0.58
Male, *n* (%)	79 (69.9)	8 (61.5) *P*=0.536	5 (55.6) *P*=0.458	57 (65.5)	23 (74.2) *P*=0.375	12 (70.6) *P*=0.69
MV, *n* (%)	52 (46.0)	10 (76.9) *P*=0.076	3 (33.3) *P*=0.511	41 (47.1)	17 (54.8) *P*=0.46	7 (41.2) *P*=0.65
PICU stay (days), median (IQR)	11 (6-22)	7 (5-8.5) *P*=0.528	11 (4.5-14.5) *P*=0.845	11 (6-20)	8 (5-15) *P*=0.412	12 (4.5-20.5) *P*=0.46
MV days, median (IQR)	7 (3-15)	4.5 (2-10) *P*=0.350	4 (3-13) *P*=0.683	5 (2-11)	8 (3.5-12.5) *P*=0.342	15 (3-28) *P*=0.23
Fluid boluses, *n* (%)	29 (25.6)	8 (61.5) *P*=0.007	1 (11.1) *P*=0.45	22 (25.3)	13 (41.9) *P*=0.08	3 (17.6) *P*=0.76
Inotropes, *n* (%)	31 (27.4)	8 (61.5) *P*=0.012	1 (11.1) *P*=0.443	24 (27.6)	13 (41.9) *P*=0.14	3 (17.6) *P*=0.55
Sepsis, *n* (%)	24 (21.2)	9 (69.2) *P*=0.000	2 (22.2) *P*=1.00	22 (25.3)	13 (41.9) *P*=0.14	2 (11.7) *P*=0.23
Serum ALP IU/L						
Median (IQR)	171 (127-239)	160 (84-344)	88 (75-182)	168 (103-239)	170 (127-238)	156 (127-285)
Mean (SD)	193.5 (112)	400 (550) *P*=0.83	161.3 (153) *P*=0.07	189 (120)	273 (379) *P*=0.58	209 (124) *P*=0.59
Serum PO_4 (mg/dL)						
Median (IQR)	4.3 (3.6-5.3)	3.9 (3.4-5.3)	4.2 (3.4-4.9)	4.2 (3.6-5.1)	4.0 (3.2-5.7)	4.6 (4.1-5.2)
Mean (SD)	4.56 (1.5)	4.25 (1.39) *P*=0.531	4.2 (1.27) *P*=0.607	4.5 (1.5)	4.4 (1.6) *P*=0.55	4.8 (1.5) *P*=0.15
Hypophosphatemia, *n* (%)	32 (28.3)	4 (30.7) *P*=1.00	3 (33.3) *P*=1.00	26 (29.9)	11 (35.5) *P*=0.49	2 (11.8) *P*=0.14
Hyperphosphatemia, *n* (%)	13 (11.5)	1 (7.6) *P*=1.00	0 (0) *P*=0.58	9 (10.3)	4 (12.9) *P*=0.73	1 (5.9) *P*=0.68
Serum Vitamin D (ng/mL)						
Median (IQR)	4.12 (3-13.9)	3 (3-5.3)	3 (3-3.7)	4.03 (3-11)	3 (3-9.6)	4.12 (3-21.2)
Mean (SD)	10.5 (13)	6.06 (6.53) *P*=0.087	4.4 (3.6) *P*=0.04	10 (13.2)	8.2 (9.9) *P*=0.46	4.4 (3.6) *P*=0.70
Vitamin D >30 ng/mL, *n* (%)	9 (7.9)	0 (0) *P*=0.596	0 (0) *P*=1.00	7 (8.0)	1 (3.2) *P*=0.68	1 (5.9) *P*=1.00
20-30 ng/mL	8 (7)	2 (15.3) *P*=0.233	0 (0) *P*=1.00	5 (5.7)	2 (6.4) *P*=1.00	3 (17.6) *P*=0.12
<20 ng/mL	86 (76.1)	11 (84.6) *P*=1.00	9 (100) *P*=0.358	75 (86.2)	28 (90.3) *P*=0.76	13 (76.5) *P*=0.39
PRISM score, median (IQR)	3 (0-7)	6 (2.5-10) *P*=0.10	4 (1.5-6) *P*=0.62	3 (0-7)	7 (3-8) *P*=0.05	0 (0-3) *P*=0.02
Mortality	21 (18.6)	7 (53.8) *P*=0.006		16 (19.5)	12 (40) *P*=0.03	

PICU: Pediatric intensive care unit, ALP: Alkaline phosphatase, PRISM: Pediatric risk of mortality, SD: Standard deviation, IQR: Interquartile range, MV: Mechanical ventilation

significantly higher incidence of sepsis and those with sepsis had lower mean calcium levels. Higher incidence of sepsis among the hypocalcemic patients was found by Chernow *et al*.[2] ($P = 0.01$ for total hypocalcemia) and Cardenas-Rivero *et al*.[5] ($P = 0.03$ for ionized hypocalcemia). Hypocalcemia was found in 57% and 83% of the children with sepsis in studies by Singhi *et al*.[3] and Naik and Dandge, respectively.[21] Calcium level in the setting of sepsis has been found to be inversely related to the levels of inflammatory mediators, e.g. tumor necrosis factor, interleukin-6, and procalcitonin.[22] Raised calcitonin precursors have also been implicated as a cause of hypocalcemia in septic patients.[23]

Calcium is an important cation for neuromuscular transmission, muscle contraction, and membrane stability. Studies have shown significant association of hypocalcemia with hypotension and requirement of cardiovascular support.[3,5,21,24] Vincent *et al*.[25] showed that infusion of intravenous calcium in the critically ill patients was associated with significant increase in mean arterial pressure that lasted for about 1 h. We also found significant association of hypocalcemia with fluid and inotrope requirement. Children with hypocalcemia had significantly higher mortality compared to those with normal or high serum calcium. Our observation was consistent with other studies.[3-5,21]

Higher proportion of the children with hypocalcemia required mechanical ventilation compared to those with normal serum calcium, but the difference was not

Table 3: Association of Vitamin D levels with outcome and calcium/phosphate levels

Parameter	Deficient Vitamin D <20 ng/mL (*n*=116)	Insufficient Vitamin D 20-30 ng/mL (*n*=10)	Sufficient Vitamin D >30 ng/mL (*n*=9)	*P*
Age (months)				
Median (IQR)	36 (8-96)	13 (2-39)	6 (5-42)	0.051
Mean (SD)	54 (48.9)	22.7 (26.7)	29.4 (37.4)	
PICU stay (days)				
Median (IQR)	11 (6-19)	10.5 (3.7-16.7)	16 (8.5-33.5)	0.36
Mean (SD)	15.8 (14.7)	16.3 (20.1)	12.6 (17.9)	
Duration of ventilation				
Median	5 (3-11)	8 (2-16)	9 (3-20)	0.24
Mean (SD)	8.6 (8.6)	9.3 (6.8)	18.5 (16.8)	
PRISM III score				
Median (IQR)	3 (0-7)	3 (0-3.3)	3 (1-7.5)	0.9
Mean (SD)	4.9 (5.6)	3.7 (3.5)	4.6 (4.2)	
Serum ALP				
Median (IQR)	167 (117-239)	128 (97-204)	188 (133-297)	0.35
Mean (SD)	216.4 (221)	153.4 (68)	209.8 (89.7)	
Serum calcium, mean (SD)	9.9 (1.3)	9.3 (1.3)	10.2 (0.6)	0.33
Serum ionized calcium, mean (SD)	1.07 (0.19)	1.09 (0.23)	1.11 (0.13)	0.83
Serum phosphate				
Median (IQR)	4.2 (3.5-5.3)	4.3 (3.8-5.1)	4.4 (4.3-5.8)	0.49
Mean (SD)	4.5 (1.5)	4.6 (1.3)	4.9 (1.2)	

PICU: Pediatric intensive care unit, ALP: Alkaline phosphatase, SD: Standard deviation, IQR: Interquartile range, PRISM: Pediatric risk of mortality

Table 4: Association of Vitamin D deficiency with biochemical abnormalities and outcome

Vitamin D level	Deficient (<20 ng/mL), *n* (%) (*n*=116)	Nondeficient (>20 ng/mL), *n* (%) (*n*=19)	*P*
Age (months), median (IQR)	36 (8-96)	5.5 (3-36)	0.045
Male, *n* (%)	79 (68.1)	13 (68.4)	0.98
Female, *n* (%)	37 (31.9)	6 (31.6)	
MV, *n* (%)	52 (44.8)	13 (68.4)	0.056
Fluid boluses, *n* (%)	34 (29.3)	4 (21)	0.54
Inotropes, *n* (%)	36 (31)	4 (21)	0.43
Sepsis, *n* (%)	31 (26.7	6 (31.6)	0.66
Mortality, *n* (%)	26 (22.4)	4 (21)	0.89
Hypocalcemia, *n* (%)	11 (9.5)	2 (10.5)	1.00
Hypercalcemia, *n* (%)	9 (7.7)	0 (0)	0.36
Hypocalcemia (ionized), *n* (%)	28 (24.1)	3 (15.8)	0.76
Hypercalcemia (ionized), *n* (%)	13 (11.2)	4 (21)	0.29
Hypophosphatemia, *n* (%)	36 (31)	3 (15.8)	0.26
Hyperphosphatemia, *n* (%)	12 (10.3)	2 (10.5)	1.00

IQR: Interquartile range, MV: Mechanical ventilation

statistically significant. We did not find any significant association of total hypocalcemia with the PRISM III score. This was in contrast to other studies which showed higher severity of illness among hypocalcemic patients.[5,26,27] The children with ionized hypocalcemia had significantly higher PRISM scores. Patients with hypocalcemia have been shown to stay in the PICU for longer period, but we did not find any association of hypocalcemia with the duration of ventilation or ICU stay.[2,3,21] Our study did not show any significant association of hypercalcemia with severity of illness, duration of ventilation or PICU stay, need for cardiovascular support, or mortality.

Hypophosphatemia is a common metabolic abnormality in critically ill children and adults. Hypophosphatemia is known to develop during the ICU stay, and studies have shown that 60%–75% children developed hypophosphatemia during the PICU stay.[6,7,28] We analyzed phosphate levels only at the PICU admission. The incidence of hypophosphatemia in our study was lower than the study by Santana e Meneses *et al*.[28] Malnutrition has been described as an independent risk factor for the occurrence of hypophosphatemia.[6,28] In our study, malnutrition was present in 43.6% of the hypophosphatemic patients which was similar to the findings of de Menezes *et al*. and Santana e Meneses *et al*.[6,28] Hypophosphatemia was significantly associated with malnutrition in the study of de Menezes *et al*.[6] ($P = 0.04$), but our study did not show any significant association ($P = 0.73$).

We did not find any significant association of hypophosphatemia with requirement and duration of mechanical ventilation and duration of PICU stay. Our findings were similar to those of de Menezes *et al*.[6] and

Ruiz Magro *et al*.[8] while Kilic *et al*.[7] found significant association of hypophosphatemia with the duration of mechanical ventilation and ICU stay ($P = 0.02$ and 0.001, respectively).

Studies have reported the incidence of hypophosphatemia among patients with sepsis to be up to 80%.[7,29] Our study showed that 35% of the children with sepsis had hypophosphatemia and 13.5% had hyperphosphatemia. High levels of inflammatory cytokines are associated with hypophosphatemia.[29] In our study, 23% of normophosphatemic and 33% of hypophosphatemic patients had sepsis ($P = 0.24$). This observation was in contrast to Kilic *et al*.[7]

Bollaert *et al*.[30] showed a significant increase in the left ventricular stroke volume and arterial pressure immediately after intravenous phosphate infusion, and it was also associated with increase in arterial pH. However, we did not find any significant association of hypophosphatemia with the requirement of fluid bolus and inotrope among the critically ill children. This observation was similar to de Menezes *et al*.[6]

In our study, the median PRISM III score was significantly higher among the hypophosphatemic ($P = 0.013$) and hyperphosphatemic children ($P = 0.008$) compared to the normophosphatemic patients. de Menezes *et al*.[6] did not find any such association. In the study by Kilic *et al*.,[7] the mean PRISM score was higher among the hypophosphatemic patients, but the difference was not significant. We could not find any study comparing the incidence of hyperphosphatemia with duration of ventilation, occurrence of sepsis, PRISM score, and mortality.

We found higher mortality among the children with abnormal serum phosphate levels. Incidence of hypophosphatemia and hyperphosphatemia was significantly higher among nonsurvivors. Suzuki *et al*.[31] showed that patients with at least one episode of hypophosphatemia had higher mortality, but on multivariate regression analysis, hypophosphatemia was not an independent predictor of mortality. Severe hypophosphatemia has been found to be associated with eightfold increase in risk of mortality in septic patients.[32] Haider *et al*.[33] found that hyperphosphatemia was significantly associated with mortality. The deleterious effect of low serum phosphate can be explained by its effect on myocardial function, response to vasopressors, and ATP generation.

Incidence of Vitamin D deficiency in critically ill children ranges from 28% to 71%.[9,34,35] Incidence of Vitamin D deficiency in our study (85.9% deficient and 7.4% insufficient) was higher than the other Indian study by Lodha *et al*.[35] (71%). Some studies from the same city have shown that the incidence of Vitamin D deficiency in healthy children is 85%–90%.[16,17] It is difficult to state whether the high incidence of Vitamin D deficiency in our study population is due to critical illness or only a reflection of the population prevalence. In the critically ill children, Vitamin D levels may decline further during the ICU stay due to insufficient replacement and the absence of ultraviolet-B exposure.[14] We, however, did not repeat the vitamin levels during PICU stay.

The effects of Vitamin D are mediated through Vitamin D receptor. Vitamin D acts on both the adaptive and innate immunity systems. Vitamin D deficiency has been implicated in various immune disorders, e.g. inflammatory bowel disease, asthma, and type one diabetes.[36,37] Studies have shown significant association of Vitamin D deficiency with occurrence of sepsis in children as well as in adults.[12,38] We did not find any significant association of Vitamin D deficiency with the occurrence of sepsis. Similar observation was made by Amrein *et al*.[13] Vitamin D deficiency has been found to be associated with a higher requirement of cardiorespiratory support.[9,10] Severe Vitamin D deficiency is associated with decreased muscle strength and may lead to prolonged ventilation requirement and difficulty in weaning.[39] Some studies have found association of Vitamin D deficiency with a longer duration of stay,[9] while others have failed to demonstrate such association.[13,15,39-41] We did not find any significant association of Vitamin D deficiency with the cardiorespiratory support requirement, duration of PICU stay, and duration of mechanical ventilation, and this observation was similar to other studies.[10,14,15] Amrein *et al*.[14] found that the mortality was lower among the adult ICU patients who were on Vitamin D supplementation compared to those on placebo. We did not find any significant association of Vitamin D deficiency with mortality.

Strength of our study was that it was a prospective study and we analyzed calcium, phosphate, and Vitamin D together and tried to find a correlation among them. The limitations of our study were small sample size and that we did not analyzed parathyroid hormone levels as a cause of calcium and phosphate abnormalities. In our study, most of the patients had Vitamin D deficiency or insufficiency. Very small number of patients in our study had normal Vitamin D levels, and this may be the reason for not finding any significant association with the outcome.

CONCLUSION

Our study provides data regarding the prevalence of calcium, phosphate, and Vitamin D abnormalities in critically ill children in a developing country. Calcium deficiency has a significant association with cardiovascular morbidity and incidence of sepsis. Abnormality of calcium and phosphate is associated with poorer outcome in critically ill children. We found very high incidence of Vitamin D deficiency. In view of very low number of patients having sufficient Vitamin D levels group, the association of Vitamin D deficiency with various PICU morbidities could not be analyzed accurately.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Risteli J, Winter WE, Kleerekoper CA, Risteli L. Disorders of bone and mineral metabolism. In: Burtis CA, Ashwood ER, Bruns DE, editors. Tietz textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. Saunders: Elsevier; 2014. p. 741-68.
2. Chernow B, Zaloga G, McFadden E, Clapper M, Kotler M, Barton M, *et al*. Hypocalcemia in critically ill patients. Crit Care Med 1982;10:848-51.
3. Singhi SC, Singh J, Prasad R. Hypocalcaemia in a paediatric intensive care unit. J Trop Pediatr 2003;49:298-302.
4. Broner CW, Stidham GL, Westenkirchner DF. Significance of ionized calcium measurements in critically ill children. Pediatr Res 1987;21:198A.
5. Cardenas-Rivero N, Chernow B, Stoiko MA, Nussbaum SR, Todres ID. Hypocalcemia in critically ill children. J Pediatr 1989;114:946-51.
6. de Menezes FS, Leite HP, Fernandez J, Benzecry SG, de Carvalho WB. Hypophosphatemia in critically ill children. Rev Hosp Clin Fac Med Sao Paulo 2004;59:306-11.
7. Kilic O, Demirkol D, Ucsel R, Citak A, Karabocuoglu M. Hypophosphatemia and its clinical implications in critically ill children: A retrospective study. J Crit Care 2012;27:474-9.
8. Ruiz Magro P, Aparicio López C, López-Herce Cid J, Martínez Campos M, Sancho Pérez L. Metabolic changes in critically ill children. An Esp Pediatr 1999;51:143-8.
9. McNally JD, Menon K, Chakraborty P, Fisher L, Williams KA, Al-Dirbashi OY, *et al*. The association of Vitamin D status with pediatric critical illness. Pediatrics 2012;130:429-36.
10. Madden K, Feldman HA, Smith EM, Gordon CM, Keisling SM, Sullivan RM, *et al*. Vitamin D deficiency in critically ill children. Pediatrics 2012;130:421-8.
11. Rech MA, Hunsaker T, Rodriguez J. Deficiency in 25-hydroxyvitamin D and 30-day mortality in patients with severe sepsis and septic shock. Am J Crit Care 2014;23:e72-9.
12. Moromizato T, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. Crit Care Med 2014;42:97-107.
13. Amrein K, Zajic P, Schnedl C, Waltensdorfer A, Fruhwald S, Holl A, *et al*. Vitamin D status and its association with season, hospital and sepsis mortality in critical illness. Crit Care 2014;18:R47.
14. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, *et al*. Effect of high-dose Vitamin D3 on hospital length of stay in critically ill patients with Vitamin D deficiency: The VITdAL-ICU randomized clinical trial. JAMA 2014;312:1520-30.
15. Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, Diaz-Fuentes G. Vitamin D deficiency is associated with mortality in the medical intensive care unit. Crit Care 2011;15:R292.
16. Puri S, Marwaha RK, Agarwal N, Tandon N, Agarwal R, Grewal K, *et al*. Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: relation to nutrition and lifestyle. Br J Nutr 2008;99:876-82.
17. Marwaha RK, Sripathy G. Vitamin D & bone mineral density of healthy school children in Northern India. Indian J Med Res 2008;127:239-44.
18. Egi M, Kim I, Nichol A, Stachowski E, French CJ, Hart GK, *et al*. Ionized calcium concentration and outcome in critical illness. Crit Care Med 2011;39:314-21.
19. Greenbaum LA. Electrolyte and acid base disorders. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Saunders Elsevier; 2013. p. 212-42.
20. Balasubramanian S, Dhanalakshmi K, Amperayani S. Vitamin D deficiency in childhood-A review of current guidelines on diagnosis and management. Indian Pediatr 2013;50:669-75.
21. Naik N, Dandge V. Role of calcium in critically ill children-Incidence of hypocalcemia in pediatric intensive care unit set up. Indian J Appl Res 2014;4:409-12.
22. Lind L, Carlstedt F, Rastad J, Stiernström H, Stridsberg M, Ljunggren O, *et al*. Hypocalcemia and parathyroid hormone secretion in critically ill patients. Crit Care Med 2000;28:93-9.
23. Müller B, Becker KL, Kränzlin M, Schächinger H, Huber PR, Nylèn ES, *et al*. Disordered calcium homeostasis of sepsis: Association with calcitonin precursors. Eur J Clin Invest 2000;30:823-31.
24. Desai TK, Carlson RW, Thill-Baharozian M, Geheb MA. A direct relationship between ionized calcium and arterial pressure among patients in an intensive care unit. Crit Care Med 1988;16:578-82.
25. Vincent JL, Bredas P, Jankowski S, Kahn RJ. Correction of hypocalcaemia in the critically ill: What is the haemodynamic benefit? Intensive Care Med 1995;21:838-41.
26. Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia: A pervasive metabolic abnormality in the critically ill. Am J Kidney Dis 2001;37:689-98.
27. Dias CR, Leite HP, Nogueira PC, Brunow de Carvalho W. Ionized hypocalcemia is an early event and is associated with organ dysfunction in children admitted to the intensive care unit. J Crit Care 2013;28:810-5.
28. Santana e Meneses JF, Leite HP, de Carvalho WB, Lopes E Jr. Hypophosphatemia in critically ill children: Prevalence and associated risk factors. Pediatr Crit Care Med 2009;10:234-8.
29. Barak V, Schwartz A, Kalickman I, Nisman B, Gurman G, Shoenfeld Y. Prevalence of hypophosphatemia in sepsis and infection: The role of cytokines. Am J Med 1998;104:40-7.
30. Bollaert PE, Levy B, Nace L, Laterre PF, Larcan A. Hemodynamic and metabolic effects of rapid correction of hypophosphatemia in patients with septic shock. Chest 1995;107:1698-701.
31. Suzuki S, Egi M, Schneider AG, Bellomo R, Hart GK, Hegarty C. Hypophosphatemia in critically ill patients. J Crit Care 2013;28:536.e9-19.
32. Shor R, Halabe A, Rishver S, Tilis Y, Matas Z, Fux A, *et al*. Severe hypophosphatemia in sepsis as a mortality predictor. Ann Clin Lab Sci 2006;36:67-72.
33. Haider DG, Lindner G, Wolzt M, Ahmad SS, Sauter T, Leichtle AB, *et al*. Hyperphosphatemia is an independent risk factor for mortality in critically ill patients: Results from a cross-sectional study. PLoS One 2015;10:e0133426.
34. Ayulo M Jr., Katyal C, Agarwal C, Sweberg T, Rastogi D, Markowitz M, *et al*. The prevalence of Vitamin D deficiency and its relationship with disease severity in an urban pediatric critical care unit. Endocr Regul 2014;48:69-76.

35. Lodha R, Shah R, Gupta N, Irshad M, Kabra SK. Vitamin D levels in critically ill children. Pediatr Crit Care Med 2014;15:59-60.
36. Sun J. Vitamin D and mucosal immune function. Curr Opin Gastroenterol 2010;26:591-5.
37. Massey K, Dickerson RN, Brown RO. A review of Vitamin D deficiency in the critical care population. Pharmacy 2014;2:40-9.
38. Kempker JA, Tangpricha V, Ziegler TR, Martin GS. Vitamin D in sepsis: From basic science to clinical impact. Crit Care 2012;16:316.
39. Amrein K, Schnedl C, Berghold A, Pieber TR, Dobnig H. Correction of Vitamin D deficiency in critically ill patients-VITdAL@ICU study protocol of a double-blind, placebo-controlled randomized clinical trial. BMC Endocr Disord 2012;12:27.
40. Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. Intensive Care Med 2012;38:2055-62.
41. Rey C, Sánchez-Arango D, López-Herce J, Martínez-Camblor P, García-Hernández I, Prieto B, *et al*. Vitamin D deficiency at pediatric intensive care admission. J Pediatr (Rio J) 2014;90:135-42.

Original Article

Correlation of severity of asthma with serum Vitamin D3 and serum magnesium level in children aged 5–14 years

Preeti Sharma, Alok Khanna, Kundan Mittal

Department of Pediatrics, Pandit Bhagwat Dayal Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India

Abstract

Background: Asthma is a common chronic respiratory disease affecting 1%–18% of the population in different countries. Many factors, such as genetic predisposition, early allergen exposure, infections, diet, tobacco smoke exposure, pollution, and Vitamin D3 status, are all proposed to influence the development and severity of asthma. Vitamin D3 alters human airway smooth muscle expression of chemokines and inhibits the expression of a steroid-resistant gene. Magnesium ion has an inhibitory action on smooth muscle contraction, histamine release from mast cells, and acetylcholine release from cholinergic nerve terminals, thus influencing the function of respiratory smooth muscles.

Aim: The aim is of this study is to assess serum Vitamin D3 level and serum magnesium level in children with asthma aged 5–14 years.

Materials and Methods: This was a cross-sectional study involving 75 children of 5–14 years of age having asthma, who were classified into intermittent, mild, moderate, and severe asthma, and serum Vitamin D3 levels and magnesium levels were estimated.

Results: Serum Vitamin D3 levels were significantly lower in children with severe asthma as compared to those with mild, moderate, or intermittent asthma, but serum magnesium levels were found to have no correlation with the severity of asthma in our study.

Conclusion: Vitamin D3 insufficiency is widely prevalent in Indian children with asthma and significantly correlated with the severity of asthma. Serum magnesium levels within the normal range and correlation of the severity of asthma with serum magnesium levels cannot be established in our study.

Keywords: Asthma, magnesium, Vitamin D3

Address for correspondence: Dr. Preeti Sharma, Department of Pediatrics, Pandit Bhagwat Dayal Sharma Postgraduate Institute of Medical Sciences, Rohtak - 124 001, Haryana, India.
E-mail: preetirose40@gmail.com

INTRODUCTION

Asthma is a heterogeneous disease which is characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation affecting an estimated 330 million individuals worldwide with a reported prevalence of 5%–20% in children aged between 6 and 15 years.[1,2] In India, the estimated burden of asthma is >30 million. In children, incidence reported by 6–7 years and 13–14 years are 2.3% and 3.3%,

Received: 02-01-2020 **Revised:** 22-01-2020
Accepted: 18-02-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_13_20

How to cite this article: Sharma P, Khanna A, Mittal K. Correlation of severity of asthma with serum Vitamin D3 and serum magnesium level in children aged 5–14 years. J Pediatr Crit Care 2020;7:69-72.

Table 1: Classifying asthma severity in children 5-11 years of age[8]

		Persistent		
	Intermittent	Mild	Moderate	Severe
Symptoms	<2 day/week	>2 days/week but not daily	Daily	Throughout day
Night awakening	<2×/month	3-4×/month	>1×/week but not nightly	>7×/week
SABA use	<2 days/week	>2 days/week but not daily	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung functions	Normal FEV1 between exacerbations FEV1 >80% predicted FEV1/FVC >85%	FEV >80% predicted FEV1/FVC >80%	FEV1=60%-80% predicted FEV1/FVC=75%-80%	FEV1 <60% predicted FEV1/FVC reduced <75%

FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 s, SABA: Short-acting beta agonists

respectively.[3,4] Vitamin D3 has been shown to have a role in both innate and adaptive immunity by promoting phagocytosis and modulating the effects of TH1, TH2, and regulatory T-cells.[5] Further evidence suggests that Vitamin D3 alters human airway smooth muscle expression of chemokines and inhibits the expression of a steroid-resistant gene.[6] Magnesium is a cation having modulatory effect on the contractile state of smooth muscle cells in various tissues. Hypomagnesemia leads to contraction while hypermagnesemia leads to relaxation.[7] Hence, this study was carried out to detect the prevalence of hypomagnesemia with Vitamin D insufficiency and deficiency among asthmatic children group (5–14 years) of India. This study also aims to assess the relationship between serum magnesium and Vitamin D levels with the severity of asthma.

MATERIALS AND METHODS

This study was a cross-sectional observational study conducted in the Department of Pediatrics, in PGIMS Rohtak, from January 2018 to February 2019, including 75 children of age group 5–14 years who were diagnosed case of asthma and classified according to the severity as per the EPR3 (guidelines for the diagnosis and management of asthma Table 1.[8] Among these children, 50 (66.55%) were male and 25 (33.34%) were female. Children with chronic renal disease, disease of calcium, and bone metabolism or those who were on Vitamin D3 supplementation, calcium therapy were excluded from the study. The ethics committee approved the study. After taking informed consent, a prestructured pro forma was used to record the relevant information from individual cases selected for the study. A detailed clinical examination was conducted, and under aseptic precautions, blood was drawn for relevant investigations, and then, the child was subjected for pulmonary function test (peak expiratory flow rate).

Vitamin D3 level was measured in the serum of patients using chemiluminescent immunoassay on Beckman Coulter, Access 2 instrument technique.

Reference range:[9]

- Category – serum Vitamin D3 levels
- Sufficiency: >20 ng/ml (>50 nmol/L)
- Insufficiency: 12–20 ng/ml (30–50 nmol/L)
- Deficiency: <12 ng/ml (<30 nmol/L).

Magnesium: serum magnesium was measured by using spectrophotometry technique.

Reference range: 1.7–2.5 mg/dL.[10]

Statistical analysis

At the end of the study, the data were collected and entered into Microsoft Excel. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as number/percentage. Statistical analysis was performed using SPSS version 20.0 (IBM SPSS Statistics).

1. Differences between continuous variables were assessed using Student's *t*-test for normally distributed data
2. Differences between categorical variables were assessed using the Chi-square test or Fischer's exact test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Table 2 shows the demographic profile of the children according to gender and the severity of asthma. A total of 26 males and 17 females found to be intermittent, 15 males and 5 females with mild persistent and 9 males and 3 females as moderate persistent. Severe persistence was not seen in any of the patients. Figure 1 and Table 3 show a significant correlation of serum Vitamin D3 level with the severity of asthma. Among deficient patients, 71.4% had moderate persistent asthma, 28.5% mild persistent asthma and among insufficient patients, 32% had moderate persistent asthma, 12% mild persistent asthma, 56% intermittent asthma, showing that children who are Vitamin D3 insufficient or deficient have a higher incidence of severe asthma.

Moreover, results show stage-wise decline in serum levels of Vitamin D3 with an increase in the severity of asthma. There is no significant difference in serum magnesium levels in asthmatic patients. According to Table 4, Thirty-eight (50.66%) patients had serum magnesium levels in the range of 1.7–2, 36 (48%) patients had between 2.1 and 3 and only 1 (1.33%) patient had magnesium level >3. All had serum magnesium levels within the normal range. As shown in Table 5, no significant correlation can be established between hypomagnesemia and asthma severity. Furthermore, the duration of pediatric intensive care unit stay, number of acute exacerbations, asthma control at the time of presentation compared in our study to the asthma severity but did not show any significant correlation.

DISCUSSION

Bronchial asthma is a chronic condition characterized by recurrent bronchospasm resulting from reversible bronchial hyperresponsiveness in response to stimuli of a level or intensity which usually does not cause such narrowing in most individuals.[11] Asthma is the major health problem worldwide and increase in the prevalence of asthma has been reported in recent years, particularly in developing countries like India with the prevalence of about 2%. Calcitriol (active form of Vitamin D3) is involved in insulin secretion, inhibition of interleukin production by T-lymphocytes and immunoglobulin by B-lymphocytes, differentiation of monocyte precursor cells, and modulation of cell proliferation. Cells of the immune system such as T-lymphocytes activated B-lymphocytes, and dendritic cells express Vitamin D3 receptors.[12] The age of children in the study population ranged from 5 years to 14 years. The mean age of the study patients was 8.75 ± 2.64 years. The study included 50 males and 25 females with a male-to-female ratio of 2:1. The slightly higher number of males in the study was probably a bias due to small sample size. A male preponderance in asthma has been reported by various authors. Vittal have been reported a higher prevalence in boys (3.1%) as compared to girls (4.1%) in a study from Shimla.[13] A study by Chhabra *et al.* from Delhi has shown a significantly higher prevalence of current asthma in boys as compared to girls (12.8% and 10.7%, respectively).[14] Our result demonstrated that 66.66% of patients admitted with asthma had Vitamin D3 insufficiency and 9.33% had deficiency and among deficient patients, 71.4% had moderate persistent asthma as compared to 28.5% had mild persistent asthma, while no patient with intermittent asthma had Vitamin D deficiency. The study showed that children who are Vitamin D3 insufficient or deficient have a higher incidence of severe asthma but statistically found to be insignificant correlation between the level of asthma control and Vitamin D3 sufficiency levels.

All the children included had serum magnesium levels within the normal range that is 1.7–2.5 mg/dL. No controls were included; therefore, comparison in serum magnesium levels between asthmatic and nonasthmatic children cannot be established. Thus, our study showed no significant correlation between serum magnesium level and asthma severity. Youssef aimed at outlining the possible role of magnesium in the pathogenesis and treatment of bronchial asthma including 27 asthmatic children and 15 healthy controls, measuring both intracellular and extracellular magnesium levels. The results found a significant correlation between the severity of asthma

Table 2: Severity of asthma according to gender

	Male (*n*=50)	Female (*n*=25)	Statistical significance
Intermittent	26	17	*P*=0.186 (>0.05 NS)
Mild persistent	15	5	*P*=0.355 (>0.05 NS)
Moderate persistent	9	3	*P*=0.404 (>0.05 NS)
Severe persistent	0	0	-

NS: Not significance

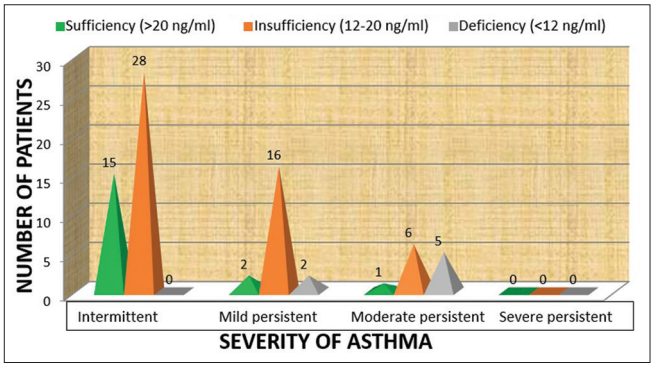


Figure 1: Comparison of serum Vitamin D3 levels with severity of asthma

Table 3: Correlation between the severity of asthma and Vitamin D3 levels

	Vitamin D3 status			Statistical analysis
	Sufficiency (>20 ng/ml)	Insufficiency (12-20 ng/ml)	Deficiency (<12 ng/ml)	
Intermittent	15	28	0	<0.001 significant
Mild persistent	2	16	2	<0.001 significant
Moderate persistent	1	6	5	<0.001 significant
Severe persistent	0	0	0	-

Table 4: Distribution of patients according to their serum magnesium level

Serum magnesium (range)	Number of patients (%)
1.7-2	38 (50.66)
2.1-3	36 (48)
>3	1 (1.33)

Table 5: Correlation between the severity of asthma and magnesium levels

	Magnesium levels			Statistical analysis
	1.7-2 (*n*=38)	2.1-3 (*n*=36)	>3 (*n*=1)	
Intermittent	22	20	1	*P*=0.151 (>0.05 NS)
Mild persistent	10	10	0	*P*=0.186 (>0.05 NS)
Moderate persistent	6	6	0	*P*=0.573 (>0.05 NS)
Severe persistent	0	0	0	-

NS: Not significance

and serum magnesium levels, both intracellular and extracellular.[15] Similarly, Kakish *et al.* conducted a study comparing serum magnesium levels of 176 children with asthma acute exacerbation and 94 with chronic stable asthma with 232 healthy controls concluded that there was no significant difference in serum magnesium levels when compared in asthmatic children during acute attack and between exacerbation with that of control.[16]

Hence, there are limited data suggesting correlation between the severity of asthma and serum magnesium level in children, also with the studies available having inconclusive results regarding the same, further studies need to be conducted.

CONCLUSION

We conclude that Vitamin D3 insufficiency is widely prevalent in Indian children with asthma. Vitamin D3 deficiency was found to be significantly associated with the severity of asthma and patients with more severe asthma were found to have significantly lower Vitamin D3 levels as compared to cases with mild or intermittent asthma. All children have serum magnesium levels within the normal range and correlation of the severity of asthma with serum magnesium levels cannot be established in study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, *et al.* National surveillance for asthma – United States, 1980-2004. MMWR Surveill Summ 2007;56:1-54.
2. Aït-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, *et al.* Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. Allergy 2009;64:123-48.
3. Sharma SK, Banga A. Prevalence and risk factors for wheezing in children from rural areas of north India. Allergy Asthma Proc 2007;28:647-53.
4. Awasthi S, Kalra E, Roy S, Awasthi S. Prevalence and risk factors of asthma and wheeze in school-going children in Lucknow, North India. Indian Pediatr 2004;41:1205-10.
5. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J 2005;19:1067-77.
6. Banerjee A, Damera G, Bhandare R, Gu S, Lopez-Boado Y, Panettieri R Jr., *et al.* Vitamin D and glucocorticoids differentially modulate chemokine expression in human airway smooth muscle cells. Br J Pharmacol 2008;155:84-92.
7. de Valk HW, Kok PT, Struyvenberg A, van Rijn HJ, Haalboom JR, Kreukniet J, *et al.* Extracellular and intracellular magnesium concentrations in asthmatic patients. Eur Respir J 1993;6:1122-5.
8. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007 [published correction appears in J Allergy Clin Immunol 2008;121:1330]. J Allergy Clin Immunol 2007;120(5 Suppl):S94-S138. doi:10.1016/j.jaci.2007.09.043.
9. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, *et al.* Global consensus recommendations on prevention and management of nutritional rickets. Horm Res Paediatr 2016;85:83-106.
10. Shaikh MN, Malapati BR, Gokani R, Patel B, Chatriwala M. Serum magnesium and Vitamin D levels as indicators of asthma severity. Pulm Med 2016;2016:1643717.
11. Agarwal R, Dhooria S, Aggarwal AN, Maturu VN, Sehgal IS, Muthu V, *et al.* Guidelines for diagnosis and management of bronchial asthma: Joint ICS/NCCP (I) recommendations. Lung India 2015;32:S3-42.
12. Aranow C. Vitamin D and the immune system. J Investig Med 2011;59:881-6.
13. Vittal BG. A study of magnesium and other serum electrolyte levels during nebulized salbutamol therapy. J Clin Diagn 2010;4:3460-4.
14. Chhabra P, Sharma G, Kannan AT. Prevalence of respiratory disease and associated factors in an urban area of delhi. Indian J Community Med. 2008;33:229-32. doi:10.4103/0970-0218.43227.
15. Youssef MF. Magnesium status and therapeutic effects in asthmatic children. EC Paediatr 2018;73:194-203.
16. Kakish KS. Serum magnesium levels in asthmatic children during and between exacerbations. Arch Pediatr Adolesc Med 2001;155:181-3.

Original Article

Diagnostic accuracy of microalbuminuria among sickle cell children with nephropathy

Sitanshu Kumar Meher, Nihar Ranjan Mishra, Deepak Kumar Khamari, Bijan Kumar Nayak

Department of Pediatrics, Veer Surendra Sai Institute of Medical Sciences and Research, Sambalpur, Odisha, India

Abstract

Objective: The aim of this study is to detect the diagnostic accuracy of microalbuminuria (MA) among sickle cell children with nephropathy.

Materials and Methods: Five hundred and seven sickle cell homozygous children between 5 and 14 years of age group were enrolled after receiving written informed consent from the parents and/or caregiver. Children with preexisting kidney diseases, albuminuria, and taking any drugs that will affect renal function were excluded from the study. Sickle cell nephropathy (SCN) was diagnosed by using the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines.

Study Design: The study design involves diagnostic study Phase I.

Statistical Analysis: Descriptive statistics were done using SPSS version 25.0 (IBM, NY, USA), and diagnostic statistics such as receiver operating characteristic curve (ROC) and others were done by Dxt version 1.0 software (BRTC, Vellore, India).

Results: Of 507 patients, 268 (52.8%) were male and 239 (47.1%) were female. The mean age of the study population was 9.42 ± 2.56 years. Cutoff value of MA was ≥47 mg/day (sensitivity [Sn]: 73.9%, specificity [Sp]: 90.5% and area under curve was 0.841 [0.56, 0.91] with $P = 0.001$). Sn of MA was 76.1% (61.1%, 80.7%), Sp: 90.9% (87.8%, 93.5%), positive predictive value: 62.4% (52.2%, 71.8%), negative predictive value: 93.8% (91%–96%), likelihood ratio positive (LR+): 7.894 (5.672, 10.986), likelihood ratio negative (LR-): 0.312 (0.224, 0.436), odds ratio: 25.266 (14.277, 44.713) with diagnostic accuracy of 83.62%.

Conclusions: MA can be used as a good screening tool for early detection of SCN. However, larger studies with a good level of evidence are awaited.

Keywords: Children, microalbuminuria, receiver operating characteristic curve, sickle cell nephropathy

Address for correspondence: Dr. Nihar Ranjan Mishra, Department of Pediatrics, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India.
E-mail: drnihar.mishra@gmail.com

INTRODUCTION

Sickle cell disease (SCD) is one of the most frequent genetic disorders in the world. It predominantly affects people of African descent as well as individuals from the Middle East, India, and Mediterranean regions. Recent estimates report about 305,800 babies with SCD are born every year in the world, and over two-thirds are in sub-Saharan Africa rising to over 404,200 by 2050.[1,2] The most common and severe form of SCD is sickle

Received: 21-01-2020 **Revised:** 02-03-2020
Accepted: 09-03-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_2_20

How to cite this article: Meher SK, Mishra NR, Khamari DK, Nayak BK. Diagnostic accuracy of microalbuminuria among sickle cell children with nephropathy. J Pediatr Crit Care 2020;7:73-8.

cell anemia (SCA), which is caused by the homozygous inheritance of the sickle gene.[3,4]

The chronic manifestations of recurrent end-organ damage, such as sickle cell nephropathy (SCN), have become a significant issue as comprehensive care and effective treatments have significantly improved survival.[5,6] Nephropathy is a serious complication of SCD that begins in childhood and may progress to overt renal failure.[6] Renal involvement is one of the major factors of early death in sickle cell populations.[6,7] Previous studies reported that renal complications occur in 5%–18% of sickle cell children and adolescents and >9% of deaths in young adults were due to complications related to kidney diseases.[7-9] End-stage renal disease (ESRD) develops in 4.2%–11.6% of cases with homozygous sickle cell disease (HbSS) and is an independent predictor of premature mortality in young adults.[6,7]

Urine microalbumin has been identified as an early marker of glomerular dysfunction long before glomerular filtration rate (GFR) declines, which is usually asymptomatic and appears to be associated with more rapid decline in renal function.[8] Urine microalbumin, which occurs in the subclinical phase of SCN, appears in the first decade of life and precedes the appearance of massive and persistent proteinuria.[8] Till now, no such studies were done on the diagnostic accuracy of urine microalbumin for early detection of nephropathy among sickle cell children.

MATERIALS AND METHODS

This is an observational cross-sectional analytical diagnostic study (Diagnostic Study Phase I), conducted in the in-patient Department of Pediatrics in an 1100-bedded tertiary care teaching hospital of Western Odisha, from November 2017 to October 2019. All the high-performance liquid chromatography/hemoglobin (Hb) Electrophoresis confirmed cases of sickle cell homozygous children of either gender between the age group of 5 and 14 years were included in the study. Children with preexisting renal diseases such as congenital renal anomalies, nephrotic/nephritic syndrome, those with previously diagnosed cases with diabetes mellitus or hypertension, those with albuminuria in urine routine test and cases on regular angiotensin converting enzymes inhibitors therapy for >1 month were excluded from the study. Estimation of sample size was done based on the diagnostic test-confidence interval (CI) estimating sensitivity (Sn) of a new test-absolute precision method (n Master Version 2.0, Biostatistics Resource and Training Centre, Vellore). As per the rule of assumption, we have taken 50% Sn of urine microalbumin to detect nephropathy in sickle cell homozygous children as there is no previous study. Taking CI to be 95% and absolute precision of 5%, the minimum sample size was calculated to be 507 after adjusting for correction factor and attrition. Of 2563 SCA patients admitted to in-patients department of Pediatrics during the study period, 2131 sickled children were included as per the predefined inclusion and exclusion criteria. From this study pool, 532 cases were selected by systematic random sampling with sampling interval of 4. Of these, 25 cases did not give consent to participate in the study; hence, 507 cases were enrolled in the study [Figure 1].

Urine microalbumin was estimated by human micro-albuminuria (MA) detection kit (Nephlometry) with the trade name of mALB (YZB/Guangdong-0053–2013, Genrui Biotech Inc., China). Parents/caregiver of enrolled children were provided with a properly labeled universal bottle for the collection of early morning mid-stream urine samples and another bigger container for 24 h urine collection (from 7:00 a.m. to next day 7:00 a.m.) of their child. When tests could not be performed within the 1st h of urine collection, urine was stored in the refrigerator (at 2°C–8°C) and tested within 2 h of storage in the refrigerator. Refrigerated urine was kept at room temperature for 15 min before tests were performed. Measured spot urine microalbumin value was then converted to 24 h urine microalbumin value by taking into account the 24 h urine output. GFR was estimated using modified Schwartz's formula.[10] Serum creatinine estimation was done using autoanalyzer (Roche Hitachi Cobas C 311, USA). Body mass index (kg/m^2) was computed using weight (in kilogram) divided by height (in meters squared). Hb level was estimated by using Sahli's hemoglobinometer from fingertip blood sample. The resting systolic blood pressure (SBP) measurement was obtained from the right upper arm with an age-appropriate blood pressure cuff size for children. Clinical events such as no of hospitalizations, number of frequent vaso-occlusive crisis (fVOC), number of units of blood transfusion, and the duration of hydroxyurea therapy in months were taken from the medical record. Urine albumin level between 30 and 300 mg/day was taken as MA.[11] estimated GFR value <60 ml/min/1.73 m^2 was taken as having nephropathy.[12] fVOC was defined as ≥3 episodes of VOC in the past 1 year.[13,14] Systolic hypertension was defined as SBP >95th percentile for age and sex.[15]

All the relevant data were recorded in a predesigned case report format. Data validation was done manually by two separate persons not involved in the study. Continuous data were expressed in mean ± standard deviation;

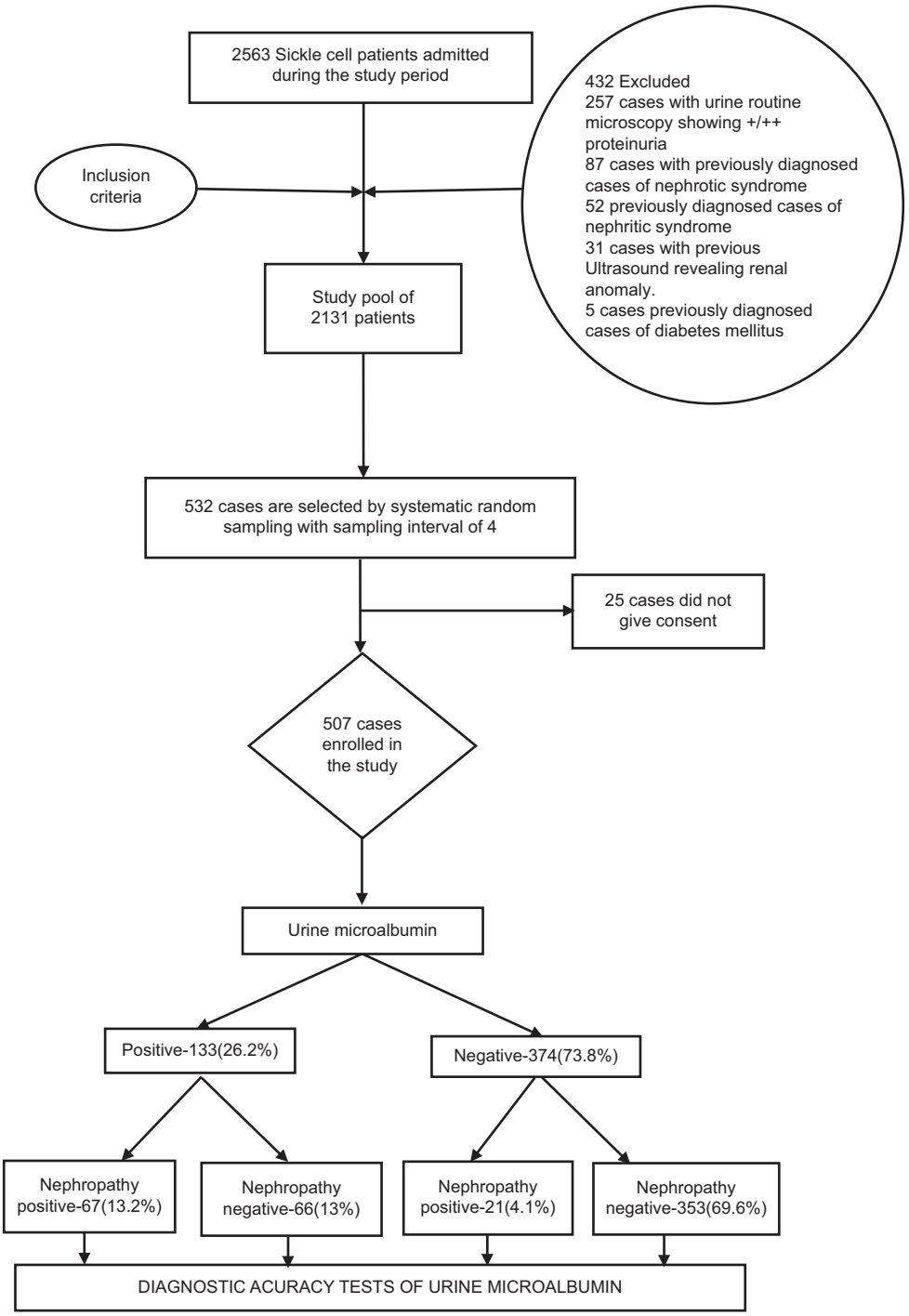


Figure 1: Flow chart

categorical data were expressed in proportions. Data normalcy testing of continuous data was done using Shapiro–Wilk test, and no transformation was required. All the descriptive statistics were done by SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N. Y., USA), and all the diagnostic accuracy tests were done by Dxt Software for Windows, version 1.0 (Biostatistics Resource and Training Centre, Vellore). For all statistical purposes, $P < 0.05$ was considered statistically significant. Youden index J > 0.5 was considered acceptable for diagnostic accuracy tests.

RESULTS

A total of 507 subjects made up the study group. Of these, males were 268 (52.8%) and 239 (47.1%) were female, with being a male:female ratio of 1.12:1. Table 1 shows the baseline characteristics of the study participants.

Fifty-seven (11.2%) had prehypertension. 253 (49.9%) were with the history of fVOC. One hundred and thirty-three (26.2%) out of 507 were tested positive for MA. Out of 133 cases with MA, 76 (57.1%) were male and 57 (42.9%) were female, 22 (16.9%) had prehypertension, 78 (58.6%) had history of fVOC.

Eighty-eight (17.4%) were identified of having nephropathy, of which 67 (76.1%) were MA positive and 21 (23.9%) were MA negative. From those sickle cell children with nephropathy (88), 47 (53.4%) were male and 41 (46.6%) were female, 14 (15.9%) had prehypertension, 81 (92%) were with history of fVOC.

The level of MA (mg/day) was analyzed in response to the presence of nephropathy using receiver operating characteristic curve [Figure 2]. Cutoff value of urine microalbumin (urine micral) was estimated to be 47 mg/day with Sn of 73.9% and specificity of 90.5%, $LR^+ = 7.737$, $LR^- = 0.289$ and Youden index J = 0.643, with area under curve = 84.1% (75.4%, 90.6%). Applying this above cutoff value for urine micral in our study participants, various diagnostic parameters of urine micral are summarized in Table 2. The overall diagnostic accuracy of urine micral with cutoff value of ≥47 mg/day for detecting nephropathy was found to be 83.62%.

DISCUSSION

The present study was conducted in the Department of Pediatrics, VIMSAR, Burla, situated in the Western part of Odisha where the prevalence of SCD is very high. The prevalence of MA and nephropathy was found to be 26.2% and 17.4%, respectively, in our study.

As per the diagnostic test used in our study, the cutoff value for urine microalbumin to detect nephropathy was estimated to be ≥47 mg/day. With this cutoff value, urine micral will identify approximately 74% of homozygous sickle cell children those who are with nephropathy. Likewise, urine micral will identify approximately 90.5% of homozygous sickle cell children those who do not have nephropathy. Furthermore, probability of homozygous sickle children who have positive urine micral and actually having nephropathy is 50.3% and also the probability of homozygous sickle child with negative urine micral test and actually do not have nephropathy is 94%.

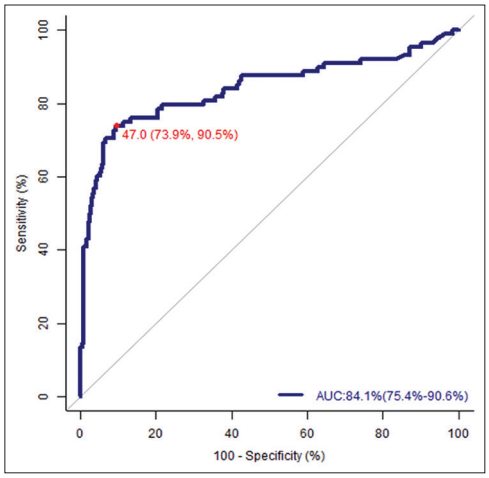


Figure 2: Receiver operating characteristic curve

Urine micral level ≥47 mg/day, the probability of nephropathy among sickle cell children increases by eight folds and <47 mg/day the probability of detecting nephropathy in sickle cell children decreases by 1/3rd. Hence, overall diagnostic accuracy of MA in detecting MA came to be 83.26%.

Similar results, in terms of the prevalence of MA, have been reported in several studies worldwide with frequencies ranging from 18% to 23%.[16-28] Furthermore, the proportion of MA in sickle cell children >10 years of age was 55.6%. Our findings corroborate those of a previous study, which reported 62% of MA among children >10 years of age in the USA.[23] The prevalence of nephropathy in our study is 17.4%, which in accordance with previous studies.

Table 1: Baseline characteristics of the study participants

Variables	Mean±SD
Age (years)	9.42±2.56
Height (cm)	122.94±13.21
Weight (kg)	21.37±5.38
BMI (kg/m^2)	14±1.85
SBP (mmHg)	96±7
Haemoglobin (g/dl)	7.77±1.68
Number of previous hospitalisation	6±5
Number of previous blood transfusion	4±4
Duration of hydroxy-urea treatment in months	77.19±32.62
Serum creatinine (mg/dl)	0.63±0.18
Microalbuminuria level (mg/day)	36.37±49.52
eGFR (ml/min/1.73 m^2)	86.66±22.26

BMI: Body mass index, SBP: Systolic blood pressure, eGFR: Estimated glomerular filtration rate, SD: Standard deviation

Table 2: Diagnostic parameters of urine microalbumin in detecting nephropathy

Diagnostic parameters	Value	95% CI
True prevalence	17.4	14.2-20.9
Sensitivity	71.6	61-80.7
Specificity	90.9	87.8-93.5
PPV	62.4	52.2-71.8
NPV	93.8	91-96
Positive likelihood ratio	7.894	5.672-10.986
Negative likelihood ratio	0.312	0.224-0.436
Odds ratio	25.266	14.277-44.713
Youden index	62.5	48.7-74.2

CI: Confidence interval, NPV: Negative predictive value, PPV: Positive predictive value

McKie *et al.* found abnormal albuminuria in 19.4% of 191 children with homozygous sickle cell disease (HbSS) and observed a significant association of albuminuria with age and lower baseline Hb.[19] Alvarez *et al.* demonstrated abnormal albuminuria in 16.8% of HbSS children.[20] In a smaller pediatric cohort, Becton *et al.* found abnormal albuminuria in 19.7% of children with HbSS.[27] In our study, we found that MA and nephropathy in sickle cell children are significantly associated.

The study provides insight into the relationship between MA and SCA. The study is easy and economical to conduct. It has provided us important information on the distribution and burden of nephropathy among sickle cell children admitted to our institute. In addition to that, we have found urine micral test as a valuable screening procedure for early detection of nephropathy among sickle cell children to prevent the progression to ESRD in future.

The present study has some limitations such as cross-sectional study design, use of "estimated GFR" using Schwartz formula, instead "measured GFR" would have been the ideal method, but could not be done because of the cost issue. Furthermore, it would have been ideal if GFR value was followed up across 3 months to identify nephropathy. The study has limited value for the etiological relationship between urine micral and nephropathy among sickle cell children. Furthermore, selection bias, lead-time bias, diagnosis bias, could not be prevented so far as the study design is concerned. We conducted the study with one-morning urine microalbumin level, but repeated samples of urine would have increased the strength of our study. Those cases found to have nephropathy should have been followed for the progression of nephropathy.

CONCLUSIONS

Urine micral can be used as a good screening tool for early detection of nephropathy among sickle cell children. As our study is a first of its kind, basing on the above strength and limitations better study design with multicentric approach is very much awaited for a better level of evidence. We recommend further prospective studies to be conducted to evaluate the causal relationship between SCN and urine micral for the early detection of albuminuria and timely administration of treatments to prevent progression to renal dysfunction and ESRD.

Acknowledgment

We are thankful to our Head of the Department, Colleagues who have continuously encouraged us and at last but not least, the patients without whom this study would not have been possible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, *et al.* Global epidemiology of sickle haemoglobin in neonates: A contemporary geostatistical model-based map and population estimates. Lancet 2013;381:142-51.
2. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010;376:2018-31.
3. Williams TN, Thein SL. Sickle cell anemia and its phenotypes. Annu Rev Genomics Hum Genet 2018;19:113-47.
4. Demirci S, Uchida N, Tisdale JF. Gene therapy for sickle cell disease: An update. Cytotherapy 2018;20:899-910.
5. Lanzkron S, Carroll CP, Haywood C Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public Health Rep 2013;128:110-6.
6. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: A 4-decade observational study of 1056 patients. Medicine (Baltimore) 2005;84:363-76.
7. Powars DR, Elliott-Mills DD, Chan L, Niland J, Hiti AL, Opas LM, *et al.* Chronic renal failure in sickle cell disease: Risk factors, clinical course, and mortality. Ann Intern Med 1991;115:614-20.
8. Scheinman JI. Sickle cell disease and the kidney. Nat Clin Pract Nephrol 2009;5:78-88.
9. Guasch A, Navarrete J, Nass K, Zayas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: Prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol 2006;17:2228-35.
10. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, *et al.* New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-37.
11. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1:1430-2.
12. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.
13. Darbari DS, Onyekwere O, Nouraie M, Minniti CP, Luchtman-Jones L, Rana S, *et al.* Markers of severe vaso-occlusive painful episode frequency in children and adolescents with sickle cell anemia. J Pediatr 2012;160:286-90.
14. Nebor D, Bowers A, Hardy-Dessources MD, Knight-Madden J, Romana M, Reid H, *et al.* Frequency of pain crises in sickle cell anemia and its relationship with the sympatho-vagal balance, blood viscosity and inflammation. Haematologica 2011;96:1589-94.
15. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, *et al.* clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140:e20171904.
16. Datta V, Ayengar JR, Karpate S, Chaturvedi P. Microalbuminuria as a predictor of early glomerular injury in children with sickle cell disease. Indian J Pediatr 2003;70:307-9.
17. Dharnidharka VR, Dabbagh S, Atiyeh B, Simpson P, Sarnaik S. Prevalence of microalbuminuria in children with sickle cell disease. Pediatr Nephrol 1998;12:475-8.
18. McBurney PG, Hanevold CD, Hernandez CM, Waller JL, McKie KM. Risk factors for microalbuminuria in children with sickle cell anemia. J Pediatr Hematol Oncol 2002;24:473-7.
19. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. J Pediatr Hematol Oncol

2007;29:140-4.
20. Alvarez O, Montane B, Lopez G, Wilkinson J, Miller T. Early blood transfusions protect against microalbuminuria in children with sickle cell disease. Pediatr Blood Cancer 2006;47:71-6.
21. Imuetinyan BA, Okoeguale MI, Egberue GO. Microalbuminuria in children with sickle cell anemia. Saudi J Kidney Dis Transpl 2011;22:733-8.
22. Mawanda M, Ssenkusu JM, Odiit A, Kiguli S, Muyingo A, Ndugwa C. Micro-albuminuria in Ugandan children with sickle cell anaemia: A cross-sectional study. Ann Trop Paediatr 2011;31:115-21.
23. Marsenic O, Couloures KG, Wiley JM. Proteinuria in children with sickle cell disease. Nephrol Dial Transplant 2008;23:715-20.
24. Wigfall DR, Ware RE, Burchinal MR, Kinney TR, Foreman JW. Prevalence and clinical correlates of glomerulopathy in children with sickle cell disease. J Pediatr 2000;136:749-53.
25. Bayazit AK, Noyan A, Aldudak B, Ozel A, Anarat A, Kilinç Y, *et al*. Renal function in children with sickle cell anemia. Clin Nephrol 2002;57:127-30.
26. King L, MooSang M, Miller M, Reid M. Prevalence and predictors of microalbuminuria in Jamaican children with sickle cell disease. Arch Dis Child 2011;96:1135-9.
27. Becton LJ, Kalpatthi RV, Rackoff E, Disco D, Orak JK, Jackson SM, *et al*. Prevalence and clinical correlates of microalbuminuria in children with sickle cell disease. Pediatr Nephrol 2010;25:1505-11.
28. Ranque B, Menet A, Diop IB, Thiam MM, Diallo D, Diop S, *et al*. Early renal damage in patients with sickle cell disease in sub-Saharan Africa: A multinational, prospective, cross-sectional study. Lancet Haematol 2014;1:e64-73.

Original Article

Risk factors for bronchiolitis

Preeti Kulhalli, Dakshayini J. N., Vinod H. Ratageri, I. Shivanand, Prakash K. Wari

Department of Pediatrics, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India

Abstract

Background: Bronchiolitis is a common acute respiratory illness with significant morbidity and mortality in children aged <2 years. Many risk factors have been proposed though none conclusively proven.

Objective: The objective of the study is to determine the risk factors for bronchiolitis in children aged <24 months.

Methodology: This was a retrospective study conducted at Karnataka Institute of Medical Sciences, Hubli, from July to September 2018 on children aged <24 months, with clinically diagnosed bronchiolitis considered as cases and age-matched children admitted during the same period for nonrespiratory causes as controls.

Results: Totally, 85 children and 91 controls were included in the study with a mean age at presentation being 5.5 months (interquartile range = 2–8 months) and male-to-female ratio of 1.42:1. The most common symptoms were cough (98.8%), fever (84.7%), cold (64.7%), hurried breathing (58.8%), chest indrawing (42.2%), and noisy breathing (35.3%). On univariate analysis, low socioeconomic status (SES), overcrowding, unimmunized status, exposure to pets, and birth by cesarean section (CS) were significant risk factors. On applying multiple logistic regression (odds ratio, 95% confidence interval), low SES, unimmunized status, exposure to pets, and birth by CS were found to be significant.

Conclusion: Low SES, partial/unimmunized status, exposure to pets, and birth by CS were deduced to be important significant risk factors for bronchiolitis.

Keywords: Bronchiolitis, infants, pets, risk factors, socioeconomic

Address for correspondence: Dr. Vinod H. Ratageri, Department of Pediatrics, Karnataka Institute of Medical Sciences, Hubli - 580 021, Karnataka, India.
E-mail: ratageri@rediffmail.com

INTRODUCTION

Bronchiolitis is an acute respiratory illness of importance that affects infants and young children and is one of the most common clinical conditions treated by practicing pediatricians worldwide. Children typically aged <2 years are affected.[1] Occurrence peaks in winter and rainy seasons. The incidence of bronchiolitis is estimated to range from 265/1000 infants to 16.4/100 children.[2] Mortality rate is approximately 2/100,000 infants and is higher in developing than developed countries.[3]

A number of risk factors and clinical findings have been proposed to predict the severity of disease in children with bronchiolitis. Host-related factors such as prematurity, low birth weight (LBW), age <6–12 weeks, chronic pulmonary disease, hemodynamically significant congenital heart disease, and immunodeficiency have been implicated.[4] Malnutrition, nonimmunization, and nonbreastfeeding were some significant risk factors for severe bronchiolitis. The other risk factors deduced in other studies include

Received: 02-02-2020 **Revised:** 28-02-2020
Accepted: 08-03-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_23_20

How to cite this article: Kulhalli P, Dakshayini JN, Ratageri VH, Shivanand I, Wari PK. Risk factors for bronchiolitis. J Pediatr Crit Care 2020;7:79-83.

socioeconomic factors such as parental illiteracy, low SES, overcrowding, prelacteal feeds, and early weaning.[5] Environmental factors such as presence of older sibling and passive smoke exposure have been implicated.

However, there is a paucity of literature on risk factors for the development of bronchiolitis, in the Indian context, and hence, the present study was undertaken.

Aim

The aim of the study is to determine risk factors for bronchiolitis in children aged <24 months.

METHODOLOGY

Study design

This was a retrospective study in children admitted to the Pediatrics Department, Karnataka Institute of Medical Sciences, Hubli, from July 2018 to September 2018, who satisfy the inclusion criteria.

Inclusion criteria

All children aged <24 months with clinically diagnosed bronchiolitis were enrolled in the study.[6] Children admitted during this period for nonrespiratory pathology who were <24 months old, with no prior history of bronchiolitis, were considered as controls.

Exclusion criteria

1. Confirmed bronchopneumonia
2. Children with chronic illness (cardiac, pulmonary, neurologic, chromosomal, or craniofacial comorbidities)
3. Previously diagnosed with asthma.

The study was approved by the institutional ethical committee.

Demographic and risk factor data collected

The medical records of children included in this study were reviewed, and the information was collected in a predesigned Proforma.

The following demographic data were recorded: age in months, sex, delivery by normal or cesarean section (CS), premature birth (gestational age <37 weeks), and LBW (<2500 g); immunization status was categorized into two groups: group 1 "fully/completely immunized" and group 2 partial/unimmunized. Fully immunized defined as a receipt of six vaccines by 12 months of age as per the National Institute of Health and Family Welfare guidelines.[7] Socioeconomic class defined as per the Modified Kuppuswamy scale 2017;[8] malnutrition defined by the WHO for severe and moderate acute malnutrition as (I) weight for height/length <−3Z score and −2 to −3Z, respectively; (II) presence of visible severe wasting; (III) nutritional edema; (IV) mid-upper arm circumference of <115 mm, family history of asthma, allergies, history of bottle feeding, overcrowding,[9] and coexistence with pets.

Statistical analysis

The data were analyzed using R software version 3.1 (R Foundation for Statistical Computing, Vienna, Austria); a $P \leq 0.05$ was accepted statistically significant. Simple associations were compared with Chi-square test as appropriate. Odds ratios with 95% confidence interval (CI) were calculated by risk assessment of Chi-square analysis, and logistic regression by the entry method was performed using variables found to be statistically different between two groups.

RESULTS

Totally, 85 children aged <24 months and 91 controls were included in the study. Figure 1 shows the flowchart of selection of cases.

The mean age at presentation was 5.5 months (median - 5 months; interquartile range - 2–8 months). The male-to-female ratio 1.42:1, with a male preponderance of 58.8% ($n = 50$) in the study group and 1.02:1 ($n = 46$) in the control group. Age at presentation in the order of frequency was <6 months ($n = 57$, 67.05%), 7–12 months ($n = 25$, 29.41%), and 13–24 months ($n = 3$, 3.5%), with P value being significant for under 6 months of age. Details are summarized in Table 1.

The common clinical symptoms in the order of frequency were as follows: cough ($n = 84$, 98.8%), fever ($n = 72$, 84.7%), cold ($n = 55$, 64.7%), hurried breathing ($n = 50$, 58.8%), chest

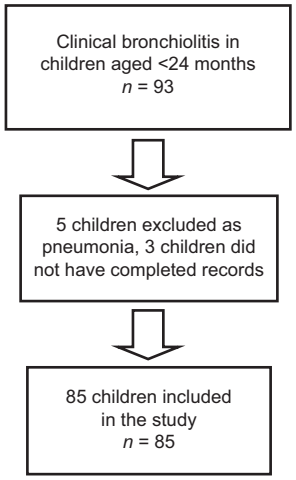


Figure 1: Selection of cases for the study

indrawing (n = 36, 42.4%), and noisy breathing (n = 30, 35.3%). However, stridor was not observed in any case. On examination, rhonchi in n = 54, 63.5%, and crepitations in n = 52, 61.2%, were also noted. Bilateral hyperinflation on the chest X-ray was seen in n = 77, 90.6%.

Table 2 shows the risk factors for bronchiolitis. Low SES, overcrowding, incomplete immunization, exposure to pets, and birth by CS were the significant risk factors. However, preterm birth, LBW, maternal allergy, atopy, maternal diabetes/hypertension, malnutrition, family history of asthma, and bottle feeding showed no significant association as risk factors.

After application of multiple logistic regression analysis [Table 3] with the application of odds ratio with 95% CI, the results showed significance for lower SES, birth by lower segment CS, exposure to pets, and partial/incomplete immunization only.

DISCUSSION

Bronchiolitis is a common respiratory illness in pediatrics that causes acute inflammation, edema, necrosis of epithelial cells, increased mucus production, and inadequate oxygenation and could be potentially life-threatening.

This study aimed at assessing the risk factors for acute bronchiolitis. There was male preponderance identified in the study. As evidenced by literature, there is a greater incidence of bronchiolitis in boys.[5] The study by Bakalovic *et al*.[10] at Sarajevo University also stated the higher percentage of hospitalized male infants. This could be attributable to increased sensitivity of males to aeroallergens.[11]

The median age at presentation was 5 months. Similar to this, others have found a significant association between the age of <6 months and a higher risk of hospitalization and severe bronchiolitis.[4,12] This is probably secondary to reduced immunity in early infancy toward viral infections.

In this study, of 13 risk factors initially considered, five risk factors namely low SES, overcrowding, exposure to pets, birth by CS, and incomplete immunization showed significance on univariate analysis. However, on application of multiple logistic regression analysis, four risk factors, such as low SES, birth by CS, exposure to pets, and incomplete immunization, showed significance.

Table 1: Comparison of sex and age of presentations between cases and controls

	Cases	Controls	*P*
Male:female ratio	50:35	46:45	0.270 (NS)
Mean age of presentation (months)			
<6	57	19	0.025 (S)
7-12	25	23	0.538 (NS)
13-24	03	49	0.512 (NS)

S: Significant, NS: Not significant

Low SES was found as significant risk factor for bronchiolitis, similar to the study done by Díez Domingo *et al*.[13] Higher incidence of hospital admission due to respiratory infection in poor was found in study by Jansson *et al*.[14] The possible explanations could be that children from low SES are more vulnerable to air pollution, infection, nutritional deficiency, and numerous environmental hazards and possibly because disadvantaged mothers have less access to healthcare services.[15,16] In a large-scale study done by Alvarez *et al*.[17] in Brazil, low SES was found as a major risk factor along with birth by CS.

Birth by CS was identified as a second major risk factor. Similar results were obtained by a study done at Denmark, where increased incidence of bronchiolitis and respiratory syncytial virus (RSV) infection was seen in CS born children aged <2 years.[18] Shang *et al*.[19] found almost double the incidence of bronchiolitis in children born by CS. The same findings were however refuted by Achten *et al*.[20] in 2015 and Hendaus *et al*.,[21] where no enhanced incidence was found. The possible analogy could be that CS or delivery without preceding labor may result in impaired immunity in newborn, leading to increased risk of early viral lower respiratory tract infections.[22]

Another significant variable in this study was exposure to pets in the house. However, studies have shown protection of exposed infants from bronchiolitis.[23] Others have reported that contact with pets either increases the risk or induces sensitization or protects against them or has no association at all.[24] Exposure to pets was implicated as risk factor in the study done by Malla *et al*.[25] in Nepal. Incidence was statistically higher in those exposed to pets as in the study by Nenna *et al*.[26] similar to the current study. Even with this, it is ridden with controversy regarding the correlation of pet exposure to bronchiolitis and hence needs more validation in the future studies.

RSV and influenza virus have been implicated as major pathogens in causation of bronchiolitis and targeting them has been stressed.[27] However, vaccination for them was not given in the present study group due to constraints. This, in addition to lack of cross-protection in these incompletely immunized patients, probably explains the enhanced incidence and its role as a major risk factor. In a study done by Das *et al*.,[28] similar results of nonvaccinated

Table 2: Risk factors for bronchiolitis (*n*=85) - univariate analysis

	Case	Control	Total	Chi-square test
Gender				
Male	50 (58.8)	46 (50.5)	96 (54.5)	χ^2=1.214, *P*=0.271
Female	35 (41.2)	45 (49.5)	80 (45.5)	
Total	85 (100)	91 (100)	176 (100)	
Fever				
Yes	72 (84.7)	21 (23.1)	93 (52.8)	χ^2=66.986, *P*<0.005
No	13 (15.3)	70 (76.9)	83 (47.2)	
Total	85 (100)	91 (100)	176 (100)	
Preterm birth				
Yes	8 (9.4)	7 (7.7)	15 (8.5)	χ^2=0.167, *P*=0.683
No	77 (90.6)	84 (92.3)	161 (91.5)	
Total	85 (100)	91 (100)	176 (100)	
LBW				
Yes	15 (17.6)	12 (13.2)	27 (15.3)	χ^2=0.673, *P*=0.412
No	70 (82.4)	79 (86.8)	149 (84.7)	
Total	85 (100)	91 (100)	176 (100)	
Low SES				
Yes	32 (37.6)	62 (68.1)	94 (53.4)	χ^2=16.413, *P*<0.005
No	53 (62.4)	29 (31.9)	82 (46.6)	
Total	85 (100)	91 (100)	176 (100)	
Maternal allergy/asthma/smoking				
Yes	7 (8.2)	4 (4.4)	11 (6.2)	χ^2=1.105, *P*=0.292
No	78 (91.7)	87 (95.6)	165 (93.7)	
Total	85 (100)	91 (100)	176 (100)	
Maternal DM/HTN				
Yes	4 (4.7)	2 (2.2)	6 (3.4)	χ^2=0.839, *P*=0.359
No	81 (95.2)	89 (97.8)	170 (96.5)	
Total	85 (100)	91 (100)	176 (100)	
Overcrowding				
Yes	12 (14.1)	25 (27.5)	37 (21)	χ^2=4.721, *P*=0.03
No	73 (85.9)	66 (72.5)	139 (79)	
Total	85 (100)	91 (100)	176 (100)	
Partial/incomplete immunization				
Yes	18 (21.2)	5 (5.5)	23 (13.1)	χ^2=9.514, *P*=0.002
No	67 (78.8)	86 (94.5)	153 (86.9)	
Total	85 (100)	91 (100)	176 (100)	
Exposure to pets				
Yes	19 (22.3)	8 (8.8)	27 (15.3)	χ^2=6.223, *P*=0.0126
No	66 (77.6)	83 (91.2)	149 (84.6)	
Total	85 (100)	91 (100)	176 (100)	
SAM				
Yes	9 (10.6)	7 (7.7)	16 (9.1)	χ^2=0.446, *P*=0.504
No	76 (89.4)	84 (92.3)	160 (90.9)	
Total	85 (100)	91 (100)	176 (100)	
Family history of asthma				
Yes	3 (3.5)	1 (1.1)	4 (2.2)	χ^2=1.168, *P*=0.279
No	82 (96.4)	90 (98.9)	172 (97.7)	
Total	85 (100)	91 (100)	176 (100)	
LSCS				
Yes	21 (24.7)	12 (13.2)	33 (18.8)	χ^2=3.828, *P*=0.05
No	64 (75.3)	79 (86.8)	143 (81.3)	
Total	85 (100)	91 (100)	176 (100)	
Bottle feeding				
Yes	5 (5.9)	1 (1.1)	6 (3.4)	χ^2=3.054, *P*=0.081 (Exact=0.108)
No	80 (94.1)	90 (98.9)	170 (96.6)	
Total	85 (100)	91 (100)	176 (100)	

SES: Socioeconomic status, HTN: Hypertension, DM: Diabetes mellitus, LBW: Low birth weight, SAM: Severe acute malnutrition, LSCS: Lower-segment cesarean section

children having increased incidence of bronchiolitis in 55.55% of patients were seen.

The pros of this study were the inclusion of several modifiable risk factors and descriptive cases and controls; however, the limitation was, as it was a retrospective study and hence we did not have satisfactory access to variables being collected from control group.

We identified several risk factors for acute bronchiolitis such as low SES, partial/incomplete immunization, exposure to pets, and unindicated births by CS. This

Table 3: Multiple logistic regression analysis for risk factors for bronchiolitis

	B	SE	OR (95% CI)	*P*
Low SES	−1.323	0.359	0.266 (0.132-0.538)	<0.005
Overcrowding	−0.643	0.463	0.526 (0.212-1.304)	0.165
Partial/nonimmunization	2.102	0.595	8.184 (2.548-26.28)	<0.005
Birth by CS	1.005	0.446	2.733 (1.141-6.544)	0.024
Exposure to pets	1.002	0.441	2.613 (0.842-7.321)	0.019

SE: Standard error, OR: Odds ratio, CI: Confidence interval, CS: Cesarean section, SES: Socioeconomic status

information would help public health authorities draw up effective preventive measures for bronchiolitis. Early identification and prevention of the same may help reduce the overall incidence. Due to dearth of studies on risk factors of bronchiolitis, this study explores novel factors to be considered for future research.

CONCLUSION

Low SES, incomplete immunization, exposure to pets, and birth by CS were deduced to be the important significant risk factors for bronchiolitis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr 2003;143:S112-7.
2. Muñoz-Quiles C, López-Lacort M, Úbeda-Sansano I, Alemán-Sánchez S, Pérez-Vilar S, Puig-Barberà J, *et al*. Population-based analysis of bronchiolitis epidemiology in Valencia, Spain. Pediatr Infect Dis J 2016;35:275-80.
3. Holman RC, Shay DK, Curns AT, Lingappa JR, Anderson LJ. Risk factors for bronchiolitis-associated deaths among infants in the United States. Pediatr Infect Dis J 2003;22:483-90.
4. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, *et al*. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360:588-98.
5. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr 2003;143:S118-26.
6. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. Pediatr 2006;118:1774-93.
7. Immunization Handbook for Medical Officers. Department of Health and Family Welfare, Government of India; 2008. Available from: http//www.mohfw.nic.in. [Last accessed on 2019 Nov 21].
8. Singh T, Sharma S, Nagesh S. Socio-economic status scales updated for 2017. Int J Res Med Sci 2017;5:3264-7.
9. World Health Organization. Household crowding. In: Housing and Health Guidelines. Geneva: World Health Organization; 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535289/B. [Last accessed on 2019 Nov 21].
10. Bakalovic G, Dzinovic A, Baljic R, Dizdar S, Selimovic A. Epidemiological features of bronchiolitis in the Pediatric Clinic of Clinical Center of Sarajevo University. Mater Sociomed 2015;27:154-7.
11. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, *et al*. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004;114:1282-7.
12. Papenburg J, Hamelin MÈ, Ouhoummane N, Carbonneau J, Ouakki M, Raymond F, *et al*. Comparison of risk factors for human metapneumovirus and respiratory syncytial virus disease severity in young children. J Infect Dis 2012;206:178-89.
13. Díez Domingo J, Ridao López M, Ubeda Sansano I, Ballester Sanz A. Incidence and cost of hospitalizations for bronchiolitis and respiratory syncytial virus infections in the autonomous community of Valencia in Spain (2001 and 2002). An Pediatr (Barc) 2006;65:325-30.
14. Jansson L, Nilsson P, Olsson M. Socioeconomic environmental factors and hospitalization for acute bronchiolitis during infancy. Acta Paediatr 2002;91:335-8.
15. Leem JH, Kim HC, Lee JY, Sohn JR. Interaction between bronchiolitis diagnosed before 2 years of age and socio-economic status for bronchial hyperreactivity. Environ Health Toxicol 2011;26:e2011012.
16. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L, Brauer M. Descriptive epidemiology of bronchioloits in a population based cohort. Pediatr 2008;122:1196-203.
17. Alvarez AE, Marson FA, Bertuzzo CS, Arns CW, Ribeiro JD. Epidemiological and genetic characteristics associated with the severity of acute viral bronchiolitis by respiratory syncytial virus. J Pediatr (Rio J) 2013;89:531-43.
18. Kristensen K, Fisker N, Haerskjold A, Ravn H, Simões EA, Stensballe L. Caesarean section and hospitalization for respiratory syncytial virus infection: A population-based study. Pediatr Infect Dis J 2015;34:145-8.
19. Shang X, Liabsuetrakul T, Sangsupawanich P, Xia X, He P, Cao H. Elective cesarean delivery as a predisposing factor of respiratory syncytial virus bronchiolitis in children. J Med Assoc Thai 2014;97:827-34.
20. Achten NB, Wu P, Bont L, Blanken MO, Gebretsadik T, Chappell JD, *et al*. Interference between respiratory syncytial virus and human rhinovirus infection in infancy. J Infect Dis 2017;215:1102-6.
21. Hendaus MA, Alhammadi AH, Khalifa MS, Muneer E. Does cesarean section pose a risk of respiratory syncytial virus bronchiolitis in infants and children? Asian Pac J Trop Med 2014;7S1:S134-6.
22. Moore HC, de Klerk N, Holt P, Richmond PC, Lehmann D. Hospitalisation for bronchiolitis in infants is more common after elective caesarean delivery. Arch Dis Child 2012;97:410-4.
23. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A; NAC Manchester Asthma and Allergy Study Group. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: A randomised trial. Lancet 2001;358:188-93.
24. Dharmage SC, Lodge CL, Matheson MC, Campbell B, Lowe AJ. Exposure to cats: Update on risks for sensitization and allergic diseases. Curr Allergy Asthma Rep 2012;12:413-23.
25. Malla T, Poudyal P, Malla KK. Modifiable demographic factors that differentiate bronchiolitis from pneumonia in Nepalese children less than two years – A hospital based study. Kathmandu Univ Med J (KUMJ) 2014;12:175-80.
26. Nenna R, Cutrera R, Frassanito A, Alessandroni C, Nicolai A, Cangiano G, *et al*. Modifiable risk factors associated with bronchiolitis. Ther Adv Respir Dis 2017;11:393-401.
27. Behzadi MA, Leyva-Grado VH. Overview of current therapeutics and novel candidates against influenza, respiratory syncytial virus, and middle east respiratory syndrome coronavirus infections. Front Microbiol 2019;10:1327.
28. Das PK, Saha JB, Basu K, Lahiri S, Sarkar GN. Some clinic-epidemiological aspect of bronchiolitis among infants and young children – A hospital based study. Indian J Public Health 2003;47:66-71.

Case Report

Haberland syndrome: Encephalocraniocutaneous syndrome presenting as status epilepticus

V. S. V. Prasad, Anzad Madathil Amanullah

Pediatric Intensive Care Unit, Lotus Hospitals for Women and Children, Hyderabad, Telangana, India

Abstract

We report a 5-year-old female child who presented with fever and status epilepticus with a history of global developmental delay, patchy alopecia over the frontal region, and bilateral dermolipoma in the conjunctiva and sclera. These findings are consistent with a diagnosis of encephalocraniocutaneous lipomatosis. This is a rare condition reported infrequently across the world. The child also had the specific neurological manifestations of this condition, specifically epilepsy presenting as status epilepticus.

Keywords: Encephalocraniocutaneous lipomatosis, haberland syndrome, status epilepticus

Address for correspondence: Dr. V. S. V. Prasad, #6-2-29, Lotus Hospitals for Women and Children, Lakdikapul, Hyderabad, Telangana, India.
E-mail: drvsvprasad@gmail.com

INTRODUCTION

Status epilepticus is a common diagnosis encountered in the pediatric intensive care unit (PICU). We report a rare etiology of status epilepticus, i.e., Haberland syndrome. Encephalocraniocutaneous lipomatosis is a rare neurocutaneous condition defined in 1970 by Haberland and Perou.[1] This condition mostly involves unilateral ectodermal and mesodermal tissues of the skin/scalp, eyes, and brain. Till date, around eighty cases have been reported, with some of them being in the pediatric age group. A few of these children are known to have brain atrophy with global developmental delay. A third of them are known to develop epilepsy warranting treatment. This condition is also known as Fishman syndrome.

Received: 06-02-2020 **Revised:** 25-02-2020
Accepted: 02-03-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_25_20

CASE REPORT

A 5-year-old Indian female child presented with a history of fever for 1 day, followed by multifocal convulsions lasting for around 10 min. She was admitted with a working diagnosis of status epilepticus. She was evaluated at a medical center and commenced on antiepileptic medications and referred to our hospital. On obtaining a detailed history, we found that this was her third episode of seizures. She had her first episode of seizure in the immediate neonatal period lasting for a few minutes, and she was admitted into the neonatal intensive care unit for a couple of days. She was noted to have a patch of alopecia in the frontal area of the scalp. She also had a bony swelling in the right temporomandibular area. There were also lesions involving the conjunctiva and sclera of both eyes. The second episode of seizure occurred around 3 years of age, presenting as status epilepticus, which was associated with fever. She was on antiepileptic medications since then, which were discontinued by the

How to cite this article: Prasad VS, Amanullah AM. Haberland syndrome: Encephalocraniocutaneous syndrome presenting as status epilepticus. J Pediatr Crit Care 2020;7:84-7.

parents after 2 months without proper medical advice. She was lost for follow-up for an extended length of time. At the time of this admission, she underwent investigations for a febrile illness, wherein she was diagnosed with acute dengue fever with warning signs. She was treated according to the standard PICU protocol for her dengue fever and status epilepticus.

Her developmental history had revealed a global developmental delay. She started walking at 3 years of age, with some weakness in the left lower limb causing her to limp. She underwent a magnetic resonance imaging scan previously at 1 year of age, which revealed an arachnoid cyst and bilateral cerebellopontineangle lipomas. There was also atrophy of the right cerebral hemisphere noted in this scan. A repeat computed tomography (CT) scan was performed before this admission to review any progression of the lesions. The CT scan revealed no change in any of her lesions in the brain. We would like to report the phenotype of this child and describe each of the specific features we observed. The first striking feature was the alopecic patch in the frontal scalp area [Figure 1]. This patch of skin is called nevus psiloliparus, which is a hairless fatty tissue nevus. The next striking feature was the lesions in her eyes. There were epibulbar choristoma and connective tissue nevus in the eye [Figure 2]. As mentioned, seizures are common in these children, and our patient had them as early as the neonatal period. Unfortunately, the parents chose to discontinue the treatment. During this admission, she had presented to us with a breakthrough seizure. She was also noted to have mild developmental delay with a developmental age of 3½ years with a chronological age of 5 years. The other external phenotype noted was the notable bony swelling in the right temporal bone, which was a calvarial exostosis. On neurological examination, she was found to have mild left-sided hemiparesis, especially involving the lower limbs with a subtle circumduction gait. Her brain imaging showed atrophy of the right cerebral hemisphere and cerebellopontine tumors (lipoma) bilaterally [Figures 3 and 4].

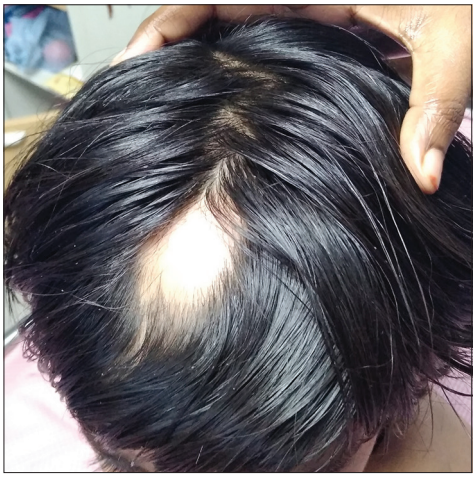


Figure 1: Nevus psiloliparis

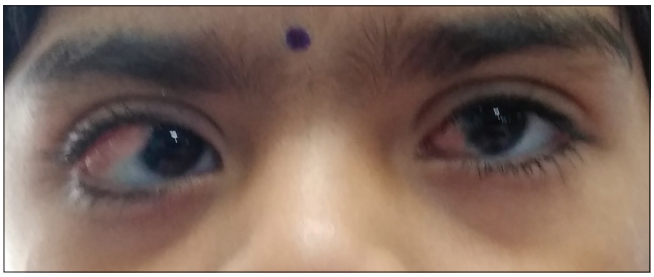


Figure 2: Epibulbar choristoma

DISCUSSION

Encephalocranialcutaneouslipomatosis is a rare condition which is thought to have somatic mosaicism as the pathophysiology. It is rare and has no preference for

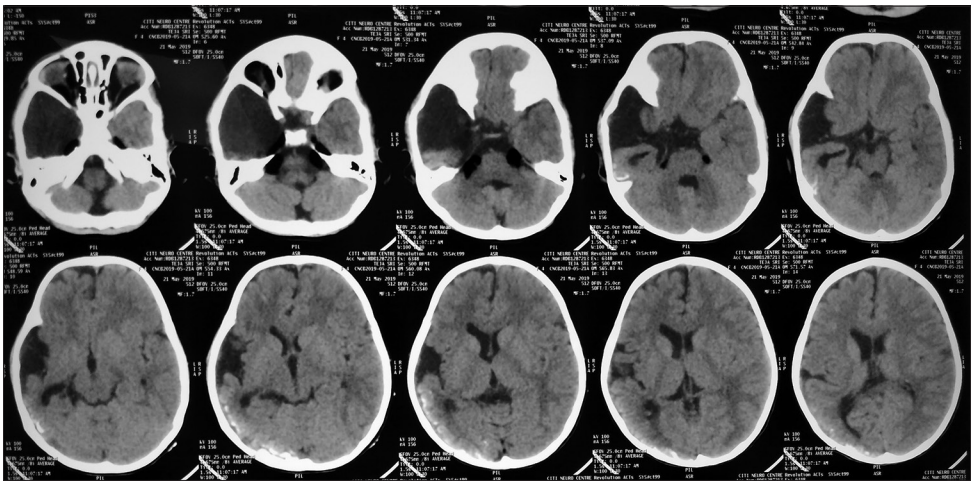


Figure 3: Cerebral atrophy

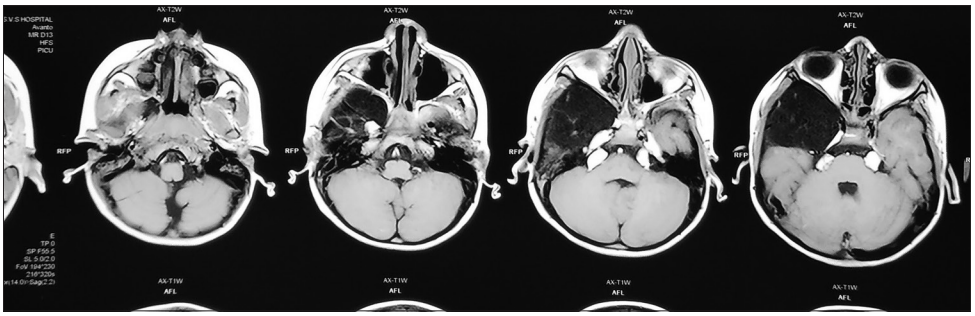


Figure 4: Cerebellopontine tumor (lipoma)

gender or race. The dysgenesis of the neural tube crest is another hypothesis for this condition. The syndrome has multisystem involvement of the brain, skin, bone, and eyes.

There are diagnostic criteria for the diagnosis of encephalocraniocutaneous lipomatosis which was proposed by Hunter and modified by Moog[2] [Table 1].

The major and minor criteria are mentioned in the table.

A definite case is one in which

1. Three systems are involved, with major criteria ≥2 or
2. Three systems involved, proven nevus psiloliparus (NP) or possible NP and ≥1 of minor skin criteria 2–5
3. Two systems involved with major criteria, one of which proven NP +. ≥1 minor skin criteria 2–5.

Probable case is defined as one with,

1. Two systems involved with major criteria in both
2. Two systems involved with proven or possible NP.

Clinically, the main differential diagnosis include proteus syndrome, neurofibromatosis, Sturge–Weber syndrome, epidermal nevus syndrome, and Goldenhar syndrome.[3] The natural course of the disease can allow some children to lead normal lives.[4] Some of them can have the central nervous system (CNS) morbidity affecting their quality of life.[5] The child may develop seizures, sometimes facial paralysis, hemiplegia, spasticity of the opposite limb, sensorineural hearing loss, and behavioral changes.[6] There is an increased risk of developing CNS tumors in these children which includes low-grade glioma and astrocytoma.[7,8] Other neoplasms such as extrapharyngeal angiofibroma of the gingiva and papillary glioneuronal tumor[9,10] is also documented. Hence, regular screening for these tumors is an essential part of follow-up care. The ocular manifestations can be treated by surgical techniques based on the extent of the choristoma. There is no specific therapy for the condition except for anticonvulsant therapy for seizures or status epilepticus and cosmetic treatment for the skin and ocular lesions, but regular follow-up for the child for the above-mentioned complications are imperative.

Table 1: Diagnostic criteria

Eye
Major criteria
Choristoma with or without associated anomalies
Minor criteria
Corneal and other anterior chamber anomalies
Ocular or eyelid coloboma
Skin
Major criteria
Proven NP
Possible NP and ≥1 of minor criteria 2-5
≥2 of minor criteria 2-5
Minor criteria
Possible NP
Patchy or streaky nonscarring alopecia
Subcutaneous lipomas in the frontotemporal region
Focal skin aplasia/hypoplasia on the scalp
Small nodular skin tags on eyelids or between the outer canthus and tragus
CNS
Major criteria
Intracranial lipoma
Intraspinal lipoma
≥2 minor criteria
Minor criteria
Abnormal intracranial vessels
Arachnoid cyst or other abnormality of the meninges
Complete or partial atrophy of a hemisphere
Porencephalic cyst
Asymmetrically dilated ventricles or hydrocephalus
Calcification (not basal ganglia)
Other systems
Major criteria
Jaw tumor
Multiple bone cysts
Aortic coarctation

NP: Nevus psiloliparus, CNS: Central nervous system

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Haberland C, Perou M. Encephalocraniocutaneous lipomatosis. A new example of ectomesodermal dysgenesis. Arch Neurol 1970;22:144-55.
2. Moog U. Encephalocraniocutaneous lipomatosis. J Med Genet 2009;46:721-9.
3. Thakur S, Thakur V, Sood RG, Thakur CS, Khanna S. Encephalocraniocutaneous lipomatosis with calvarial exostosis – Case report and review of literature. Indian J Radiol Imaging 2013;23:333-6.
4. Parazzini C, Triulzi F, Russo G, Mastrangelo M, Scotti G. Encephalocraniocutaneous lipomatosis: Complete neuroradiologic evaluation and follow-up of two cases. AJNR Am J Neuroradiol 1999;20:173-6.
5. Chan CC, Chen JS, Chu CY. Haberland syndrome. Dermatol Sin 2005;23:41-5.
6. Hunter AG. Oculocerebrocutaneous and encephalocraniocutaneous lipomatosis syndromes: Blind men and an elephant or separate syndromes? Am J Med Genet A 2006;140:709-26.
7. Brassesco MS, Valera ET, Becker AP, Castro-Gamero AM, de Aboim Machado A, Santos AC, *et al*. Low-grade astrocytoma in a child with encephalocraniocutaneous lipomatosis. J Neurooncol 2010;96:437-41.
8. Valera ET, Brassesco MS, Scrideli CA, de Castro Barros MV, Santos AC, Oliveira RS, *et al*. Are patients with encephalocraniocutaneous lipomatosis at increased risk of developing low-grade gliomas? Childs Nerv Syst 2012;28:19-22.
9. Andreadis DA, Rizos CB, Belazi M, Peneva M, Antoniades DZ. Encephalocraniocutaneous lipomatosis accompanied by maxillary compound odontoma and juvenile angiofibroma: Report of a case. Birth Defects Res A Clin Mol Teratol 2004;70:889-91.
10. Phi JH, Park SH, Chae JH, Wang KC, Cho BK, Kim SK. Papillary glioneuronal tumor present in a patient with encephalocraniocutaneous lipomatosis: Case report. Neurosurg 2010;67:E1165-9.

Case Report

Mycoplasma pneumoniae-induced cerebral venous sinus thrombosis with autoimmune hemolytic anemia

Sayali Deshpande, Bhakti Sarangi, Venkat Sandeep Reddy, Ajay Walimbe

Department of Pediatrics, Bharati Hospital, Pune, Maharashtra, India

Abstract

Mycoplasma pneumoniae (MP) is a common organism causing pneumonia in school-going children. Although the disease is usually mild, it can rarely lead to severe extrapulmonary complications which may be life-threatening. We hereby report a case of an 8-year-old male child who presented with fever, cough, a maculopapular rash, and difficulty in breathing for 8 days who, after initially receiving treatment as community-acquired pneumonia with synpneumonic effusion, went on to develop severe autoimmune hemolytic anemia and cerebral venous thrombosis with features of vasculitis. With utilization of DNA polymerase chain reaction along with other laboratory parameters, the diagnosis of MP infection was made. The child was treated with oral clarithromycin, pulse dose methylprednisolone, low-molecular-weight heparin, and intravenous immunoglobulin while he also required mechanical ventilation, transfusions, and vasopressor support. He responded to these measures and survived with no neurological sequelae.

Keywords: Autoimmune hemolytic anemia, cerebral venous sinus thrombosis, low-molecular-weight heparin, methyl prednisolone, *Mycoplasma pneumoniae*

Address for correspondence: Dr. Venkat Sandeep Reddy, Department of Pediatrics, Bharati Hospital, Pune, Maharashtra, India.
E-mail: kvsandeepreddy@gmail.com

INTRODUCTION

Mycoplasma pneumoniae (MP) is a common cause of community-acquired pneumonia most frequently affecting school-going children. Extrapulmonary complications due to *Mycoplasma* are rare, most common being hematological manifestations such as hemolytic anemia. Central nervous system (CNS) manifestations such as meningoencephalitis, thrombosis, optic neuritis, transverse myelitis, and stroke have also been occasionally reported apart from dermatological, gastrointestinal, connective tissue, cardiac, ocular, and renal complications.

Received: 31-01-2020 **Revised:** 07-03-2020
Accepted: 10-03-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_20_20

MP have specialized transmembrane proteins (e.g., P1 and P30) that help in adherence and gliding motility along the respiratory epithelium. These adherence proteins of MP have an affinity for respiratory tract epithelium, and after attachment, they produce hydrogen peroxide and superoxide radicals, causing injury to epithelial cells and cilia. The clinical manifestations of MP infection are determined by the immune competency and response of the host, indicating that some of the pathogenic features of MP infection, particularly extrapulmonary manifestations (e.g., hemolysis and encephalitis), are immune mediated. The antibodies produced against the glycolipid antigens of MP cross-react with human red cells and brain cells and may act as autoantibodies.

How to cite this article: Deshpande S, Sarangi B, Reddy VS, Walimbe A. *Mycoplasma pneumoniae*-induced cerebral venous sinus thrombosis with autoimmune hemolytic anemia. J Pediatr Crit Care 2020;7:88-91.

CASE REPORT

An 8-year-old male child was referred to our hospital with complaints of fever and cough for 8 days, maculopapular rash and difficulty in breathing for 2 days, and having received treatment for community-acquired pneumonia (intravenous [IV] ceftriaxone and oral doxycycline). Chest X-ray showed left lung consolidation with synpneumonic effusion [Figure 1]. Diagnostic tap revealed lymphocytic predominant cell count. On admission to our hospital, his sensorium was normal (Glasgow Coma Scale [GCS]: 15/15) with the only significant findings on examination being tachypnea (respiratory rate: 48/min), decreased oxygen saturation (90% in room air), mild intercostal retractions, and decreased air entry over the left side.

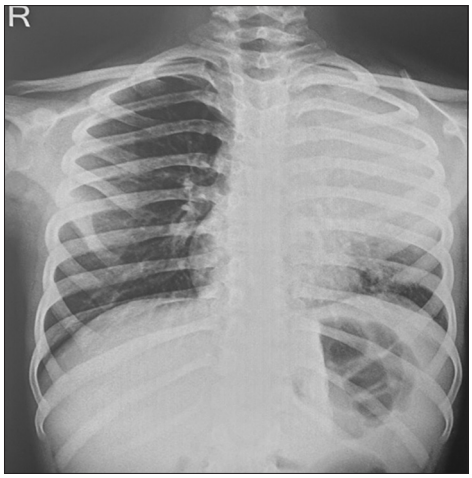


Figure 1: Chest X-ray done on admission

Considering persistent pneumonia, the child was continued on oxygen therapy with injection piperacillin-tazobactam and injection vancomycin as antibiotic cover after sending cultures. Computed tomography chest showed consolidatory changes in both lungs predominantly on the left [Figure 2]. He continued to remain intermittently febrile with gradual improvement in respiratory findings and radiological improvement. On day 8 of admission, he was noticed to have significant pallor followed by a steady fall in his GCS score from 15/15 to 12/15 and subsequently to 10/15 over a period of 4 h. Examination revealed poor sensorium, tachycardia, and severe pallor with CNS examination showing signs of pyramidal tract dysfunction. On investigation, his hemoglobin had shown a fall from 9.1 g/dl to 2.1 g/dl [Table 1]. He was electively intubated and put on mechanical ventilation. Due to drastic fall in hemoglobin. suspecting hemolysis, direct and indirect coombs test were done which were both positive (4+) with cold agglutination. The child was transfused with packed cells of blood group O negative due to inability to cross-match compatible blood type, and IV methylprednisolone pulse therapy was started to suppress the autoimmune hemolysis. Magnetic resonance imaging (MRI) brain done showed thrombosis of the left transverse and sigmoid sinus, part of the left internal jugular vein, and partial thrombosis of the right transverse sinus with restricted diffusion in both frontal regions suggesting cytotoxic edema/venous infarcts [Figure 3].

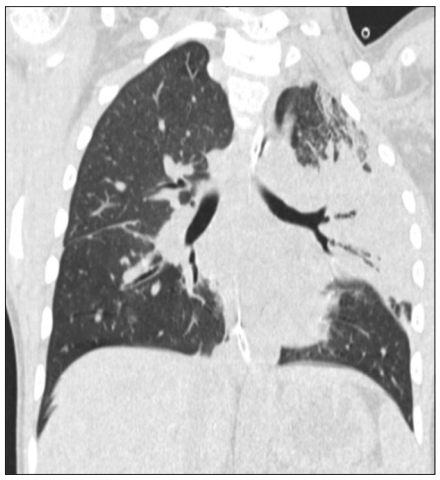


Figure 2: Consolidatory changes noted on computed tomography

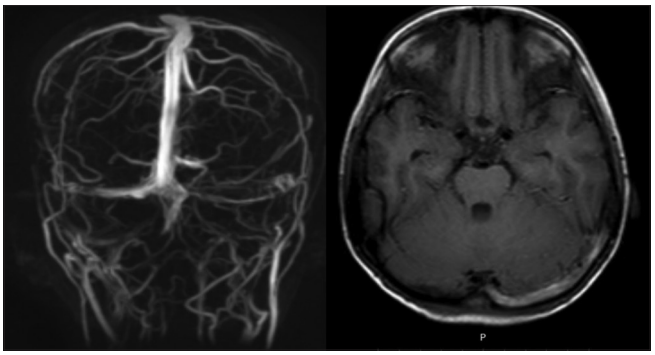


Figure 3: First magnetic resonance imaging brain showing thrombosis of the left transverse and sigmoid sinus, visualized part of the left internal jugular vein, and partial thrombosis of the right transverse sinus

With evidence of vasculitis on MRI, IV immunoglobulin (IVIG) (at 2 g/kg) was also added along with low-molecular-weight heparin. Considering possible causes for hypercoagulability and the child's clinical presentation, polymerase chain reaction (PCR) of tracheal aspirate for MP was done and was positive while blood specimen tested positive for *Mycoplasma* IgM antibodies. Following this, oral clarithromycin was added. Antiphospholipid antibodies (beta-2 glycoprotein-1 IgM) and cardiolipin antibody anticardiolipin (ACL) IgM were found to be positive. The child responded to the above measures, and his sensorium improved. He was

extubated after 4 days of ventilation. Repeat MRI brain done after 10 days showed findings similar to previous MRI with near-total recanalization of the right transverse sinus [Figures 4 and 5]. Serial investigations showed reducing evidence of hemolysis. The child was discharged on oral steroid and clarithromycin after complete clinical resolution of respiratory and neurological signs with a plan to repeat thrombotic workup after 3 months.

DISCUSSION

MP, acquired through respiratory secretions of an infected person, usually presents with symptoms including fever, malaise, sore throat, and cough and becomes noticeable after the first 1–3 weeks of exposure. Often referred to as "walking pneumonia," most cases of MP are uncomplicated.

Table 1: Laboratory investigations

Investigations in PICU	Result
Hemogram	
Hb	2.1
TLC (/cumm)	12,000
Neutrophils (%)	80
Leukocytes (%)	8
Platelet (L/cu mm)	5.33
Marked autoagglutination	Positive 4+
Direct and indirect Coombs test	Positive 4+
Serum electrolytes	Normal
Retic count (%)	0.5 (0.2-2)
Serum ferritin (ng/ml)	7568 (7-140)
DNA PCR for *Mycoplasma* in tracheal aspirates	Positive (high)
Mycoplasma IgM (blood)	Positive (34.08 NTU)
Urine for hemosiderin	Positive
Cold agglutinin titer	Positive (1:256)
Beta-2 glycoprotein 1	
IgM (RU/mL)	Positive (88.16)
IgG	Negative
ANA	Negative
Cardiolipin antibody ACL IgM (U/mL)	Positive (65.08)
Lupus anticoagulant	Absent

Hb: Hemoglobin, TLC: Total leukocyte count, PCR: Polymerase chain reaction, ACL: Anticardiolipin, PICU: Pediatric intensive care unit, ANA: Anti-nuclear antibody

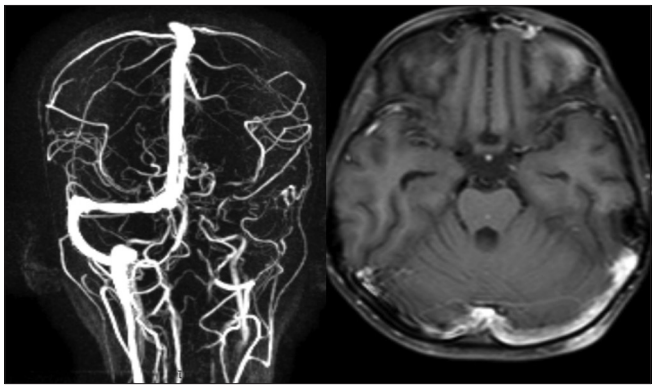


Figure 4: Repeat magnetic resonance imaging showing near total recanalization of the right transverse sinus. Few collateral vessels are seen along the surface of the sinus

However, extensive pulmonary disease in the form of massive lobar pneumonia with pleural effusions as well as necrotizing pneumonia has been reported.[1-3] Pleural fluid data available from these reports have shown the pleural effusion to be lymphocyte predominant rather than polymorphonuclear leukocyte predominant as was the case with our child. While all of these children have protracted periods of fever and respiratory distress, early-stage diagnosis is difficult due to the lack of obvious symptoms.

MP can be detected by PCR, including multiplex PCR panels which can be performed rapidly and have a high sensitivity and specificity. They can be done on a respiratory specimen (e.g., nasopharyngeal or throat swab). The yield from cerebrospinal fluid is low. Culture can take as long as 3 weeks and does not take on gram stain as it lacks a cell wall. If PCR is not available, MP IgM and IgG enzyme immunoassay can be done.

Drugs used in treatment include erythromycin, azithromycin, clarithromycin, tetracyclines, chloramphenicol, aminoglycosides, and quinolones. The most commonly used is azithromycin given at 10 mg/kg/day on day 1, followed by 5 mg/kg/day for 4 days, while clarithromycin at 15 mg/kg/day is administered every 12 h for 10 days.[4]

Among the various extrapulmonary manifestations, hemolytic anemia has been frequently associated with MP pulmonary infection.[5] Steroids have been used in the management of encephalitis and hemolytic anemia. Splenectomy may be necessary if there is no response to steroids or if the remission is not maintained when the dose of prednisolone is reduced. Immunosuppressive drugs such as azathioprine and cyclophosphamide may be effective. Thrombosis occurs as a part of extrapulmonary complications and responds to anticoagulation. MP

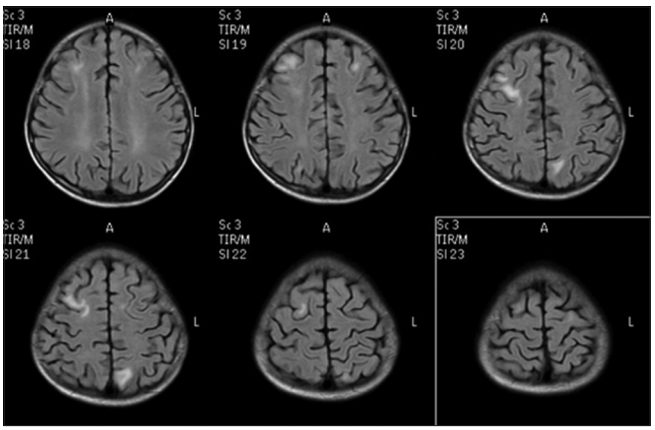


Figure 5: Repeat magnetic resonance imaging brain showing hyperintense signals on T2- and fluid-attenuated inversion recovery images

is known to cause prothrombotic state leading to the positivity of antiphospholipid antibodies. Antibody titers during the active infection and at a later date (~3 months) help to differentiate underlying autoimmune conditions from MP-related prothrombotic state.

IVIG (at 2 g/kg) has been used successfully in refractory MP infection, especially when there is suspicion of an autoimmune process with reports showing neurological improvement occurring within 48 h of administration of IVIG.[6,7] Plasmapheresis remains another therapeutic intervention.[8]

In MP infections and other viral infections, lupus anticoagulant, ACL antibodies, and beta-2 glycoprotein antibody can be present transiently and require to be documented after a period of 3 months to confirm the prothrombotic state secondary to the infection.[9]

CONCLUSION

Although often benign, MP can present with severe pulmonary and extrapulmonary complications. Newer diagnostic techniques such as DNA PCR for *Mycoplasma* for direct detection of the antigen are proving useful for rapid etiological diagnosis. Treatment of complications such as autoimmune hemolytic anemia includes administration of steroids while the CNS complications warrant the use of IVIG and plasmapheresis. Underlying autoimmune conditions should be differentiated from MP-related prothrombotic state by repeating antibody titers after a 3-month period.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Matsumoto M, Nagaoka K, Suzuki M, Konno S, Takahashi K, Takashina T, *et al*. An adult case of severe life-threatening *Mycoplasma pneumoniae* pneumonia due to a macrolide-resistant strain, Japan: A case report. BMC Infect Dis 2019;19:204.
2. Jo SY, Na KW, Kim SW, Hwang YH. *Mycoplasma pneumoniae*-associated necrotizing pneumonia in children: A case-report. Kosin Med J 2019;34:57-64.
3. Cha SI, Shin KM, Jeon KN, Yoo SS, Lee J, Lee SY, *et al*. Clinical relevance and characteristics of pleural effusion in patients with *Mycoplasma pneumoniae* pneumonia. Scand J Infect Dis 2012;44:793-7.
4. Costagliola ML. Pediatric Respiratory Diseases. In: Community-acquired pneumonia. Cham: Springer; 2020. p. 299-307.
5. Bell A, Hughes J, Williams C, Knox S. G547(P) Oh my… a very unusual coincidence! the case of a boy who developed haemolysis following a trip to the swimming pool. Archives of Disease in Childhood 2019;104:A221.
6. Attilakos A, Palaiologou P, Lagona E, Voutsioti A, Dinopoulos A. *Mycoplasma pneumoniae* encephalopathy: Recovery after intravenous immunoglobulin. Pediatr Neurol 2008;38:357-9.
7. Daba M, Kang PB, Sladky J, Bidari SS, Lawrence RM, Ghosh S. Intravenous immunoglobulin as a therapeutic option for *Mycoplasma pneumoniae* encephalitis. J Child Neurol 2019;34:687-91.
8. Hanzawa F, Fuchigami T, Ishii W, Nakajima S, Kawamura Y, Endo A, *et al*. A 3-year-old boy with Guillain-Barré syndrome and encephalitis associated with *Mycoplasma pneumoniae* infection. J Infect Chemother 2014;20:134-8.
9. Wang Chun K, See Wan Y, Poon Chuen W. Transient presence of lupus anticoagulant associated with *Mycoplasma* pneumonia. Asian Cardiovasc Thorac Ann 2016;24:286-7.

Case Report

Amitraz, an unusual poison

Yogesh N. Parikh, Mayur C. Gwalani, Aarti Makwana, Divyaraj A. Bavishi

Department of Pediatrics, Rajkot Civil Hospital, Pandit Deendayal Upadhyay Medical College, Rajkot, Gujarat, India

Accidental poisoning in children is a common pediatric emergency. Here, we report the case of a 7-year-old girl with Amitraz poisoning. Ingestion and dermal contact with a dissolved solution of Amitraz lead to acute toxicity, which mimicked organophosphate poisoning. The patient lost consciousness which prompted their presentation to the pediatric emergency department. Limited literature is available regarding Amitraz poisoning. This case report attempts to document the findings and raise awareness to hasten identification and treatment of a rare and newer poison, Amitraz.

Keywords: Amitraz, pesticide, poisoning, toxicology

Address for correspondence: Dr. Mayur C. Gwalani, Block 972, New GHB Colony, Sanala Road, Morbi, Rajkot, Gujarat, India.
E-mail: gwalani.mayur0813@gmail.com

INTRODUCTION

Amitraz is a formamidine pesticide that is often used by vets and agriculturists as an insecticide. It is also used for controlling ectoparasites in cattle and pets. Amitraz is available in India under the brand name NITRAZ and A-MTIRAZZ at 12.5% concentration as an over-the-counter pesticide at pet, local chemical, and even on online stores, which is then diluted in water for application.

It acts as a central α_2 adrenergic receptor agonist and peripheral α_1 and α_2 adrenergic receptor agonist. Amitraz also inhibits prostaglandin E2 synthesis and monoamine oxidase enzyme activity (dose dependent).[1]

Poisoning via Amitraz can occur through inhalational (most potential), cutaneous, and ingestional routes.[2] Signs and symptoms of toxicity include nausea, vomiting, bradycardia, hypotension/hypertension, hypothermia, hyperglycemia, polyuria, decreased gastrointestinal motility and intestinal distension, miosis, central nervous system (CNS) depression with drowsiness, respiratory depression, convulsions, and coma.[1]

Only limited literature is available regarding Amitraz poisoning, especially in the Indian scenario.

CASE REPORT

We report the case of a 7-year-old female child who presented with symptoms of poisoning, which was retrospectively confirmed as Amitraz.

The patient suddenly woke up at night and started screaming but soon lost consciousness, for which she was brought to the pediatric emergency department. She was admitted as a case of unknown poisoning; approximately 6 h after, the first symptoms became apparent to the parents. The patient was completely all right the previous night and went to sleep until midnight when she woke the

Received: 22-01-2020 **Revised:** 07-03-2020
Accepted: 10-03-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_3_20

How to cite this article: Parikh YN, Gwalani MC, Makwana A, Bavishi DA. Amitraz, an unusual poison. J Pediatr Crit Care 2020;7:92-4.

parents up with incomprehensible screaming and soon lost consciousness. There was no history of trauma.

On preliminary examination, the temperature was normal, heart rate was 48/min (bradycardia), and respiratory rate was 16/min. CNS examination showed altered sensorium with a Glasgow Coma Scale of 3 (eye opening – 1, verbal response – 1, and motor response – 1). The respiratory system had bilaterally equal air entry and normal breath sounds with no crepitations or rhonchi. Cardiovascular system examination yielded normal heart sounds without murmurs. The patient was also seen to have miosis, polyuria, and a low pulse volume. An unknown poison was highly suspected, but no history of exposure could be elicited.

The patient was intubated and kept on pressure assist-control mode (FiO_2 at 100%, positive end-expiratory pressure at 6, and positive inspiratory pressure at 15). The patient was given a normal saline bolus of 60 ml/kg along with inotropes (adrenaline and noradrenaline) and atropine (for miosis and bradycardia) at standard pediatric doses. Immediate improvement in the vitals on the administration of inotropes and atropine was noted.

A battery of tests was conducted meanwhile to aid the identification of the unknown poison and find the antidote. Electrocardiogram was normal; hemoglobin – 11.1 g%; white blood cell count – 4700/mm^3; differential count (%) – 55/43/1/1/0; platelet count – 219,000/mm^3; and malarial parasite on peripheral smear was absent. Random blood glucose was 126 mg/dL; serum urea – 29 mg/dL; serum creatinine – 0.8 mg/dL; serum sodium – 136 mEq/L; serum potassium – 3.9 mEq/L; serum creatine kinase-mb – 22 IU/L; serum cholinesterase – 7354 IU/L (normal); prothrombin time – 13.4 s; and activated partial thromboplastin time – 35.8 s. International normalized ratio was 1.07.

Urine routine and microscopy were normal. The tests did not help to determine the causative poison, and hence, supportive treatment was continued.

The inotropes were tapered and the patient was extubated after 11 h of admission with the improvement of consciousness (Glasgow Coma Scale – 15) and stable maintenance of SpO_2 (99%). The patient was subsequently shifted from intravenous (IV) fluids to oral fluids. Recovery was complete.

On regaining consciousness, the patient recounted the incident of poisoning, and the father, a dog trainer, identified the poison as Amitraz. In this case, dermal and oral ingestional (mucosal) poisoning seemed to have been the probable routes of exposure to Amitraz.

The patient was discharged after 2 days of uneventful observation.

DISCUSSION

In our case, complete recovery was achieved through supportive treatment without any sequelae after 11 h of admission. Maintaining adequate hydration, airway, breathing, and circulation formed the crux of the administered supportive treatment.

CNS symptoms and bradycardia were the primary presenting signs in our patient (α_2 adrenergic receptor agonist action). Miosis and bradycardia were indications for atropine initiation and its administration led to an improvement in both. Inotropes (adrenaline and noradrenaline) and IV fluids (normal saline) were started to treat the state of hypovolemic shock in the patient. Intubation and mechanical ventilation were undertaken, as the Glasgow Coma Scale was 3. (Standard pediatric doses were used for all of the above-mentioned drugs and fluids administered.)

Bradycardia and miosis can be clinically mistaken as signs of organophosphate poisoning,[3] a common clinical scenario, but Amitraz poisoning yields normal serum cholinesterase levels, making serum cholinesterase an important differentiating test.[3] Opioid poisoning should also be ruled out.[4]

There is no exact antidote for Amitraz poisoning, and most existing literature deems supportive and symptomatic treatment highly effective. Decontamination methods such as gastric lavage and activated charcoal could be considered if a history of oral ingestion of Amitraz is present,[5] but their role remains unclear.[6] Some studies report the use of Atropine for bradycardia and miosis, but no controlled studies proposing its efficacy in a sufficient sample size are available. Atropine can be considered in cases with a predominance of bradycardia.[5] In a systematic review, of 310 cases, nearly 20% and 11.9% of the patients required mechanical ventilation and inotropic support, respectively. Amitraz poisoning carried a good prognosis with only six reported deaths (case fatality rate, 1.9%).[6]

To conclude, Amitraz poisoning should be suspected in poisoning cases if there is a history of exposure to cattle insecticide associated with CNS depression, bradycardia, miosis, and normal serum cholinesterase levels. As

documented in this case report, prompt administration of supportive treatment on recognizing the above-mentioned signs forms the crux of the treatment of a case of Amitraz poisoning.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Jorens PG, Zandijk E, Belmans L, Schepens PJ, Bossaert LL. An unusual poisoning with the unusual pesticide amitraz. Hum Exp Toxicol 1997;16:600-1.
2. Aydin K, Kurtoğlu S, Poyrazoğlu MH, Uzüm K, Ustünbaş HB, Hallaç IK. Amitraz poisoning in children: Clinical and laboratory findings of eight cases. Hum Exp Toxicol 1997;16:680-2.
3. Dhooria S, Behera D, Agarwal R. Amitraz: A mimicker of organophosphate poisoning. BMJ Case Rep 2015;2015:bcr2015210296.
4. Balali-Mood M, Balali-Mood K, Shirazi H. Recent advances in treatment of acute organophosphorous nerve agents poisoning. Iranian J Pharm Res 2006;2:79-87.
5. Eizadi-Mood N, Sabzghabaee AM, Gheshlaghi F, Yaraghi A. Amitraz poisoning treatment: Still supportive? Iran J Pharm Res 2011;10:155-8.
6. Dhooria S, Agarwal R. Amitraz, an underrecognized poison: A systematic review. Indian J Med Res 2016;144:348-58.

Clinical Update

Chloride in intensive care

Kundan Mittal

Department of Pediatrics, Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India

Abstract Chloride has significant role in the body fluid management and action potential. It also helps in the regulation of acid–base status and facilitates oxygen unloading. Hyper- and hypo-chloremia associated with certain conditions are associated with poor outcome.

Keywords: Hyperchloremia, hypochloremia, metabolic acidosis

Address for correspondence: Dr. Kundan Mittal, Department of Pediatrics, Pt. B. D. Sharma PGIMS, Rohtak - 124 001, Haryana, India.
E-mail: kundanmittal@gmail.com

INTRODUCTION

Chloride is the most common anion present in the extracellular fluid (ECF). It combines with sodium and potassium inside the human body. Chloride concentration is high in the cerebrospinal fluid, gastric, and bile secretion in comparison to ECF. Being negatively charged, it moves with sodium and helps in maintaining resting action potential, osmolality, and water balance. It also helps in maintaining acid–base balance (chloride and bicarbonate have inverse relationship), plasma oncotic pressure, and carbon dioxide transported in red cells.

Normal serum chloride level (related to RBC and free in the blood) is 96–107 mEq/L and intracellular chloride level is 4 mEq/L. It remains stable with age. Chloride balance is associated with sodium and bicarbonate, and its regulation depends on intake, excretion, and reabsorption from kidney. Chloride is mainly excreted through gastrointestinal tract (GIT), kidney, and skin.[1-5]

Received: 15-02-2020 **Revised:** 22-02-2020
Accepted: 29-02-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_33_20

FUNCTIONS OF CHLORIDE

- Acid–base homeostasis
- Regulation of sodium, potassium, and chloride reabsorption
- Chloride increases blood pressure
- It is inversely related to renin secretion and glomerular filtration rate
- Facilitates oxygen unloading
- Contributes to gastric acidity
- Maintains intestinal osmotic gradient and fluid secretion
- Protein digestion, microorganism homeostasis, nutrients' absorption
- Increased level decreases gastric-pyloric motility.

HYPERCHLOREMIA

Serum level >108 mEq/L may be associated with rise in the sodium level or alone and decrease in the bicarbonate level. High level is seen in 25%–45% of intensive care unit patients. Increased level may be due to increased intake of saline, water loss, absorption, acidosis, retention by kidneys, salicylate toxicity, respiratory alkalosis, hyperparathyroidism, hypernatremia, saline infusion, and

How to cite this article: Mittal K. Chloride in intensive care. J Pediatr Crit Care 2020;7:95-6.

drug-related retention. Various drugs associated with raised chloride level are aspirin, acetazolamide, kayexalate, phenylbutazone, and ammonium chloride. Hyperchloremia does not produce signs and symptoms directly, but indirect features related to metabolic acidosis appear. Other features include altered sensorium, fluid retention, dyspnea, tachypnea, tachycardia, hypertension, and weakness. High chloride level is also associated with increased sodium level and features suggestive of fluid retention. While assessing the chloride level, it is must to measure serum sodium, bicarbonate, and anion gap.

Hyperchloremic metabolic acidosis is associated with acute kidney injury, vasodilatation, altered neurotransmission, increased inflammatory markers, decreased cardiac activity, hemodynamic instability (both hypo and hyper are detrimental), decreased endogenous catecholamine release, and decreased cellular function. Rise more than 5 mEq/l is associated with increased mortality.

Treatment

- Prevention
- Treatment of underlying cause
- Fluid resuscitation
- Correction of other electrolytes
- Acid–base status
- In severe case, intravenous sodium bicarbonate is indicated and rarely diuretic therapy
- Monitor intake and output, vital signs including cardiac rhythm, and neurological and respiratory status
- Further, monitor serum electrolytes including bicarbonate level.

HYPOCHLOREMIA

It is defined as serum chloride level <96 mEq/L. Besides, chloride also measures serum sodium, potassium, and calcium levels. Level decreases if intake is less; loss from skin, GIT, kidney; or changes in the sodium and acid–base level. Certain drugs are also associated with low chloride level (diuretics, mannitol, corticosteroids, bicarbonate, and theophylline). Other causes include low level of sodium and potassium, metabolic alkalosis, cystic fibrosis, gastric surgery, diabetic ketoacidosis, and heart failure. If chloride loss is more than sodium, hypochloremic alkalosis develops. Signs and symptoms of the electrolytes imbalance and metabolic alkalosis appear. Other features are irritability, agitation, seizure, coma, tetany, and muscle hypertonicity. Low chloride level in congestive cardiac failure is associated with increased mortality.

Treatment

- Prevention
- Correct underlying etiology
- Correction of other electrolyte abnormalities
- Fluid therapy and intravenous or oral sodium chloride
- Monitor vitals and other electrolytes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Agrò FE. Body Fluid Management: From Physiology to Therapy. Italy: Springer; 2013.
2. Waikar SS, Murray PT, Singh AK. Core Concepts in Acute Kidney Injury. USA: Springer; 2018.
3. Kellum JA, Elbers PW. Stewart's Textbook of Acid-Base. USA: Lulu.com; 2009.
4. Mount DB, Sayegh MH, Singh AK. Core Concepts in the Disorders of Fluid, Electrolytes and Acid-Base Balance. London: Springer; 2013.
5. Reddi AS. Fluid, Electrolyte and Acid-Base Disorders. 2nd ed. USA: Springer; 2018.

Cardiac arrest secondary to Jervell-Lange-Neilson syndrome

A 6-year-old female child, with a known history of congenital severe bilateral sensory neural deafness, was taken for cochlear implant surgery. She presented with sudden cardiac arrest during the induction of general anesthesia. She was transferred to the Advanced Pediatric Critical Care Centre, Wanless Hospital, Miraj. There was no prior history suggestive of syncopal attacks. She was not on any medications before her hospitalization. There was no delay in the attainment of motor and social milestones. Congenital sensorineural deafness is present in two older female siblings but no history of syncopal attacks or sudden death in any family members.

Postresuscitation, she was hemodynamically stable on ventilator and adrenaline infusion. There were no significant findings on physical examination revealing the cause for the cardiac arrest. Laboratory findings and investigations revealed normal blood count and biochemistry. Chest radiograph showed normal lung fields and cardiac size. Electrocardiogram (ECG) revealed long QTc interval (0.62 s) [Figure 1].

Two-dimensional echo (postcardiac arrest) showed trivial TR, mild right ventricular dysfunction, left ventricular ejection fraction 55%, and structurally normal heart.

Findings of long QT interval combined with congenital sensorineural hearing impairment led to the clinical diagnosis of Jervell and Lange-Neilson syndrome, one of the rarer types of long QT syndromes (LQTSs). The child was started on oral beta-blocker metoprolol (2 mg/kg/day).

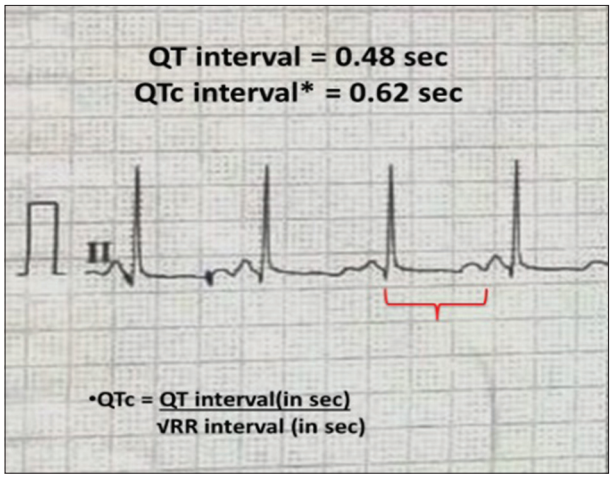


Figure 1: Electrocardiograph long lead II showing long QTc interval

She was weaned off ventilator by 24 h of hospitalization and was discharged in a stable condition on day 4. She continues to be on treatment with oral metoprolol and has had no further cardiac events post-discharge from the hospital.

LQTSs are genetic abnormalities of ventricular repolarization, with an estimated incidence of about 1 per 10,000 birth. They present as a long QTc interval on ECG (>0.47 s) and are associated with malignant ventricular arrhythmias (torsades de pointes and ventricular fibrillation). They are a cause of syncope and sudden death.[1] Jervell-Lange-Neilson syndrome (JLNS) is an autosomal recessive disorder characterized by congenital sensorineural deafness and long QT interval on ECG. It is associated with the genes KCNQ1 (JLNS type 1) and KCNE1 (JLNS type 2).

Clinical manifestation of LQTS in children is most often a syncopal episode brought on by exercise, fright, or sudden startle. They may present with seizures, presyncope, or palpitations. Approximately 10% are initially in cardiac arrest.[2] In our case, cardiac arrest was the initial presentation.

The diagnosis is based on the ECG and clinical criteria. A heart rate-corrected QT interval of >0.47 s is highly indicative, whereas a QT interval of >0.44 s is suggestive. Other features include notched T-waves in 3 leads, T-wave alternans, a low heart rate for age, a history of syncope (especially with stress), and a familial history of either LQTS or sudden death. Genotyping can identify the mutation in approximately 80% of patients known to have LQTS by clinical criteria.[1]

Treatment of LQTS includes the use of beta-blocking agents at doses that blunt the heart rate response to exercise. Some patients may require a pacemaker because of drug-induced bradycardia. In patients with continued syncope, despite treatment, an implantable cardiac defibrillator is indicated for those who do not respond to beta-blockers and those who have had a cardiac arrest.[1]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Priya Sakte, Jennifer Antin, Sachin Jangam, Vinayak Patki

Department of Pediatrics, Advanced Pediatric Critical Care Centre, Wanless Hospital, Miraj, Maharashtra, India

Address for correspondence: Dr. Priya Sakte, Department of Pediatrics, Advanced Pediatric Critical Care Centre, Wanless Hospital, Miraj, Maharashtra, India.
E-mail: pri.sakte@gmail.com

REFERENCES

1. van Hare GF. Long Q-T syndromes. In: Kleigman, Stanton, St Gene, Schor, editors. Nelson Textbook of Pediatrics. 1st South-East Asia ed., Vol. 2, Ch. 435. Elsevier India; 2015. p. 2258-9.
2. Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amlie JP, Timothy K, *et al*. The Jervell and Lange-Nielsen syndrome: Natural history, molecular basis, and clinical outcome. Circulation 2006;113:783-90.

Received: 15-02-2020 **Revised:** 28-02-2020
Accepted: 07-03-2020 **Published:** 10-04-2020

Access this article online

Quick Response Code:

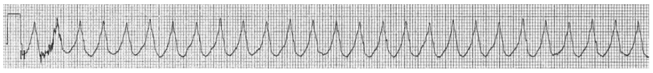
Website: www.jpcc.org.in

DOI: 10.4103/JPCC.JPCC_32_20

How to cite this article: Sakte P, Antin J, Jangam S, Patki V. Cardiac arrest secondary to Jervell-Lange-Neilson syndrome. J Pediatr Crit Care 2020;7:97-8.

PICU quiz

1. A 5-year-old child with muscular dystrophy is scheduled to undergo muscle biopsy for diagnosis. Anesthesia is induced using sevoflurane and you start injecting succinylcholine in preparation for intubation. The child develops masseter spasm immediately and temperature rises to 41°C. After immediate discontinuation of inhaled anesthesia and succinylcholine, which one of the following steps is the most appropriate?
   A. Start normal saline bolus
   B. Intravenous (IV) injection of dantrolene
   C. Arrange bed in the pediatric intensive care unit (PICU)
   D. Start 100% oxygen with a high flow rate to wash out residual sevoflurane
   E. Paralyze and intubate the child with another agent.
2. An 18-month-old boy with Type I spinal muscular atrophy is in the PICU with respiratory syncytial virus bronchiolitis which presented as fever and copious secretions. He has a respiratory rate (RR) of 56 breaths/min with deep subcostal retractions and is started on noninvasive positive-pressure ventilation (PPV) with inspiratory pressure of 15 cm H_2O and expiratory pressure of 5 cm H_2O. After a while, his retractions are much improved, and RR is 30 breaths/min. However, saturations are only 92% on 40% oxygen, and the chest radiograph reveals basilar atelectasis. Which one of the following treatment plans will best recruit her collapsed lung?
   A. Increase expiratory pressures to 10 cm of H_2O and inspiratory pressures to 20 cm H_2O
   B. Just increase expiratory pressure to 10 cm of H_2O
   C. Give glycopyrolate to decrease secretions
   D. Intubation and mechanical ventilation
   E. Chest physiotherapy with mechanical insufflation-exsufflation.
3. A 4-year-old boy is being treated for pneumococcal pneumonia and sepsis. You have noticed decreased breath sounds on the right side along with increased ventilatory settings. He has become more edematous, has decreased urine output, and has oozing around his central and arterial lines. His blood workup shows thrombocytopenia, elevated liver enzymes, coagulopathy, and worsening renal function. His chest radiograph shows a new right-sided pleural effusion. You decide to place a right-sided chest tube to evacuate the effusion. He is receiving a fentanyl drip and intermittent benzodiazepine for sedation. Which one of the following options would be the most appropriate next step in management of this patient?
   A. Use rocuronium for paralysis and start diuretics to help decrease pleural effusion
   B. Use cisatracurium for paralysis and insert the Intercostal drainage (ICD) in the fifth intercostal space (ICS) in the right mid axillary line
   C. Use cisatracurium for paralysis and insert the ICD in the second ICS in the right mid-clavicular line
   D. Use rocuronium for paralysis and insert the ICD in the fifth ICS in the right mid-axillary line
   E. Use rocuronium for paralysis and insert the ICD in the second ICS in the right mid-clavicular line.
4. A 2-month-old girl developed poor feeding and irritability early this morning. She was brought to the emergency department (ED) due to respiratory distress. On examination, she looks mottled and has weak pulses. Her rhythm strip in lead II showed the following rhythm. The emergency physician tried cardioversion with 0.5 J/kg, but rhythm on the monitor did not change.



   Which one of the following options is the next most appropriate intervention?
   A. Synchronized cardioversion with 0.25 J/Kg
   B. 25 mg/kg of IV magnesium sulfate
   C. Defibrillation with 2 J/kg
   D. Synchronized cardioversion with 2 J/kg
   E. 0.1 mg/kg of IV adenosine.
5. A 2-year-old infant is brought to the ED after his mother found him drinking an unknown substance from a soda bottle in the family's pool house. You suspect that the substance was an acidic pool cleaner. Physical examination of the child's lips, tongue, and oropharynx reveals no abnormalities. Of the following, the MOST appropriate next step in management is:
   A. Emergent upper gastrointestinal radiographic series
   B. Initiation of oral antibiotic therapy
   C. Parental reassurance and patient discharge
   D. Placement of a nasogastric tube for lavage
   E. Referral for emergency esophagoscopy.

6. A 10-year-old girl was admitted in the PICU with a history of injury over the right ankle 1 week back. The child had features of sepsis with septic shock and was ventilated for a duration of 48 h. The diagnosis of Methicillin-resistant *Staphylococcus aureus* (MRSA) septicemia was made, and she had responded well to IV vancomycin. The child was extubated onto nasal prong oxygen and showed significant clinical improvement. After 10 h of extubation, you get a call from the intensive care unit that the child had sudden deterioration in the form of increased respiratory distress, tachycardia, and hypotension. What are the possibilities you consider and intervention?
   A. Tension pneumothorax and needs an emergency ICD insertion
   B. Seizure and needs IV midazolam
   C. Bronchospasm and needs IV steroid and nebulisations
   D. Cardiac tamponade secondary to pericardial effusion leading to obstructive shock and needs urgent echocardiography (ECHO) and drainage
   E. Septic shock and needs fluid bolus.
7. The child presents with elevated serum free calcium, but parathyroid hormone (PTH) is in the normal range. What is the best conclusion?
   A. PTH is normal; therefore, problem does not lie in parathyroid gland
   B. PTH should be low if the parathyroid is functioning normally; thus, the problem is in the parathyroid gland
   C. The child is excessively sensitive to PTH since normal levels are stimulating excessive calcium mobilization from bone
   D. You need a parathyroid scan to make a conclusion.
8. Which is/are correct statements regarding the inspiratory time (Ti)
   A. At the end-Ti, the expiration phase always starts
   B. If Ti is set by the inspiration-to-expiration ratio, the Ti is independent of ventilator frequency
   C. If Ti is directly set, the expiratory time decreases with increasing ventilator frequency
   D. Normal Ti is in the range of 3–4 s.
9. Causes of right ventricular failure include/s:
   A. Acute pulmonary embolus
   B. Protamine
   C. Acute respiratory distress syndrome (ARDS)
   D. Obstructive sleep apnea
   E. All of the above.
10. Regarding prone position ventilation which is correct:
   A. The PROSEVA study group showed no mortality benefit at 28 days in severe ARDS
   B. Alveolar recruitment is affected as drainage of secretions gets impaired
   C. A more homogeneous ventilation distribution is achieved due to favorable changes in thoraco-abdominal compliance
   D. Proning increases extravascular lung water
   E. The optimal duration of prone positioning is 24 h.

ANSWERS

1. D: Start 100% oxygen with a high flow rate to wash out residual sevoflurane
   Rationale: The child has features of malignant hyperthermia. Patients with muscular dystrophy are at increased risk of malignant hyperthermia when exposed to inhalational anesthetic agents such as halothane, sevoflurane, isoflurane, and/or succinylcholine. Features of malignant hyperthermia are muscle rigidity, fever, increased carbon dioxide production, acidosis, and tachycardia. It is a fatal condition and immediate intervention in order of sequence includes discontinuation of offending agents, oxygenation with 100% oxygen to wash out the offending inhalational agent, IV injection of dantrolene, and use of cold normal saline if temperature is above 30°C. Avoid paralysis and intubation in this patient.
2. E: Chest physiotherapy with mechanical insufflation-exsufflation
   Rationale: The child will need frequent breaks from the ventilator to remove secretions. He will need assistance in the form of chest physiotherapy and cough assist. Use of these methods improves strength of cough and helps resolve atelectasis. Increasing pressures might help temporarily but will fail in due course.
3. B: Use cisatracurium for paralysis and insert the ICD in the fifth ICS in the right mid-axillary line.
   Rationale: The patient has features of multi-organ dysfunction. Cisatracurium is eliminated by Hofmann elimination, which is spontaneous degradation of the medication at physiological pH and temperature. Usual site for thoracentesis or chest tube placement is the fourth or fifth ICS in anterior or mid-clavicular line. Rocuronium is not the ideal choice for paralysis in children with renal failure, as kidneys mostly eliminate it. Diuretics are not going to be effective to decrease pleural effusion.
4. D: Synchronized cardioversion with 2 J/kg
   Rationale: This is a child with unstable ventricular tachycardia. Rhythm strip shows monophasic ventricular tachycardia. In this scenario, electrical cardioversion is recommended. If lower energy fails to convert or break ventricular tachycardia synchronized cardioversion with higher energy should be tried.
5. E: Referral for emergency esophagoscopy.
   Rationale: Upper endoscopy under anesthesia should be performed within the first 48 h of caustic ingestion to determine the extent of the esophageal injury. The objective of the endoscopy is to establish the presence or absence of an esophageal lesion and to determine the extent of the injury.
6. D: Cardiac tamponade secondary to pericardial effusion leading to obstructive shock and needs urgent ECHO and drainage
   Rationale: MRSA septicemia can lead to collection in the pericardial space which if left unnoticed and monitored can lead to increase and cause obstructive shock. Urgent ECHO and relieving the tamponade can be lifesaving. Tension pneumothorax is unlikely if the child remained stable for over 10 h postextubation and with no PPV. Other options do not fit in.
7. C: Child is excessively sensitive to PTH since normal levels are stimulating excessive calcium mobilization from bone.
8. C: If Ti is directly set, the expiratory time decreases with increasing ventilator frequency.
9. E: All of the above.
10. C: A more homogenous ventilation distribution is achieved due to favorable changes in thoraco-abdominal compliance.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Pradeep Kumar Sharma, Praveen Khilnani[1]

Department of Pediatric Critical Care and Pulmonology, Sri Balaji Action Medical Institute, [1]Department of Pediatric Critical Care and Pulmonology, Rainbow Children Hospital, New Delhi, India

Address for correspondence: Dr. Pradeep Kumar Sharma, Sri Balaji Action Medical Institute, New Delhi, India.
E-mail: drsharma025@gmail.com

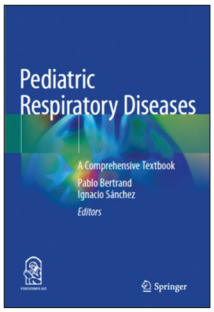
Received: 26-02-2020 **Revised:** 04-03-2020
Accepted: 10-03-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_35_20

How to cite this article: Sharma PK, Khilnani P. PICU quiz. J Pediatr Crit Care 2020;7:99-101.

Book Review

Pediatric respiratory diseases: A comprehensive textbook



Authors: Pablo Bertrand and Ignacio Sanchez
Hardcover: 807 pages
Publisher: Springer; 1st ed. 2020 edition (February 3, 2020)
Language: English
ISBN-10: 3030269604
ISBN-13: 978-3030269609
Price: $144.53

Respiratory diseases are common in pediatric population compared to adults due to certain anatomical and physiological differences. This book contains 74 chapters in five sections. This book covers from physiological basis of respiratory illnesses, assessment of pulmonary functions, immunological aspect, procedures in respiratory illness, symptoms diagnosis, to various diseases' management, including oxygen therapy, nursing care, mechanical ventilation (acute, chronic, long term), and rehabilitation, which are common in children. Special emphasis has been given on ECMO therapy and lung transplantation. This book has been written in simple language and must read for every pediatrician and intensivist.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Kundan Mittal

Department of Pediatrics, Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India

Address for correspondence: Dr. Kundan Mittal, Department of Pediatrics, Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India.
E-mail: kundanmittal@gmail.com

Received: 25-02-2020 **Revised:** 03-03-2020
Accepted: 11-03-2020 **Published:** 10-04-2020

Access this article online	
Quick Response Code:	Website: www.jpcc.org.in
	DOI: 10.4103/JPCC.JPCC_34_20

How to cite this article: Mittal K. Pediatric respiratory diseases: A comprehensive textbook. J Pediatr Crit Care 2020;7:102.

Editor Dr. Vinayak Patki. Printed and published by Wolters Kluwer India Private Limited on behalf of Intensive Care Chapter of Indian Academy of Pediatrics. Printed at Kundan Press, Jaysingpur, Dist. Kolhapur, 416101, Maharashtra, India and published by Wolters Kluwer India Private Limited from A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol, Andheri (East), Mumbai - 400 059, India.