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Article

Frequency of Iron Deficiency Anemia in Children Presenting Breath-Holding Spell at DHQ Mirpur Azad Kashmir

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ABSTRACT

Background: Breath-holding spells (BHS) are common non-epileptic events in young children, often triggered by emotional stress or minor trauma, and may present with alarming features such as transient apnea, cyanosis or pallor, and loss of consciousness. Emerging evidence suggests a strong association between BHS and iron deficiency anemia (IDA), yet region-specific data from underserved areas remain limited. **Objective**: To determine the frequency of iron deficiency anemia among children presenting with breath-holding spells at Divisional Headquarters Teaching Hospital, Mirpur, Azad Jammu and Kashmir. **Methods**: A cross-sectional study was conducted from July to December 2024, enrolling 150 children aged 6 months to 6 years presenting with BHS. Participants with malnutrition, chronic illness, recent iron therapy or blood transfusion were excluded. Demographic and clinical data were collected, and blood samples were analyzed for hemoglobin, serum ferritin, and mean corpuscular volume. IDA was defined as hemoglobin <10 g/dL and ferritin <12 ng/mL. Descriptive statistics and chi-square tests were used to analyze prevalence and associations with age and gender. **Results**: IDA was present in 62.0% of the cohort, with 58.7% classified as moderate and 3.3% as severe. No statistically significant association was observed between IDA prevalence and age (p=0.53) or gender (p=0.59). **Conclusion**: Iron deficiency anemia is highly prevalent in children with BHS regardless of age or gender, supporting the need for routine iron status screening in this population to enable timely management and potentially reduce episode frequency.

Keywords: Iron deficiency anemia, Breath-holding spells, Pediatrics, Hemoglobin, Serum ferritin, Cyanotic spells, Pakistan.

INTRODUCTION

Breath-holding spells (BHS) are commonly encountered non-epileptic events in infants and toddlers, typically manifesting as transient apneic episodes triggered by emotional stimuli such as frustration, anger, or fear. These episodes, often alarming to caregivers, may present with cyanosis or pallor and occasionally lead to loss of consciousness and opisthotonic posturing (1). Although self-resolving, their recurrent nature prompts repeated clinical visits and parental concern regarding potential neurological or systemic pathologies (2). Several theories have been proposed regarding the pathogenesis of BHS, including autonomic nervous system dysregulation, vagal overactivity, delayed brainstem maturation, and micronutrient deficiencies—particularly iron deficiency anemia (IDA)—which has drawn increasing research attention (3).

Iron is a critical cofactor in enzymatic pathways involved in neurotransmitter synthesis and myelin development, playing a vital role in optimal neurological functioning. Its deficiency has been associated with altered catecholamine metabolism and impaired neurodevelopment, which can predispose children to conditions such as BHS (4,5). The link between IDA and BHS has been substantiated by various studies, indicating that iron supplementation may significantly reduce the frequency and severity of spells (6). A systematic review and meta-analysis further supported this association, recommending early detection and correction of IDA as a primary therapeutic approach in managing BHS (7). Moreover, the clinical presentation of BHS often includes features like end-expiratory apnea, transient cyanosis or pallor, and in severe forms, seizure-like activity, which mimics epileptic syndromes but lacks epileptiform EEG patterns (8). The investigation of IDA in pediatric populations presenting with BHS is particularly pertinent in low- and middle-income countries like Pakistan, where nutritional deficiencies are prevalent. Dietary inadequacy, parasitic infections, and socioeconomic constraints have resulted in a high burden of IDA among children under five and women of reproductive age (9). This

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is especially true in geographically underserved regions such as Azad Jammu and Kashmir and Gilgit-Baltistan, where limited access to healthcare and suboptimal feeding practices contribute to a persistently high prevalence of anemia (10). However, despite regional health challenges, few localized studies have explored the magnitude of IDA in children presenting with BHS, leading to a significant gap in evidence-based policy formulation and intervention planning.

Given these considerations, this study was conducted to determine the frequency of iron deficiency anemia among children presenting with breath-holding spells at the Divisional Headquarters Teaching Hospital in Mirpur, Azad Jammu and Kashmir. The aim is to generate context-specific data to support early diagnosis and management of IDA, thereby potentially reducing the occurrence and severity of BHS in this pediatric population.

MATERIALS AND METHODS

This cross-sectional observational study was conducted to determine the frequency of iron deficiency anemia among children presenting with breath-holding spells. The research was carried out at the Department of Pediatrics, Divisional Headquarters Teaching Hospital, Mirpur, Azad Jammu and Kashmir, over a continuous six-month period from July 2024 to December 2024. The hospital is a tertiary-level public healthcare facility providing services to a wide pediatric population from both urban and rural areas. The rationale for choosing this study design stemmed from its suitability for assessing disease prevalence and identifying associations in a defined population at a single point in time.

Children aged between 6 months and 6 years who presented to the outpatient department with a clinical history suggestive of breath-holding spells were considered eligible. Breath-holding spells were defined as paroxysmal, non-epileptic events typically triggered by minor trauma or emotional upset, leading to involuntary breath-holding, possible cyanosis or pallor, and transient loss of consciousness, lasting less than one minute with spontaneous recovery. Children were included if they met this clinical description and had not previously received treatment or evaluation for anemia. Exclusion criteria included any prior history of diagnosed malnutrition, congenital anomalies, established neurological or hematological disorders, severe systemic infections, recent blood transfusions within the past three months, or ongoing iron supplementation within the preceding 90 days.

Participants were selected through a non-probability consecutive sampling technique. At the time of initial clinical evaluation, detailed information regarding the nature and frequency of breath-holding spells was collected through direct interviews with parents or guardians, using a standardized structured questionnaire. After verifying eligibility, informed written consent was obtained from the child's parent or legal guardian. Consent forms clearly explained the study's purpose, procedures, voluntary nature of participation, confidentiality safeguards, and the right to withdraw at any stage without affecting medical care.

Following consent, clinical history and demographic details were recorded, including the child's age, gender, frequency and type of breath-holding spells, family history, and any relevant medical background. Physical examinations were performed to rule out concurrent systemic illnesses. Venous blood samples were collected under aseptic conditions for hematological investigations. The primary laboratory parameters evaluated were hemoglobin (Hb), serum ferritin, and mean corpuscular volume (MCV). Hemoglobin was measured in grams per deciliter (g/dL) using an automated hematology analyzer, and serum ferritin levels were assessed in nanograms per milliliter (ng/mL) via chemiluminescent immunoassay. Mean corpuscular volume was recorded in femtoliters (fL). Iron deficiency anemia was operationally defined as a hemoglobin concentration below 10 g/dL in combination with serum ferritin less than 12 ng/mL, reflecting both depleted iron stores and functional deficiency in erythropoiesis (13).

To reduce the risk of selection bias, all eligible children who met the inclusion criteria during the study period were enrolled consecutively. Data collection tools were piloted before the study began to ensure clarity and consistency. The research team underwent standardized training in the data collection process, phlebotomy, and documentation to ensure methodological uniformity. Laboratory testing was conducted at the hospital's central diagnostic facility, which maintains internal and external quality assurance protocols.

Sample size was calculated using an expected prevalence of iron deficiency anemia in children with breath-holding spells at 51.6%, with a 5% confidence level and a precision of 8%. This yielded a required sample size of 150 participants, which was achieved within the planned study duration. All data were double-entered and cross-verified to ensure data integrity. No imputation was applied for missing data; instead, such cases were excluded from respective analyses.

Statistical analysis was performed using IBM SPSS version 25. Continuous variables such as age, hemoglobin levels, serum ferritin, and MCV were summarized using means and standard deviations. Categorical variables including gender, type of breath-holding spell, and anemia severity were expressed as frequencies and percentages. Chi-square test was applied to assess associations between categorical variables, including the stratification of iron deficiency anemia by age and gender. A p-value <0.05 was considered statistically significant. Confounding was minimized by restricting inclusion to children without comorbidities or recent interventions that could influence hematological status.

Ethical approval was obtained from the Institutional Review Board of Divisional Headquarters Teaching Hospital, Mirpur. All participants were enrolled after receiving comprehensive parental informed consent, and data were anonymized using unique coded identifiers to maintain confidentiality. All study procedures complied with national ethical standards and international principles of

biomedical research involving human subjects. To ensure reproducibility, the study employed rigorously defined clinical and laboratory criteria, used validated tools, and maintained a detailed log of procedures and training processes. All records, including consent forms, questionnaires, and laboratory reports, were securely archived for potential future audits or data verification.

RESULTS

A total of 150 children presenting with breath-holding spells were included in the study, with a mean age of 26.45 ± 11.92 months (95% CI: 24.60 to 28.29 months), and an age range of 9 to 54 months. Male participants comprised 54.0% (n=81) of the cohort, while females accounted for 46.0% (n=69). When categorizing the types of breath-holding spells, cyanotic episodes were more common, observed in 56.0% (n=84) of children, whereas 44.0% (n=66) experienced the pallid variant. Regarding the monthly frequency of spells, 52.7% (n=79) of the children experienced fewer than five episodes per month, 24.0% (n=36) had between five and ten episodes, and 23.3% (n=35) suffered from more than ten episodes monthly, indicating a substantial burden of recurrent events among nearly a quarter of the cohort.

Laboratory assessments revealed that the mean hemoglobin level among all participants was 9.25 ± 1.74 g/dL (95% CI: 8.97 to 9.54), while the average serum ferritin concentration was 17.21 ± 12.25 ng/mL (95% CI: 15.15 to 19.27). Mean corpuscular volume (MCV) was recorded at 73.19 ± 3.30 fL (95% CI: 72.63 to 73.75). Iron deficiency anemia (IDA), defined as hemoglobin <10 g/dL in conjunction with serum ferritin <12 ng/mL, was identified in 62.0% (n=93) of children. Among those diagnosed with IDA, 58.7% (n=88) had moderate anemia, with hemoglobin ranging from 7 to 9.9 g/dL, while 3.3% (n=5) were classified as having severe anemia (Hb <7 g/dL). The severity profile indicated that the majority of anemia cases were moderate, reflecting a widespread but clinically manageable deficiency.

When stratified by age, the incidence of IDA was 60.7% (n=71) in children aged ≤36 months (n=117) and 66.7% (n=22) in those older than 36 months (n=33). The chi-square test yielded a p-value of 0.53, indicating no statistically significant difference in IDA prevalence between the two age groups. The odds ratio (OR) for IDA in older versus younger children was 0.84 (95% CI: 0.38 to 1.86), suggesting a similar risk across age brackets. Gender-based analysis showed that 64.2% (n=52) of males and 59.4% (n=41) of females had IDA, with a p-value of 0.59. The OR for IDA in males compared to females was 1.22 (95% CI: 0.61 to 2.42), again showing no significant gender-based disparity in anemia prevalence.

Overall, the findings demonstrate a high burden of iron deficiency anemia among children presenting with breath-holding spells, affecting nearly two-thirds of the population studied. While moderate anemia constituted the predominant form, the presence of severe anemia in a subset of children further highlights the clinical importance of early screening. The lack of significant differences across age and gender subgroups suggests that screening and intervention strategies should be uniformly applied to all pediatric patients with breath-holding spells, regardless of demographic characteristics. These results underline the need for routine hematological evaluation in such clinical presentations to ensure timely diagnosis and management.

Table 1. Demographic and Clinical Characteristics of Children Presenting with Breath-Holding Spells

Characteristic	Value/Category	n (%)	Mean ± SD	95% CI
Age (months)	—	—	26.45 ± 11.92	24.60, 28.29
Age Range (months)	—	—	9 – 54	—
Gender	Male	81 (54.0)	—	—
	Female	69 (46.0)	—	—
BHS Type	Cyanotic	84 (56.0)	—	—
	Pallid	66 (44.0)	—	—
Frequency of BHS/month	<5	79 (52.7)	—	—
	5–10	36 (24.0)	—	—
	>10	35 (23.3)	—	—

Table 2. Laboratory Findings and Incidence of Iron Deficiency Anemia

Parameter	Mean ± SD	95% CI	n (%) with IDA	Severity
Hemoglobin (g/dL)	9.25 ± 1.74	8.97, 9.54	93 (62.0)	Moderate: 88 (58.7) Severe: 5 (3.3)
Serum Ferritin (ng/mL)	17.21 ± 12.25	15.15, 19.27	—	—
MCV (fL)	73.19 ± 3.30	72.63, 73.75	—	—

Table 3. Stratification of Iron Deficiency Anemia by Age and Gender with Group Comparisons

Variable	Group	n with IDA / Total (%)	p-value	Odds Ratio (OR)	95% CI for OR
Age	≤36 months (n=117)	71 / 117 (60.7)	0.53	0.84	0.38, 1.86
	>36 months (n=33)	22 / 33 (66.7)			
Gender	Male (n=81)	52 / 81 (64.2)	0.59	1.22	0.61, 2.42
	Female (n=69)	41 / 69 (59.4)			

Table 4. Severity Distribution of Iron Deficiency Anemia

Severity Level	n (%) of Total Cohort (n=150)	n (%) of IDA Cases (n=93)
Severe (<7 g/dL)	5 (3.3)	5 (5.4)
Moderate (7–9.9 g/dL)	88 (58.7)	88 (94.6)
Total with IDA	93 (62.0)	100

DISCUSSION

The present study revealed that iron deficiency anemia (IDA) was present in 62.0% of children presenting with breath-holding spells (BHS), with the majority (58.7%) experiencing moderate anemia and a smaller proportion (3.3%) having severe anemia. These findings reinforce the hypothesis that IDA is a highly prevalent comorbidity in children experiencing BHS, underscoring the importance of routine hematologic screening in such presentations. The observed association is consistent with previous literature indicating a significant overlap between these two conditions. Shamoon et al. reported a 51.6% prevalence of IDA among children with BHS, which closely aligns with the findings of the present study (11). Similarly, Hamed et al. identified IDA in 61% of children suffering from cyanotic BHS and demonstrated a significant reduction in episode frequency following iron supplementation, suggesting a causative role of iron deficiency in the pathophysiology of these spells (14).

The results further gain credibility through their alignment with the work of Abosdera et al., who found that 62.5% of children with BHS had IDA, and that iron supplementation markedly reduced spell frequency, establishing a strong therapeutic implication for oral iron therapy in such cases (15). In a similar vein, Chesti et al. demonstrated that iron supplementation led to statistically significant improvements in hemoglobin, ferritin, and serum iron levels, and a corresponding reduction in the frequency of BHS episodes, emphasizing the neurophysiological importance of iron in autonomic regulation (16). These findings collectively support the proposed mechanistic link between iron deficiency and BHS, likely mediated through impaired synthesis of monoamine neurotransmitters, disrupted oxygen transport, and compromised brainstem maturation, all of which are dependent on adequate iron availability during early development (4,5). Inflammation-induced hepcidin production and consequent iron sequestration may further exacerbate anemia in susceptible populations, especially in resource-limited settings such as Azad Jammu and Kashmir, where nutritional deficiencies and parasitic infections are endemic (9,10).

Interestingly, this study found no statistically significant differences in the prevalence of IDA with respect to age or gender, which aligns with prior observations by Shamoon et al. and Hanci et al., who also reported uniform distribution across demographic subgroups (11,17). These results suggest that the risk of IDA in children with BHS is independent of these variables and that targeted interventions should not be restricted based on age or sex. However, the slight predominance of the cyanotic type of BHS (56%) over pallid type (44%) observed in this study echoes the findings of Amir et al., who reported cyanotic episodes in up to 96% of cases and further validated the effectiveness of iron therapy in reducing their frequency (18). Such findings support the inclusion of hematological evaluations as a core component of diagnostic protocols for BHS, regardless of clinical subtype.

The clinical relevance of these findings is substantial. BHS, although benign, can cause significant parental distress and may lead to unnecessary neurological evaluations or antiepileptic treatments if misdiagnosed. Identifying a modifiable and treatable cause such as IDA offers a low-cost, evidence-based intervention that can substantially improve patient outcomes and reduce healthcare burden. From a mechanistic standpoint, the data support the notion that iron plays a key role in maintaining autonomic homeostasis, and its deficiency may lower the threshold for exaggerated vagal responses during emotional or physical triggers, precipitating BHS. These implications strengthen the argument for integrating nutritional screening into routine pediatric assessments, especially in regions where iron deficiency is endemic.

Despite its contributions, this study is not without limitations. The single-center design and non-probability sampling limit the generalizability of results beyond the studied population. The sample size, while adequate for estimating prevalence, may not have been large enough to detect subtle associations with demographic or clinical variables. Additionally, the study did not include longitudinal follow-up to assess the impact of iron supplementation on the resolution of BHS, which would have added significant value. Another methodological constraint was the reliance on parental recall for the frequency and severity of spells, which could introduce reporting bias. Moreover, although laboratory methods were standardized, no inflammatory markers were measured to exclude anemia of chronic disease, which may confound ferritin-based IDA diagnosis.

Nevertheless, the study's strengths lie in its clearly defined inclusion criteria, robust diagnostic standards for IDA, and comprehensive data collection methodology. These factors enhance internal validity and allow for meaningful comparisons with existing literature. The use of standardized tools and clinical definitions ensures reproducibility and contributes to the growing body of evidence supporting the link between iron deficiency and BHS.

Future research should focus on multicenter, longitudinal studies involving larger sample sizes to confirm these findings and evaluate the therapeutic impact of iron supplementation on the frequency and severity of BHS. Randomized controlled trials investigating dose-response relationships, duration of treatment, and recurrence rates post-therapy would further strengthen the clinical evidence base. Additionally, incorporating neurophysiological and inflammatory biomarkers could enhance understanding of the

pathophysiological mechanisms linking IDA and BHS. Such studies would not only validate current findings but also support the development of clinical guidelines aimed at standardizing care for pediatric patients with breath-holding spells.

CONCLUSION

This study identified a high frequency (62.0%) of iron deficiency anemia among children presenting with breath-holding spells at DHQ Mirpur, Azad Kashmir, underscoring a significant and clinically relevant association. The findings emphasize the importance of routine screening for iron status in pediatric patients with BHS, regardless of age or gender, to enable early diagnosis and effective management. Clinically, this supports the integration of iron supplementation protocols into standard care pathways for BHS, potentially reducing the frequency and severity of episodes and alleviating caregiver distress. From a research perspective, these results highlight the need for longitudinal and interventional studies to evaluate the therapeutic benefits of correcting iron deficiency in this population and to further explore the neurophysiological mechanisms underlying the observed association.

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