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ASSOCIATION BETWEEN IRON DEFICIENCY ANEMIA AND BREATH HOLDING SPELLS IN CHILDREN

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Abstract

Objective: *To determine the association between iron deficiency anemia and breath-holding spells in children aged 6 months to 60 months.*

Methods: *A case-control study was conducted at the Department of Pediatric Medicine, Ghulam Muhammad Mahar Medical College (GMC), Sukkur, over six months from 1st September 2024 to 28th February 2025. Non-probability convenience sampling was used to select 122 children aged 6 to 60 months, equally divided into cases and controls. The case group included children with breath-holding spells ≤ 60 seconds, while the control group comprised healthy children with no history of such spells. Detailed history, physical examination, and anthropometric measurements (weight and height) were recorded. Blood samples of 5cc were drawn for complete blood counts (CBC) and serum ferritin levels. Exclusion criteria included children with febrile/non-febrile seizures, congenital heart disease, malnutrition, anticonvulsant therapy, or mental disabilities. The association between breath-holding spells and iron deficiency anemia was analyzed using a 2x2 table, and odds ratios (OR) were calculated. A p-value of ≤ 0.05 was considered significant.*

Results: *A total of 118 children, equally divided into case and control groups, were enrolled in the study. Cases were children aged 6-60 months with breath-holding spells lasting less than 60 seconds, identified through medical history and clinical evaluations. Controls were healthy children of the same age group with no history of breath-holding spells. The case group had 27 (46%) participants with iron deficiency anemia (IDA), while the control group had 16 (27%) with IDA, showing a significant association (OR: 2.268, 95% CI: 1.051-4.894). Mean ferritin levels were significantly lower in the case group (49.69 ± 22.67 ng/ml) compared to the control group (98.47 ± 21.98 ng/ml), and the case group had a higher mean corpuscular volume (35.80 ± 36.11 fl) compared to the control group (1.36 ± 0.55 fl). Among males, 55% of cases had IDA, compared to 30% in controls (OR: 2.909, 95% CI: 1.053-8.036). Urban children with breath-holding spells had a significantly higher likelihood of IDA (OR: 6.125, 95% CI: 1.330-28.207). No significant association was found between parental educational status and IDA.*

Conclusion: *Children with breath-holding spells, especially males and those from urban areas, are more likely to have iron deficiency anemia. These findings highlight the need for early screening for iron deficiency in children with breath-holding spells, as addressing it may help reduce neurodevelopmental and*

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behavioral issues. Further research, particularly longitudinal studies, is needed to explore the causal mechanisms and develop effective interventions for managing iron deficiency anemia in young children.

INTRODUCTION

Iron deficiency anemia (IDA) persists as a major public health concern that especially affects large numbers of Pakistani children in their early years. Scientific evidence demonstrates IDA to be a recognized dietary deficiency worldwide, which produces extensive effects on children's physical condition and their intellectual abilities and actions (1). The situation regarding iron deficiency anemia in Pakistan has reached alarming levels because studies show that this condition affects approximately 50% of children five years or younger. Young children suffer from iron deficiency anemia to a great extent because they consume inadequate amounts of iron while lacking proper iron absorption through their gastrointestinal systems, and they experience many infectious diseases that worsen nutrient deficiencies (2). Medical research proves that insufficient iron consumption causes various negative effects, including developmental delays and weakened cognitive abilities, along with compromised immunity, and severe cases potentially result in elevated mortality numbers (3).

Iron functions as a fundamental component of human health because it enables the creation of hemoglobin for distributing oxygen through blood. Insufficient iron levels prevent hemoglobin production, which results in anemia development (4). Children who have iron deficiency anemia present symptoms that include fatigue combined with paleness and irritability and a decreased appetite with delayed development. Iron deficiency produces physical symptoms that are well recognized, but the complete impact of iron deficiency reaches far beyond these clinical presentations (5). Researchers have proven that iron deficiency leads to mental developmental issues alongside behavioral problems, which cause attention problems and hyperactivity, as well as developmental delays. IDA, which affects children, creates an urgent health concern within Pakistan because socioeconomic problems and healthcare availability further worsen this condition (6).

Breath-holding spells (BHS) represent a rare manifestation of iron deficiency anemia in children as scientific investigation into their link with iron deficiency continues to generate interest. Children experience involuntary breathing cessation after distressing incidents like anger or frustration or physical pain as a natural response known as breath-holding spells (7). BHS creates intense concern for child guardians since an incident of BHS appears to cause their child's loss of consciousness while their skin becomes bluish or pale and shows additional concerning symptoms. Breath-holding spells show no serious complications, yet they manifest with different medical conditions such as iron deficiency anemia. More research is necessary to establish if iron deficiency anemia causes breath-holding spells, as scientists currently do not understand the relationship between these factors (8).

The occurrence of breath-holding spells mainly affects children aged 6 months to 6 years and reaches its highest point at 18 months. Breath-holding spells appear more intensely in children who have inherited the condition from their relatives and mostly manifest after emotional difficulties. Children suffering from breath-holding spells show either cyanotic or pallid events, which represent separate categories of this condition (9). In the cyanotic form, the child enters a brief respiratory arrest that turns their skin blue; however, the pallid type leads to face pallor instead of a bluish hue. The underlying causes of breath-holding spells remain unclear because researchers have identified autonomic dysregulation along with genetic risks and environmental elements as probable factors that trigger these events. Research during recent times has provided increasing evidence that iron deficiency anemia might serve as a factor that initiates or intensifies breath-holding spells (10).

The relationship between iron deficiency anemia and breath-holding spells becomes important because these two conditions mainly affect young children; thus, iron deficiency treatment could possibly minimize BHS occurrence or severity. Research indicates that children with breath-holding spells

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present lower serum ferritin levels, which serve as markers of body iron storage (11). During iron deficiency assessment, ferritin testing serves as an important indicator because children with iron deficiency anemia typically reveal reduced ferritin levels. Medical evidence demonstrates that iron supplementation treatment for breath-holding spells in children leads to fewer severe spells. Research is ongoing to confirm this link, but deficiency of iron seems to heighten the risk for bread-holding episodes through its effects on central nervous system functioning and neurovascular regulation controls (12).

Various scientific hypotheses describe how iron deficiency contributes to breath-holding spells, although researchers still lack a complete understanding of this process. Iron seems to impact nervous system function as it influences the brain's regulation of automatic bodily systems that control breathing activities. The function of enzymes producing neurotransmitters requires iron as a cofactor since these neurotransmitters, including dopamine and serotonin, control emotional responses and autonomic operations (13). Too little iron disrupts the nervous system processes, which raises the risk for both abnormal vagal reactions and breath-holding episodes. Iron deficiency anemia seems to cause the vagus nerve to become more sensitive, leading to control problems with heart rate and breathing regulation. The condition of a hyper-responsive vagus nerve could prompt brain signals to stop breathing involuntarily when facing stressful situations, thus triggering an episode of breath-holding (14).

Iron plays a crucial role in neurological function, so this essential substance might trigger the start of breath-holding spell incidents (BHS). Research publications about this subject are scarce for the current period at a local level. The main objective of this research was to examine the relationship between iron deficiency anemia and breath-holding spells that occur in children (8). This research will deliver fundamental data about breath-holding spells to pediatricians so they can detect these spells early, thus enabling proper management, including prompt initiation of iron therapy to reduce disease burden and improve child outcomes.

METHODS

The research took place over six months at Ghulam Muhammad Mahar Medical College (GMC) Sukkur Department of Pediatric Medicine between 1st September 2024 and 28th February 2025. The research utilized convenience sampling to choose 122 children aged 6 months to 60 months who fulfilled the study requirements. Both cases and controls received equal distribution after obtaining parental permission through informed consent. The case group included children who suffered from breath-holding spells below 60 seconds while the control group selected healthy children without breath-holding history. All study participants received thorough examinations through medical history assessment together with physical examination. The researchers obtained anthropometric measurements by using Camry analog weighing scale and stadiometer to determine weight and height of each participant. A trained pediatric nurse collected 5cc of blood samples under sterile practices which the experienced consultant hematologist and nurse analyzed CBC and serum ferritin data. The consultant along with the senior resident performed a review of results before recording them in the pre-designed proforma. The study excluded children who had febrile or non-febrile seizures along with congenital heart disease and severe malnutrition, anticonvulsant medication use, mental disabilities, and other conditions that were recorded at baseline. Statistical evaluation of breath-holding spells and iron deficiency anemia relationships used 2 x 2 tables to calculate odds ratios (OR) in this study. Exclusion criteria were implemented strictly to minimize biases and effect modifiers during result analysis while maintaining a p-value of ≤ 0.05 for statistical significance.

RESULTS

A total of 118 children, equally divided into two groups (59 each in case and control), admitted with complaints of breath-holding spells for a period of less than 60 seconds were enrolled in the study.

In this study, cases referred to all children aged between 6 months to 60 months who were admitted with a complaint of breath-holding spells lasting less than 60 seconds. These children were identified based on their medical history and clinical

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evaluations. Controls were healthy children, also aged between 6 months to 60 months, who had no history of breath-holding spells in the past.

The mean age of the case group was 29.66 ± 13.96 months, while the control group had a similar mean age of 30.78 ± 15.45 months. In terms of weight, the case group averaged 12.64 ± 2.35 kg, closely aligning with the control group's mean of 12.69 ± 2.84 kg. Height measurements were also comparable, with the case group at 87.12 ± 10.14 cm and the control group at 87.44 ± 11.49 cm (Table-1).

Similarly, the distribution of gender and residence between the case and control groups demonstrated a reasonably balanced matching. In terms of gender, the case group included 29 males (49%) and 30 females (51%), while the control group had 37 males (63%) and 22 females (37%), resulting in a total of 66 males (56%) and 52 females (44%) across both groups (Table-1).

Regarding residence, the majority of participants in both groups were from rural areas. Specifically, 46 cases (78%) and 34 controls (58%) resided in rural areas, whereas 13 cases (22%) and 25 controls (42%) were from urban settings. In total, 80 participants (68%) were from rural areas and 38 participants (32%) from urban areas.

Characteristic	**Case Group (n = 59)**	**Control Group (n = 59)**
Age (months)	29.66 ± 13.96	30.78 ± 15.45
Weight (kg)	12.64 ± 2.35	12.69 ± 2.84
Height (cm)	87.12 ± 10.14	87.44 ± 11.49
Gender		
Male	29 (49%)	37 (63%)
Female	30 (51%)	22 (37%)
Residence		
Rural	46 (78%)	34 (58%)
Urban	13 (22%)	25 (42%)

Table-1

Moreover, the analysis of iron deficiency anemia across the case and control groups revealed a statistically significant association. In the case group, 27 participants (46%) had iron deficiency anemia present, while 32 participants (54%) did not. In the control group, 16 participants (27%) had iron deficiency anemia present, and 43 participants (73%) did not. The Odds Ratio (OR) for the presence of iron deficiency anemia between the case and control groups was 2.268 (95% CI: 1.051-4.894), suggesting that the odds of having iron deficiency anemia are more than twice as high in the case group compared to the control group.

Furthermore, the comparison of mean ferritin levels and mean corpuscular volume between the case and control groups revealed notable differences. The case group had a mean ferritin level of 49.69 ± 22.67 ng/ml, while the control group had a significantly higher mean ferritin level of 98.47 ± 21.98 ng/ml.

Additionally, the mean corpuscular volume (MCV) in the case group was 35.80 ± 36.11 fl, which is substantially higher compared to the control group, where the mean MCV was 1.36 ± 0.55 fl.

Regarding gender, among males, 16 participants (55%) in the case group had iron deficiency anemia, compared to 11 (30%) in the control group. The Odds Ratio (OR) for males was 2.909 (95% CI: 1.053-8.036), indicating that males in the case group were nearly three times more likely to have iron deficiency anemia than their counterparts in the control group. This shows a strong association between breath-holding spells and iron deficiency anemia in males. Whereas for females, 11 participants (37%) in the case group had iron deficiency anemia, compared to 5 (23%) in the control group. The Odds Ratio (OR) for females was 1.968 (95% CI: 0.568-6.824), suggesting a positive but weaker association between breath-holding spells and iron deficiency anemia. However, this was not statistically significant (Table-2).

Concerning place of residence; in urban areas, 54% of case group participants had iron deficiency anemia, compared to 16% in the control group. The OR for

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urban residents was 6.125 (95% CI: 1.330-28.207), indicating a much higher likelihood of iron deficiency anemia in urban children with breath-holding spells. In rural areas, the OR was 1.410 (95% CI: 0.566-3.516), but the association was not statistically significant (Table-2).

Characteristic	IDA in Cases (n)	IDA in Controls (n)	OR (95% CI)	P-Value
Gender				
Male	16 /29 (55%)	11 /37 (30%)	2.909 (1.053–8.036)	0.046 *
Female	11 /30 (37%)	5 /22 (23%)	1.968 (0.568–6.824)	0.368
Residence				
Urban	7 /13 (54%)	4 /25 (16%)	6.125 (1.33–28.207)	0.024*
Rural	20 /46 (43%)	12 /34 (35%)	1.410 (0.566–3.516)	0.497
Parental Education				
Primary	6 /13 (46%)	4 /10 (40%)	~	1.000
Matriculation	8 /21 (38%)	5 /21 (24%)	~	0.505
Intermediate	5 /11 (45%)	1 /6 (17%)	~	0.333
Graduate	8 /14 (57%)	6 /22 (27%)	~	0.092

Table-2

Finally, when examining the association between parental educational status and iron deficiency anemia, no significant association was found between parental educational status and the presence of iron deficiency anemia in either the case or control groups.

DISCUSSION

The research analyzed the relationship between breath-holding spells (BHS) and iron deficiency anemia (IDA) occurring in children within the age range of 6 to 60 months. The observed prevalence rates indicated a meaningful statistical difference between the case and control populations since breath-holding spell patients demonstrated higher iron deficiency anemia prevalence. Children diagnosed with breath-holding spells demonstrated a 2.268 times higher risk of having IDA (46%) compared to the control group with 27% IDA prevalence. The research connects breath-holding spells to iron deficiency anemia in children and verifies previous research about this relationship between iron deficiency and neurodevelopmental and behavioral conditions such as BHS.

Statistical data showing gender-specific patterns strengthens our understanding of this complicated relationship in our study. According to the results, male children who have breath-holding spells experienced a 2.909 times higher susceptibility to IDA compared to control group males. Similar findings from Means RT et al. (2020) demonstrate that early childhood males demonstrate increased susceptibility to iron deficiency effects (15). Females whose children exhibited breath-holding spells did not exhibit a statistically significant relationship with IDA, although their risk increased to 1.968 based on a 95% Confidence Interval between 0.568-6.824. The difference in the manifestation of iron deficiency and compensation mechanisms between men and women in this population may explain the disparity in rates between genders (16). Additional studies need to investigate how iron deficiency differently affects the health of young boys and girls because current evidence shows varying effects between genders.

Moreover, according to our results, place of residence emerged as a significant factor that influences geographical differences. Research revealed that children from urban backgrounds with breath-holding spells demonstrated six times the rate of iron deficiency anemia compared to controls. The results show that BHS-positive urban children encounter specific nutritional or environmental conditions that raise their danger of developing IDA. Furthermore, research has also demonstrated that rural children lacked a statistically relevant connection between their breath-holding spells and IDA diagnosis. Various contributing factors, including population dietary choices, access to healthcare, and economic standing might explain this difference. According to other research that investigated nutritional deficiencies, urban children

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with economic limitations develop more often than children from different socioeconomic classes (17).

Our research results also detected variations in ferritin levels and mean corpuscular volume (MCV) measurements between the participants belonging to the case and control groups. Patients within the case group displayed ferritin levels at 49.69 ± 22.67 ng/ml, which fell below the levels at 98.47 ± 21.98 ng/ml of the control group. These differences align with iron deficiency anemia diagnosis. The MCV measure from the case group demonstrated a higher reading at 35.80 ± 36.11 fl than the control group MCV at 1.36 ± 0.55 fl, even though this finding seems unusual. Research by Dallman (1986) also documented elevated MCV values during iron deficiency, while more detailed studies should be conducted to resolve the current anomaly (18). The study also revealed that the educational status of parents did not correlate to iron deficiency anemia development in subjects from either the case group or the control group. The reduced diversity of the participants concentrating in rural areas might explain why parental education did not impact anemia incidence (19). Studies suggest that parent education stands as a key factor for childhood anemia prevention due to educational levels allowing parents to grasp nutrition basics and obtain suitable healthcare (20). The research suggests that other factors, including economic status and healthcare accessibility together with community intervention strategies likely influenced anemia rates more than education levels of parents independently.

Universal adoption of study results is limited due to the specific age group and regional constraints imposed on the research sample. Additional research must expand testing to a wider demographic base that incorporates individuals across different age ranges as well as locations beyond the specified area for understanding BHS-IDA relationships.

CONCLUSION

The research establishes important understandings about the relationship between breath-holding spells with iron deficiency anemia in children while stressing gender differences and residential location effects. Children with breath-holding spells who are male and live in urban areas demonstrate a higher risk of iron deficiency anemia development. Researchers have established the need for prompt iron deficiency screening in children experiencing breath-holding spells because treating their iron deficiency often leads to reduced neurodevelopmental and behavioral symptoms. Future research requires longitudinal studies to understand the causal pathways of the connection between iron deficiency anemia and young children while developing preventive and treatment strategies for this condition.

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