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Research Article

**THE FREQUENCY OF ANEMIA AMONG CHILDREN  
PRESENTING WITH BREATH HOLDING SPELLS**<sup>1</sup> Muhammad Rafiq Khan, <sup>2</sup> Haji Gul, <sup>3</sup> Jalil Khan

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**Abstract:**

**Introduction:** Breath-holding spells (BHS) are among the common benign paroxysmal non-epileptic disorders occurring in healthy otherwise normal children. A detailed history and exam are important to diagnose these spells and help distinguish from epileptic seizures and other causes of syncope. The spells most commonly begin in the first 6 to 12 months of life and almost always by 2 years of age. Iron deficiency anemia has also been shown to play a role in the pathophysiology of breath holding spells. It has been documented that iron deficiency anemia may lead to adverse effects on oxygen uptake in the lungs and reduce available oxygen to the tissues, including central nervous system tissues.

**Objective:** To determine the frequency of anemia among children presenting with breath holding spells.

**Study Design:** Cross-sectional descriptive study.

**Site and Duration of Study:** This study was conducted in the in the Department of Pediatrics Medicine, Khalifa Gul Nawaz Teaching Hospital, from 20-03- 2018 to 20-06-2018.

**Methodology:**

A total of 148 cases of BHS were selected in a consecutive manner OPD and their hemoglobin level was determined.

**Results:** The mean age group of our sample was  $2.6 \pm 1.4$  years of which 63.5% were male and 36.5% were female children. The mean hemoglobin concentration was  $8.6 \pm 1.9$  gm/dl of blood and 39.9% of children were confirmed to have anemia.

**Conclusion:**

There is a high incidence of iron deficiency anemia associated with breath holding spells. A full blood count and where possible serum ferritin level would therefore be warranted in the work up of these children.

**Key words:** Breath holding spells, iron, hemoglobin, anemia, ferritin

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**INTRODUCTION:**

Breath-holding spells (BHS) are among the common benign paroxysmal non-epileptic disorders occurring in healthy otherwise normal children [1]. The prevalence has been estimated between 0.1% and 4.6% in the general population [2]. These were first described in 1737 by Nicholas Culpepper and were thought to be voluntary breath holding. These episodes are often precipitated by emotional stimuli like anger, frustration, sudden fright, or minor trauma [3]. A detailed history and exam are important to diagnose these spells and help distinguish from epileptic seizures and other causes of syncope. The cornerstone of therapy is reassuring the parents and educating them about the condition. Iron therapy, piracetam, levetiracetam, and atropine are considered as treatment and have shown variable efficacy [4].

The spells most commonly begin in the first 6 to 12 months of life and almost always by 2 years of age. In 90% of children the spells got remission by school age and the persistence is extremely rare [5]. The mechanism of Breath-holding spells (BHS) yet remains controversial. The presence of autonomic imbalance with cerebral anoxia, anemia and genetic disorders may be responsible in these spells [6].

Iron deficiency anemia has also been shown to play a role in the pathophysiology of breath holding spells. A study showed complete resolution of spells in 50% patients on iron therapy and 50% reduction in another 36.4% [7]. A recent Cochrane Systematic Review suggests that iron supplementation reduces the frequency and severity of breath-holding attacks, particularly in children with iron deficiency (OR 76.48; 95% CI 15.65 to 373.72;  $P < 0.00001$ ) [6]. It has been documented that iron deficiency anemia may lead to adverse effects on oxygen uptake in the lungs and reduce available oxygen to the tissues, including central nervous system tissues<sup>8</sup>. In one study, association of breath holding spells with iron deficiency anemia in children revealed as 56.67% anemia in cases with BHS and 3.33% in controls without BHS ( $P$  value 0.0001) [9]. In another study, 7.5% of anemic children had history of BHS [10]. In a study by Khan I et al, there was a statistically significant fall in the frequency of breath holding spells with 12 weeks of iron therapy. At start of therapy, 25 patients were having more than 10 episodes per week while no patient was having such episodes at 12 weeks of therapy ( $p$ -value=0.000) [11].

The present study is designed to determine the frequency of anemia among children presenting with Breath-holding spells (BHS). This type of study is

not yet done in our pediatric population and a thorough literature search suggested very rare work done on this grave issue throughout Pakistan. This study will be an attempt to establish the local magnitude of the anemia among children with Breath-holding spells (BHS). The results of this study will be shared with other local pediatricians to make them aware of the problem and to develop future recommendations for preventing and treating Breath-holding spells (BHS).

**METHADODOLOGY:**

This study was conducted in the in the Department of Pediatrics Medicine, Khalifa Gul Nawaz Teaching Hospital in the duration of 03 months from March 2018 to June 2018. It Was 148, keeping frequency of 56.6%<sup>9</sup> proportion of anemia among children with Breath-holding spells (BHS), with 95% confidence interval & 8% margin of error using World Health Organization(WHO) sample size calculator.

**SAMPLE SELECTION****Inclusion Criteria:**

1. All children presenting breath holding spells as history given by mother.
2. Both genders (male & females) was included.
3. All children with age between 6 months to 5 years.

**Exclusion Criteria:**

1. Children with thalassemia as detected on medical records.
2. Children with congenital malformations of the throat on physical examination.
3. Children with malnutrition as detected by physical examination and growth chart.
4. Children with history of multivitamin supplementation in the last two weeks.

The above mentioned conditions can act as confounders and if included will introduce bias in the study results.

**OPERATIONAL DEFINITIONS:**

**Breath Holding Spells:** Mother giving history of child breathing stopped during expiration after a deep inspiration and sudden recovery towards normal breathing within few seconds.

**Anemia:** Hemoglobin value of less than 8gm/dl at the time of presentation of the child and will be measured in hospital laboratory

**DATA COLLECTION PROCEDURE**

The study was conducted after approval from hospitals ethical and research committee. All children meeting the inclusion criteria and presenting with Breath-holding spells (BHS) was included in the

study. The purpose and benefits of the study was explained to the patient and a written informed consent was obtained. All patients were subjected to complete history and clinical examination. From all the children, a 5cc of blood was obtained under aseptic technique and sent to hospital laboratory to detect anemia. All the laboratory investigations were done under supervision of same consultant pathologist having minimum of five years of experience. All the above mentioned information including name, age, sex was recorded in a pre-designed Performa and strictly exclusion criteria were followed to control confounders and bias in the study results.

#### DATA ANALYSIS:

Data was stored and analyzed in SPSS version 20. Mean  $\pm$  SD was calculated for quantitative variables like age and hemoglobin level. Frequencies and percentages was calculated for categorical variables like gender and anemia. Anemia was stratified among age and gender to see the effect modifications. post stratification was done through chi-square test keeping p-value  $\leq$  0.05 was taken significant. All results were presented in the form of table and graphs.

#### RESULTS:

The study was conducted on 148 children presenting with breath holding spells. We analyzed their serum hemoglobin concentration to determine the presence or absence of anemia. The mean age of the sample was  $2.6 \pm 1.4$  years. The range of age in our study was 4.20 years with minimum age of 0.8 years and maximum age of 5.00 years. On grouping the sample in different age groups, we observed that 30.4% of patients were in the age group between 6 months and 1.5 years, 27.7% were in the age group 1.51 to 3.00 years and 41.9% of patients were in the age group 3.01 to 5.00 years. (Table 1) While distributing the patients with regards to gender, we observed that in our study 63.5% of the sample was male and 36.5% were female gender. (Table 2)

The mean hemoglobin concentration was  $8.6 \pm 1.9$  gm/dl of blood. As per operational definitions, we observed that 39.9% of children were confirmed to have Anemia. (Table 3) While we stratified Anemia with regards to age groups, we observed that the difference was statistically significant after applying chi square test with a p value of 0.035 (Table 4) While we stratified Anemia with regards to gender, we observed that the difference was statistically significant after applying chi square test with a p value of 0.023 (Table 5).

**Table 1**  
**AGE-WISE DISTRIBUTION OF SAMPLE (n=148)**

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Age of the Child	148	4.20	.80	5.00	2.6669	1.41942

Age Groups	Frequency	Percent
6.00 months to 1.5 years	45	30.4
>1.5 to 3 years	41	27.7
>3 years to 5 years	62	41.9
Total	148	100.0

**Table 2**  
**GENDER-WISE DISTRIBUTION OF SAMPLE (n=148)**

Gender	Frequency	Percent
Male	94	63.5
Female	54	36.5
Total	148	100.0

**Table 3**  
**FREQUENCY OF ANEMIA (n=148)**

Anemia	Frequency	Percent
Yes	59	39.9
No	89	60.1
Total	148	100.0

**Table 4**  
**AGE GROUP WISE STRATIFICATION OF ANEMIA (n=148)**

		Anemia		Total
		Yes	No	
Age Groups	6.00 months to 1.5 years	25 55.6%	20 44.4%	45 100.0%
	>1.5 to 3 years	13 31.7%	28 68.3%	41 100.0%
	>3 years to 5 years	21 33.9%	41 66.1%	62 100.0%
Total		59 39.9%	89 60.1%	148 100.0%

P VALUE: 0.035

**Table 5**  
**GENDER GROUP WISE STRATIFICATION OF ANEMIA (n=148)**

		Anemia		Total
		Yes	No	
Gender of the Child	Male	44 46.8%	50 53.2%	94 100.0%
	Female	15 27.8%	39 72.2%	54 100.0%
Total		59 39.9%	89 60.1%	148 100.0%

P VALUE: 0.023

### DISCUSSION:

Breath-holding spells represent an age-limited disorder. It usually begins between the ages of 6 and

24 months of life, peaking in frequency by around 2 to 3 years, and 90% or more of patients have their initial spells by age 2 years.<sup>12</sup> It may begin as early as

during neonatal period, and almost never after the age of 5 years. About half of the children stops experiencing spells by age 4 years, and almost all by age 6 years, beyond which their occurrence is extremely uncommon [13]. A genetic causative factor may be responsible for the disease, and autosomal-dominant inheritance is suggested. A positive family history of BHS has been reported in up to 30% of children with BHS [14].

Breath-holding spells are extremely frightening to parents. Episodes are described as infants crying, for up to a minute, and while crying excessively they will hold their breath to a point at which they might lose consciousness. On rare occasions a seizure might be witnessed immediately after the infant loses consciousness; soon thereafter, the infant will usually regain consciousness and breathe normally. Breath-holding spells are not harmful and pose no long-term risks for the infant<sup>15</sup>. Many episodes of breath holding are associated with an inciting incident in which the infant is irritated, is being disciplined, or is angry. Examples include when infants are having their hair splashed in the bath, when they insist on holding a toy, or when they experience a minor injury [16]. While considered by many to be “attention seeking” behavior, these spells are not intentional; they result from an involuntary reflex, and the child has no ability to control them [17]. In a recent study from Turkey, children with breath-holding spells and a matched control group were subjected to a brainstem auditory evoked potentials test, and the interpeak latencies were significantly prolonged in the breath-holding spells group compared with the control group ( $P = .009$  and  $P = .03$ , respectively, for type III–V and type I–V interpeak latencies). This might mean that maturation delay in myelination of the brainstem could be the cause of breath-holding spells in children [18].

Several studies, suggest an association between breath-holding spells and anemia in young infants. Among 91 children 6 to 40 months of age who were followed prospectively for an average of 2 years, 63 (69%) were found to have iron deficiency anemia<sup>19</sup>. About half (47.9%) of 165 children in another group from Turkey with breath-holding spells were found to have iron deficiency anemia, and a recent larger Turkish study confirms these findings<sup>20</sup>. Two studies established the benefit of treatment with iron. In one group treated with iron (6 mg/kg daily) for 3 months, a significant reduction in cyanotic spells was recorded, compared with those not treated (84% vs 21%). In the second study, mean levels of hemoglobin and total iron-binding capacity were predictive of a substantial reduction in the frequency

of spells (88% vs 6%) for iron-treated versus untreated children, respectively<sup>21</sup>. Owing to the high frequency of anemia among children with breath-holding spells, testing for anemia or treating empirically for iron deficiency anemia is recommended. Iron deficiency anemia has also been shown to play a role in the pathophysiology of breath holding spells<sup>22</sup>. A study showed complete resolution of spells in 50% patients on iron therapy and 50% reduction in another 36.4%. A recent study has also suggested a possible relationship between maternal iron deficiency anemia and children with breath holding spells. Iron’s role is thought to be due to it being a cofactor in catecholamine metabolism and neurotransmitter function [23].

Although the pathogenesis and the triggering factors of the disease are not quite understood, there are studies indicating that iron deficiency anemia is frequently observed in children with spells which respond well to iron therapy. Piracetam treatment has been demonstrated to be effective in children without anemia. It is well known that children with iron deficiency cry more frequently, become easily depressed, and are more irritable [24]. Similarly, the present study also documented that iron deficiency was observed with higher frequency in patients with breath-holding spells. In another study association of breath holding spells with iron deficiency anemia in children revealed as 56.67% ( $n=17$ ) in cases and 3.33% ( $n=1$ ) in control group while remaining 43.33% ( $n=13$ ) in cases and 96.67% ( $n=29$ ) in control group had no findings of this association. P value was calculated as 0.0001 and Odds Ratio was 37.92 which show a significant difference between the two groups [25]. In another study, a total of 165 children with BHS comprised the study group. A matched group of 200 children with febrile convulsions served as controls. Among the first-degree relatives, 13.3% had BHS, 1.8% had febrile convulsions and 12.1% had epilepsy. The spells were cyanotic in 140 (84.8%) children and pallid or mixed in the remainder. Eighteen patients had abnormalities in electroencephalography, however only one patient was diagnosed with epilepsy. Sixty-nine (47.9%) patients were found to have iron deficiency anemia [26]. Iron deficiency is implicated in conditions other than anemia (a late manifestation) and BHS. It is increasingly recognized to be a cause of restless legs, febrile seizures, thrombosis, impaired immunity and poor behaviour. It is known that children who have experienced BHS may become adolescents with syncopal episodes. A recent retrospective cohort study of largely non-iron deficient children with BHS showed a 29.4% incidence of concentration problems [1]. It is not known how iron deficiency leads to

BHS. It may involve the role of iron in catecholamine metabolism and the functioning of enzymes and neurotransmitters in the central nervous system<sup>10</sup>. Increased brain erythropoietin production may have a protective effect. The correction of spells during treatment with iron may be related to the functional restoration of these neurotransmitters [27]. In another study, anger and pain were the most common triggering factors (65.1 %) for BHS. A positive family history of BHS was identified in 51% and parental consanguinity was found in 30% of cases. The spells were cyanotic in 79.1% (34 children). 78% of cases were iron deficient and 53% of cases had iron deficiency anemia [25].

Infancy and childhood is the critical period for brain growth, and nutrient deficiencies during this time may affect psychomotor development and neurocognition. Iron deficient infants are often apathetic, listless, irritable and anorexic. These symptoms resolve rapidly with iron supplementation but less well known is the fact that long-term neurocognitive impairment may persist [28]. Young children with iron deficiency anemia have been found to score 12 to 15 points lower on the Bayley infant development scale than their iron sufficient peers. There is a high incidence of iron deficiency anemia associated with breath holding spells. A full blood count and where possible serum ferritin level would therefore be warranted in the work up of these children [16]. Treatment is more likely to be successful when there is concomitant iron deficiency anemia. Length of iron therapy can vary between 4 and 16 weeks. A course of 8 weeks would seem reasonable, long enough to improve anemia [15].

### CONCLUSION:

There is a high incidence of iron deficiency anemia associated with breath holding spells. A full blood count and where possible serum ferritin level would therefore be warranted in the work up of these children. Treatment is more likely to be successful when there is concomitant iron deficiency anemia. Length of iron therapy can vary between 4 and 16 weeks. A course of 8 weeks would seem reasonable, long enough to improve anemia.

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