

## Original Research Article

# Role of iron in breath holding spells and effect of iron therapy in children

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## ABSTRACT

**Background:** Breath holding spells (BHS) are paroxysmal events resulting from painful stimulus or emotional event resulting in forceful crying, occur in children's aged between 6 months to 6 years. To assess the role of iron in breath holding spells (BHS) and to assess the efficiency of iron therapy in reducing frequency of BHS.

**Methods:** This was a prospective, interventional study conducted at GMC Baramulla. A total of 70 patients between the ages of 6 months and 5 years with breath holding spells with iron deficiency and iron deficiency anemia were studied. After giving them iron therapy for 6 and 12 weeks, they were assessed for the improvement in their anemia and its impact on the frequency of breath holding spells.

**Results:** Seventy children with breath holding spells were studied prospectively. Forty (57.15%) cases were males and 30 (42.85%) females. There was a statistically significant rise in the hemoglobin level, serum ferritin, serum iron with 6 and 12 weeks of iron therapy ( $p < 0.001$ ). This rise in the hemoglobin level serum ferritin and serum iron was associated with a statistically significant fall in the frequency of breath holding spells with 6 and 12 weeks of iron therapy ( $p < 0.001$ ).

**Conclusions:** Iron supplement is effective in reducing the frequency of breath holding spells and thus iron has a role in BHS.

**Keywords:** Breath holding spells, Children and iron deficiency, Anemia and serum ferritin

## INTRODUCTION

Breath-holding spells (BHSs) are involuntary pauses of breathing, sometimes accompanied by loss of consciousness. They usually occur in response to an upsetting or surprising situation. They occur most commonly within the first 12 months of life and virtually all breath holders experience their initial spell by the age of two years.<sup>1,2</sup> In some children, BHSs may be related to iron deficiency anemia, a condition in which the body does not produce a normal number of red blood cells. In prior researches about these spells, pathophysiologic mechanisms are emphasized on autonomic nervous system dysregulation.<sup>1-3</sup> Holowach and Thurston speculated that

having an anemia in children who suffered from severe breath-holding spells might have predisposed to loss of consciousness.<sup>4</sup> They reported that different degrees of anemia were detected in patients with breath-holding spells.<sup>5</sup> Iron deficiency is still the most frequent cause of anemia in children.

BHS are classified according to the color change observed on the child during the event into cyanotic, pallid or mixed episodes. Cyanotic episodes are more common, seen in 54–62%, whereas pallid and mixed types are seen in about 19–24%, for each.<sup>6</sup> Breath holding spells is a paroxysmal event occurring in 0.1–5% of children's aged from 6 months to 6 years.<sup>7</sup> Breath holding spells may occur more in males

than females and family history may be present in one fourth of cases.<sup>8</sup> In progressive iron deficiency, a sequence of biochemical and hematologic events occurs. First, the tissue iron stores in bone marrow disappear. In this stage of iron deficiency, only the level of serum transferrin receptor (sTfR) increases. Next, there is a decrease in serum iron and the iron binding capacity of the serum increases. As the deficiency progresses, the red blood cells become smaller than normal and their haemoglobin content decreases.<sup>9</sup> The role of iron is thought to be due to its action as a cofactor in catecholamine metabolism and neurotransmitter function.<sup>10</sup>

This study was designed to show relation between iron deficiency and breath-holding spells and to assess the effect of iron therapy in reducing the breath holding spells.

## METHODS

This study was a prospective, interventional hospital-based study carried out in Government Medical College (GMC) Baramulla after obtaining ethical committee clearance from the institute, over a two-year period from august 2017 to august 2019. All children who presented with breath holding spells during the study period were included in the study. The diagnosis of BHS was made clinically by a paediatrician based on the history given by the children's mothers and on the personal observation of the spells. A "spell" was defined as the stoppage of the child's breathing during expiration after a deep inspiration while crying. A detailed history was taken for each patient included in the study, and a thorough clinical examination was conducted with special emphasis on the patient's personal history, including age and gender, complaint (i.e., type of BHS, its duration and the provoking factors), family history of similar conditions and consanguinity, and developmental history. Blood samples were obtained from all patients for complete blood count Haemoglobin value <11 g/dl, serum ferritin (normal ferritin ranges from 6-60 ng/ml; 3- serum iron (normal serum iron in children ranges from 37-145 µg/dL; 4 total iron binding capacity (normal TIBC ranges from 250-350 µg/dL).

On the basis of these tests, patients were classified into three groups according to iron status:

Normal subjects who were excluded from this study. Iron deficiency without anaemia (serum ferritin <12 ng/mL, serum iron <22 µg/dL and total iron binding capacity >400 µg/dL). Iron deficiency anaemia (Hb <11 g/dL).

### Inclusion criteria

Patients under 6 years of age. Iron deficient patients with anaemia (Hb <11 gm/dl) and without anaemia.

### Exclusion criteria

Patients with Acute illness, cases of developmental delay. Children's suffering from chronic diseases like diabetes

mellitus, chronic renal failure, congenital heart diseases, malabsorption and thalassemia. Known epileptics and febrile convulsion. Children's with normal iron profile and cases on iron therapy.

Parents were informed about the study and their consent was obtained regarding the study. Breath holding spells were classified into cyanotic, pallid and mixed. All the patients with BHS in our study received oral iron supplement at a dose of 5 mg/kg daily for 3 months. Parents were advised to keep a written record of breath holding spells. The patients were followed upto 3 months from beginning of treatment. Response to iron therapy i.e. reduction in frequency of breath holding spells, was categorised as Complete response (means no spells), Better response (means >50% reduction in frequency of BHS), poor response (means 10-50% reduction in frequency of BHS) and no response (means no reduction in frequency of BHS).<sup>11</sup> Data were analyzed using online calculators and Microsoft excel. Frequency and percentage were calculated for qualitative variables like age, sex, consanguinity, family type of BHS and compliance. While as mean and standard deviation (SD) were calculated for quantitative variables like serum ferritin, serum iron and total iron binding capacity. Paired sample t-test was applied for the comparison of serum ferritin, serum iron and total iron binding capacity pre- and post- iron supplementation. P<0.05 was considered as statistically significant. While as Chi-squared test was used to test the response of iron therapy in reducing the frequency of breath holding spells for IDA and ID without anaemia respectively.

## RESULTS

In our study, 70 cases with breath holding spells were evaluated. Out of 70 cases 40 (57.15%) were males and 30 (42.85%) of them were females. When the children's were discriminated according to ages at the presentation in our study 36 (51.42%) cases were between 6 months to 15 months of age, 27 cases (38.57%) were between 16 months to 30 months and 7 cases (10%) were between 31 to 60 months. While as family history and parental consanguinity was observed in 21 (30%) cases and 46 (65.71) cases respectively. Besides this cyanotic spells were observed in 63 (90%) cases and pallid spells were observed in 7 (10%) cases. Anaemia (IDA) was observed in 42 (60) childrens and iron deficiency (ID) without anemia was observed in 28 children (40%). Above all compliance was observed in 61 (87.15) patients and 9 (12.85) cases were non-complaint. All these parameters are depicted in (Table 1).

The frequency of breath holding attacks was studied as less than 4 attacks per week were found in 24 (34.28%) patients, 4-10 attacks per week in 32 (45.71%) patients and more than 10 attacks per week in 14 (20%) patients depicted in (Table 2).

The mean (±SD) of haemoglobin(g/dl) initially was 10.65 g/dl (±1.08) and after 12 weeks of iron supplement therapy

was 13.34 (±1.17) with significant p-value of (p<0.05) in haemoglobin levels before and after iron therapy.

**Table 1: Demographic parameters of patients with BHS.**

	6-15	16-30	31-60
Age of onset in months	36 (51.42%)	27 (38.57%)	7 (10%)
Gender	Male	40	57.15%
	Female	30	42.85%
Consanguinity	present	46	65.72
	Absent	24	34.28
Family history	Positive	21	30%
	Negative	49	70%
Spell	Cyanotic	Pallid	Mixed
	63 (90%)	7 (10%)	Nil
Iron deficiency	Without anaemia	28	40%
Iron deficiency	With anaemia	42	60%
Compliance	Yes	61	87.15%
	No	9	12.85%.

**Table 2: Age of onset (months) and frequency of BHS.**

	6-15	16-30	31-60
Frequency of BHS/ week	No (%)	No (%)	N (%)
<4	13 (18.57)	8 (11.43)	3 (4.28)
4-10	12 (17.14)	14 (20)	6 (8.57)
>10	7 (10)	5 (7.14)	2 (2.85)
Total	32 (45.71)	27 (38.57)	11 (15.71)

While as the mean (±SD) value of serum ferritin initially was 5.82 ng/ml (±1.58) and after 12 weeks of treatment with iron, mean serum ferritin increased to 34.02 ng/ml (±8.22). With significant difference (p<0.001) in serum ferritin level before and after iron supplementation.

While as the mean (±SD) value of serum iron initially was 26.75 µg/dl (±8.23). After 12 weeks of treatment, serum iron increased to 59.29 µg/dl (±9.21) with significant difference (p<0.001) in serum iron levels before and after iron supplementation.

The mean (±SD) value of total iron binding capacity at time of presentation was 442.46 µg/dl (±70.71). After 12 weeks of treatment, total iron binding capacity decreased to 293.21 µg/dl (±35.32) with significant difference (p<0.001) in total iron binding capacity levels before and after iron supplementation.

All these parameters are depicted in (Table 3).

Effect of iron treatment in reducing the frequency of BHS.

**Table 3: Serum ferritin, S. iron, total iron binding capacity and hemoglobin levels in children's with BHS before and after iron supplement therapy using paired t-test.**

Parameter		Before	After	P value
S. ferritin (ng/ml)	Mean	5.82	34.02	
	SD	1.58	8.22	<0.001
	SE	0.18	0.98	
S. iron (µg/ml)	Mean	26.75	59.29	
	SD	8.23	9.21	<0.001
	SE	0.98	1.10	
TIBC (µg/dl)	Mean	442.46	293.21	
	SD	70.71	35.32	<0.001
	SE	8.45	4.22	
Hemoglobin (g/dl)	Mean	10.65	13.34	
	SD	1.08	1.17	<0.05
	SE	0.13	0.14	

**Table 4: Comparison of frequency of BHS after 6 and 8 weeks of Iron supplementation therapy: frequency of BHS/Week (Spell Burden)**

	No Spells	<4	4-10	>10
Baseline	-			
After 6 weeks	28 (40%)	26 (37.15)	12 (17.14)	4 (5.71)
After 12 weeks	42 (60%)	23 (32.86)	4 (5.71)	1 (1.42)

In our study of 70 patients, 42 (60%) patients presented with (IDA) and 28 (40%) patients were (ID) without anaemia. Out of those 42 patients with (IDA), 28 (40%) patients showed a complete response, 10 (14.29%) a better response, 3 (4.29%) a poor response and 1 (1.42%) patient showed no response to treatment. While as among 28(40%) patients with (ID) without anaemia, 19 (27.15%) patients showed a complete response, 8 (11.43%) a better response, 1 (1.42%) a poor response. In addition, Chi square test shows no significant difference between IDA group and ID without anaemia group in reduction of BHS in response to iron therapy (P<0.05) as depicted in table 4.

In this we also analysed the reduction in frequency of spell burden after 6 and 12 weeks of iron therapy. 28 (40%) patients showed complete resolution of the spells, 26 (37.15%) patients showed less than 5 episodes per week, 12 (17.14%) patients showed 5-10 episodes per week and 4 (5.71%) patients showed more than 10 episodes per week after 6 weeks of iron therapy while as 42 (60%) patients showed complete response to the treatment, 23 (32.86%) patients showed less than 5 episodes per week, 4 (5.72%) showed 5-10 episodes per week and only 1 (1.42%) patients showed more than 10 episodes per week after 12 weeks of iron therapy as depicted in table 5.

## DISCUSSION

The results of our study shows the association between breath holding spells and iron deficiency and anaemia particularly iron deficiency anemia, we also observed iron therapy can reduce breath holding spells in iron deficiency with or without anemia respectively.

Breath holding spells are non-epileptic paroxysmal phenomenon frequently seen in childhood, from 6 months to 5 years although the onset of BHS before 6 months is rare.<sup>12</sup> Some authors reported that treatment with iron in children with iron deficiency anaemia resulted in reduction of the frequency or elimination of spells.<sup>13-1</sup> In the present study, we also found that iron supplementation decreased the frequency of BHS, and complete or partial remission of symptoms in 55% of patients treated with iron was observed.<sup>16,17</sup> Also Low haemoglobin level results in decreased oxygen-carrying capacity of blood and reduced oxygenation of the brain, which is considered a risk for BHS.<sup>18</sup> Because iron acts as a cofactor for degrading enzymes of the cerebral catecholamines, iron deficiency may lead to catecholamine disruption and subsequent autonomic dysregulation.<sup>19,20</sup> Orii et al showed that autonomic dysregulation in children with BHS can be improved by iron supplementation.<sup>20</sup> Another hypothesis is that oxidative stress may cause an impairment of catecholamine metabolism and neurotransmitter function in patients with BHS, especially in those with iron-deficiency anemia.<sup>21</sup> Oxidative stress levels were found to be higher in iron-deficient children than non-iron-deficient ones, leading to an increased oxidative stress burden in BHS.

This study revealed a significant increase in serum ferritin and serum iron after iron therapy and significant decrease in total iron binding capacity, ideal in iron deficiency treatment. These indices resulted in significant decrease in breath holding spells for both iron deficiency anaemia and iron deficiency without anaemia patients, however In this study the main cause of poor and no response to iron therapy was the poor compliance of parents to iron treatment.

Our study showed decrease in the frequency of BHS after 6 weeks of treatment and this agreed with other studies, who reported a statistically significant decrease in the frequency of BHS after 12 weeks of iron therapy.<sup>22,23</sup> Young children with iron deficiency anaemia have been found to score 12 to 15 points lower on the Bayley infant development scale than their iron sufficient peer.<sup>24,25</sup> Moreover, current study revealed that there was no significant difference between iron deficiency anaemia group and iron deficiency without anaemia group as both groups were responsive to iron supplement. Taken together, these studies indicate that iron therapy is effective in the treatment of BHS, especially in iron-deficient children.

## Limitations

The main limitation in our study was the small sample size, while in future studies we will try to study larger study group in order to further strengthen our evidence regarding the present study and to eliminate random bias.

## CONCLUSION

There is a high incidence of iron deficiency associated with BHS. This study shows that there is significant decrease in frequency of breath holding spells in children's when treated with iron supplements.

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