

# Effect of Iron Supplementation in Anaemic Children with Breath Holding Spells at a Tertiary Care Hospital (KGH - Visakhapatnam) in Southern India

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## ABSTRACT

### BACKGROUND

Breath holding spells (BHS) are common, non-epileptic paroxysmal events that occur in children below 6 years, whose diagnosis is made many times clinically. Exact aetiology is not known, but iron deficiency was one among many proposed aetiological factors. Very few studies were published till date to determine role and effect of iron supplementation in children with breath holding spells. Hence the present study was taken up to assess the presence of iron deficiency and the effect of iron supplementation in children with breath holding spells.

### METHODS

This prospective interventional study was performed from May 2012 to April 2017. 125 children below six years of age brought with the complaint of breath holding spells were screened for presence of anaemia and other systemic illnesses. Ten children were excluded with other organic causes and only 85 children were found to have anaemia and were supplemented with 6 mg/kg/day of ferrous sulphate for 3 months and followed up for a total period of 6 months. Response to iron supplementation was assessed in these children by measuring total number of attacks of BHS before starting iron supplementation, after supplementation of iron for three months and also at the end of follow-up period. The results were analysed by using Microsoft Office Excel.

### RESULTS

76.52 % (85/115) of patients had anaemia and were supplemented with 6 mg/kg/day of ferrous sulphate for 3 months. The remaining 27 cases had normal Hb % & red blood cells (RBC) indices and were not included. Response to iron therapy was assessed in anaemic children with breath holding spells and we found complete response in 78.41 %, partial response in 15.91 % and no response in 5.7 %.

### CONCLUSIONS

This study proved the role of iron therapy in anaemic children with breath holding spells.

### KEYWORDS

Breath Holding Spells (BHS), Iron Deficiency, Anaemia, Haemoglobin

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## BACKGROUND

Breath holding spells are common non-epileptic, repetitive, reflexive events described under "behavioural disorders" of children and are initiated by provocative events that cause anger, frustration or pain causing the child to cry.<sup>1</sup> Breath holding spells are broadly classified into two types. Type – 1 is pallid breath holding spells, caused by reflex bradycardia and asystole. Type – 2 is cyanotic breath holding spells caused by prolonged expiratory apnoea and intra pulmonary shunting. Some authors described a third variety as mixed breath holding spells (both pallor and cyanosis in one spell). Breath holding spells generally start with a cry and progress to apnoea and cyanosis. These spells are rare below six months, usually begin between six months to eighteen months of age. Breath holding spells peak by two years and abate by five years of age. Injury, anger and frustration particularly with surprise are common triggers. The prevalence of breath holding spells is between 5 % to 15 %.<sup>2</sup> Exact aetiology of breath holding spells were not known. In some cases of breath holding spells, a genetic component is present, especially in those with pallid breath holding spells. About twenty five percent have a family history of breath holding spell or fainting. In some cases, breath holding spells may be associated with anaemia caused by an iron deficiency, although this is controversial. Some previous studies have linked breath holding spells with iron deficiency anaemia.<sup>3,4,5,6</sup> But very few studies were published till date to determine the role of iron deficiency anaemia in causing breath holding spells and effect of iron supplementation in its management. Hence the present study was taken up to assess the presence of iron deficiency in children with breath holding spells and also the effect of iron supplementation on the frequency of breath holding spells.

## Objectives

To assess the presence of iron deficiency and evaluate the effectiveness of iron supplementation on the frequency of breath holding spells in anaemic children with breath holding spells.

## METHODS

This was a prospective interventional study conducted from May 2012 to April 2017 at our child health clinics at Visakhapatnam. During the study period, a total of one hundred and twenty-five children below six years of age brought to our "child health clinics" for the complaint of breath holding spells were screened. Patients with previous history of seizures, epilepsy, developmental delay, congenital heart diseases or other major systemic illnesses were excluded from the study by conducting relevant investigations such as electrocardiogram (ECG), 2D-ECHO (2D Echo cardiogram) and EEG (Electro encephalogram) wherever appropriate to rule out other diseases which mimic breath holding spells (such as prolonged QT syndrome, congenital cyanotic heart diseases with cyanotic spells and seizures / epilepsy etc.) under differential diagnosis. Out of

one hundred and twenty screened cases, ten children were excluded from the study since they had other associated problems (Atrial septal defect, Ventricular septal defect, Febrile convulsions etc;), and the remaining one hundred and fifteen children were enrolled. In all the 115 children, the diagnosis of breath holding spells were made at initial consultation by a detailed medical history including age of the child at the time of initial spells, gender of the child, type of breath holding spell, triggering factors, family history of similar illness and parental consanguinity etc. Once the diagnosis of breath holding spell was made clinically, we have conducted laboratory investigations - complete haemogram in one hundred and fifteen children and out of them 88 children (76.52 %) were found to be anaemic included in the study and were supplemented with 6 mg/kg/day of ferrous sulphate for 3 months and followed up for a total period of 6 months from the date of inclusion in the study. The remaining 27 cases who had normal Hb % & RBC indices were also excluded from the study. The clinical condition of the patient, number of attacks of breath holding spells were recorded before starting iron supplementation and at 3 months and 6 months follow up visits according to the information given by the mother. At the end of 6 months of follow up, the response was evaluated. We defined the response as follows: "complete response" - the attacks disappeared completely; "partial response"- more than 50 % reduction in the number of attacks; and "no response"- no change in the number of attacks.

## Statistical Analysis

The data was analysed by using Microsoft Office Excel. Percentage of children with anaemia was calculated, haematological characters were analysed by calculating mean  $\pm$  SD, and response to iron supplementation was analysed by calculating percentages of children showing complete, partial or no response by calculating frequency of attacks after iron supplementation.

## RESULTS

In the present study, out of one hundred and fifteen children included, eighty-eight children that is 76.52 % were found to have iron deficiency anaemia and the remaining 27 that is 23.47 % were found to be normal (not anaemic) as shown by their complete haemogram report and the same is depicted in table 1 below.

Total Number of Children with Breath Holding Spells	115 (100 %)
Number of children with anaemia	88 (76.52 %)
Number of children with normal haemoglobin and RBC indices	27 (23.47 %)

**Table 1. Number of Children with Anaemia among Total 115 Children with Breath Holding Spells Initially Included in the Present Study**

In the present study, the mean haematological characters calculated from the haemogram are suggestive of presence of iron deficiency anaemia, which were shown in table 2 below.

Parameter	Mean
Hb (gm%)	8.91 ± 1.12
Haematocrit (%)	28.4 ± 3.24
MCV (fl)	70.1 ± 7.11
MCH (pg)	20.64 ± 3.22
Sr. Iron (µg/dl)	52.41 ± 34.41
Sr. Ferritin (ng/ml)	12.12 ± 15.12
Total Iron binding capacity (µg/dl)	341.75 ± 75.12

**Table 2. The Mean Haematological Parameters of Present Study Population**

In the present study, at the end of treatment and follow up, we found, out of 88 children supplemented with 6 mg/kg/day of ferrous sulphate for 3 months, 69 children (78.4 %) showed complete response, 14 children (15.9 %) showed partial response and five children (5.7 %) of our study population showed no response, which was shown in table 3. The results suggest that there is significant reduction in the frequency of attacks of breath holding spells.

Remission/Response	Number (%)
Complete	69 (78.41 %)
Partial	14 (15.91 %)
No response	05 (5.7 %)

**Table 3. Response to Iron Therapy in Anaemic Children with Breath Holding Spells in the Present Study**

## DISCUSSION

Breath holding spells is a common behavioural disorder of early childhood associated with a lot of parental anxiety, besides carrying a potential for misdiagnosis.<sup>7</sup> Usually the child with a typical breath holding spell either cries or gasps, forcibly exhales and stops breathing, due to which the child may turn blue or pale and the entire episode lasts for about two to twenty seconds. The child may faint or briefly lose consciousness in case of simple breath holding spell. Recovery of the child without fainting is not considered as a true breath holding spell by some paediatricians. In a severe or complicated breath holding spell, the child may throw a fit or small seizure at the height of breath holding, while unconscious. This whole episode lasts usually less than one minute. Following the spell, the child regains consciousness immediately and normal breathing resumes and colour resumes to normal. Many episodes in a single day to only one episode in a year. But in most children with the BHS frequency varies from two to three episodes a day (33 %) to one episode in a month (33 %). But frequency varies in the same individual and a child with sporadic episodes of breath holding spells may have several episodes in a single day. Around twenty five percent of children with BHS have a positive family history. Most common differential diagnosis for breath holding spells is a seizure disorder and the treating physician or paediatrician may be confused with a seizure disorder. They are sometimes observed in response to frustration during disciplinary conflict. Though the physiology of breath holding spells is not well determined, they are considered as involuntary reflexes caused by respiratory centre of hind brain in association with cardiovascular, respiratory and autonomic nervous systems. The diagnosis of a breath-holding spell is made clinically after excluding other differential diagnoses such as seizures,

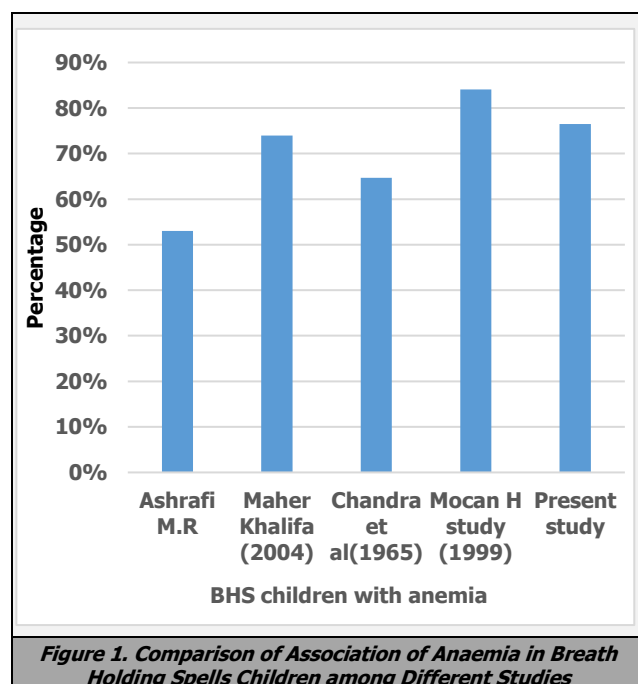
syncopal attacks etc. To exclude seizures and to diagnose breath holding spells, a detailed history of entire episode in sequential order, lack of incontinence and post ictal phase will help. Witnessing the spell is crucial for diagnosis and hence when there is doubt, the parents are advised to make a video recording of the events to aid diagnosis. In children with pallid breath holding spell, an ECG is recommended to exclude cardiac arrhythmias as children with long QT syndrome may have breath holding spells in response to exertion or excitement. However, as long QT syndrome is a serious cardiac rhythm abnormality, paediatrician usually advice a baseline ECG in all cases of suspected breath holding spells. If the breath holding spell occurs for the first time, a paediatrician should be consulted and thorough clinical examination and required laboratory investigations should be done to exclude epileptic disorders and other medical conditions which have similar symptoms, especially if it occurs below 6 months or above 4.5 years of age, if it occurs during feeding or diaper changing, or if it becomes more severe, if its frequency increases or pattern changes or if it lasts for more than one minute, with continuous body stiffening and relaxing.

In atypical or resistant cases of breath holding spells, the paediatricians should exclude rare disorders which can cause involuntary breath holding spells like Rett syndrome, Batten disease, ceroid lipofuscinoses, Riley-Day syndrome and familial dysautonomia. Breath holding spells can be distinguished from epileptic seizures by taking thorough history and clinical examination. Main differentiating feature of BHS is the episode which is provoked by an event or situation, change in skin colour and loss of consciousness precedes any seizure type jerking which is brief with rapid recovery, whereas in epileptic seizures convulsions and muscle weakness precedes change in skin colour and loss of consciousness with an abnormal electrical activity in electroencephalogram (which is normal in BHS). There is some evidence that children with anaemia ( especially iron deficiency) may be more prone to breath-holding spells. Once the diagnosis of BHS is made by the paediatrician, he should console the apprehensive, frightened family members as they resolve spontaneously, and no definitive treatment is required in most of the cases. Some clinical trials showed that iron therapy is effective though the child with BHS do not have anaemia. Some other studies showed that use of piracetam over two months causes significant reduction in the incidence of BHS (60 %) when compared with a placebo. Atropine sulphate 0.1 mg three times a day should be considered in consultation with a cardiologist or neurologist to prevent frequent and severe pallid breath holding spells. Anti-epileptic drugs have no role in the treatment of breath holding spells. The striking association of anaemia with breath holding spells was first reported in 1963 by Halowach and Thurston.<sup>8</sup> It was hypothesized that the low haemoglobin causes rapid cerebral anoxia due to decreased oxygen carrying capacity of blood that in turn leads to breath holding spells. It was also thought that the anaemic children being irritable may be more predisposed to breath holding spells. In the present study out of one hundred and fifteen children with breath holding spells 88 (76.52 %) had anaemia. This finding was in agreement with

previous studies such as Meher Kalifa study (93 out of 126 – 74 %), Mocan H study (63 out of 91 – 69.2 %), and Ashrafi MR study (23 out of 43 – 53 %).

Study	BHS Children with Anaemia	Total Number of Children Studied
Ashrafi M. R	23 (53 %)	n = 43
Maheer Khalifa (2004)	93 (74 %)	n = 126
Chandra et al. (1965)	86 (64.67)	n = 133
Mocan H study (1999)	63(69.2 %)	n = 91
Present study	88 (76.52 %)	n = 115

**Table 4. Comparison of Association of Anaemia in Breath Holding Spells Children among Different Studies**



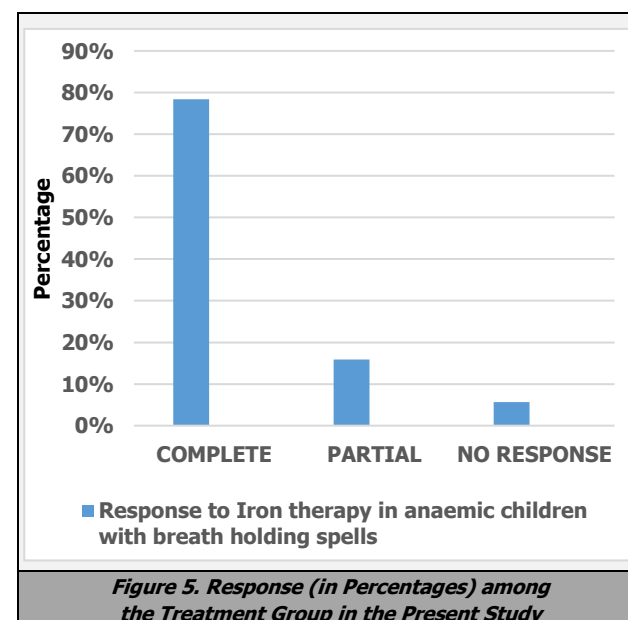
In the present study, at the end of treatment and follow up, we found complete response in 78.4 %, partial response in 15.9 % and no response in 5.7 % of our study population. This was in agreement with previous studies (Table - 5). The study by Chandra et al. reported in august 1965 carried out in Chandigarh was one of the earliest to demonstrate association between breath holding spells and anaemia and also supported the therapeutic role of iron in the management of children with breath holding spells.<sup>9</sup> This study also showed that the control of breath holding spells with iron supplementation was more remarkable in children with iron deficiency anaemia. In Chandra et al. study they included 133 children with breath holding spells, out of which 46 children were treated with oral haematinics and monitored for 12 weeks. They demonstrated partial to complete response in 39 out of 46 children who received oral iron, whereas only 15 out of 40 children in placebo group reported similar relief. Studies done by Holowach et al. and Bhatia et al. found significantly low Hb %, Serum iron and transferrin saturation and an increase in iron binding capacity in children with breath holding spells when compared to control group. In another study done by Colina and Abelson, breath holding spells were subsided after correction of anaemia in two children. Efficacy of iron supplementation in children with breath holding spells was also demonstrated by Daoud et al. study. Meher Khalifa et al. concluded that children with breath holding spells require

investigation for iron deficiency anaemia and treatment with iron whereever appropriate.<sup>10</sup> Mocan H et al. concluded that treating iron deficiency anaemia is effective in reducing the frequency of breath holding spells.<sup>11</sup>

Iron has a role as a cofactor in catecholamine metabolism in central nervous system.<sup>12</sup> It is thought that interaction of cerebral erythropoietin, nitric oxide and interleukin-1 may be responsible for clinical profile and haematological associations of breath holding spells.<sup>13</sup> From the results of present as well as previous studies, the beneficial effect of iron therapy in reducing frequency of attacks in children with BHS with associated iron deficiency anaemia was established. However, not all children with breath holding spells have iron deficiency at baseline, and some children without anaemia also respond to iron therapy as there may be a relative deficiency of iron stores and distribution rather than a depletion of the total amount of body iron.<sup>10,12,13</sup>

Study	Response (Complete + Partial)	No Response
Mocan H study -1999 (n = 63)	84 % (53/63)	16 % (10/63)
Meher Khalifa study – 2003 (n = 93)	84.9 % (79/93)	15.1 % (14/93)
Present study (n = 88)	94.3 % (83/88)	5.7 % (5/88)

**Table 5. Comparison of Response (in %) to Iron Therapy in Anaemic Children with Breath Holding Spells in Different Studies**



Other treatment options described by various authors such as atropine<sup>14</sup> or transdermal scopolamine<sup>15</sup> found beneficial especially in breath holding spell cases with prolonged asystole. In some individual case studies, they have used drugs like glycopyrrolate, theophylline, fluoxetine and levetiracetam.<sup>7</sup> Refractory cases of breath holding spells have benefited from implantation of cardiac pacemaker.<sup>16,17</sup> Recently an effective and safe role of piracetam in controlling breath holding spells in hyper active children was described.<sup>18,19</sup> Treatment with iron is recommended in children with iron deficiency anaemia and a trial can be considered even without its presence.<sup>20</sup> But for none of

these therapies larger robust studies documenting their safety and efficacy are not available.

## CONCLUSIONS

Diagnosis of breath holding spells remains primarily clinical, based on suggestive history with a normal physical and nervous system examination. Basic management of breath holding spells comprises chiefly of parental counselling and reassurance. In the present study, our data suggests that anaemia (including iron deficiency) is a common associated clinical problem in children with breath holding spells and correction of anaemia led to significant response in anaemic children with breath holding spells. Hence, we conclude that children with breath holding spells require investigations for anaemia and iron deficiency and treatment with iron supplementation should be given wherever appropriate.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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