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IRON STATUS IN CHILDREN WITH SEVERE BREATH- HOLDING SPELLS

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ABSTRACT

Breath-holding spells, one of the most common non-epileptic paroxysmal events in children which are very stressful to the family despite their benign nature. The pathophysiology of breath-holding spells is not fully understood. Iron deficiency anemia may be a factor contributing to breath-holding spells. This case-control study had been carried out on children with severe breath-holding spells to assess iron status among these patients. Forty six children (28 boys, 18 girls) aged between 6 to 36 months with severe breath holding spellsattending pediatric outpatient department of Basra General Hospital during the period from September 2008 to April 2009 and 50 cases (38 boys,12 girls) without breath holding spells (control) were enrolled in this study. A number of blood indices (Hemoglobin, mean cell volume, serum iron, serum ferritin, and total iron binding capacity) were assessed in both groups. The study showed that children with severe breath- holding spells showed a significantly low hemoglobin, mean cell volume, serum iron, and serum ferritin compared to control group (p <0.05), while total iron binding capacity was significantly higher in patients with breath holding spells than control group (p <0.05), the study also revealed that there was no significant differences between different types of breath-holding spells in relation to the studied blood and iron indices (p>0.05). The results of this study could supports the view of iron deficiency in breath holding spells and recommends investigations for iron deficiency anemia in children with severe breath- holding spells.

KEYWORDS: Breath - Holding Spells, Iron Deficiency

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INTRODUCTION

Breath - holding spells (BHS) are a common problem affecting approximately 5% of healthy children.[1] BHS are involuntary, self-limited episodes that are usually outgrown by school age. [2] The spells are rare before 6 month of age, peak at about 2 year of age, and cease by 5 year of age. [3]

BHS are generally benign but may cause intense parental concern [4].Three clinical subtypes of spells are recognized based on the child's coloration during these events: cyanotic, pallid, and mixed.[5]. The cyanotic breath holding spell (the most common form) usually occurs in response to anger or frustration while the pallid spells produce a pale appearance to a child's skin; and is typically initiated by a painful experience, or a sudden startle[6]. Children experience one predominate type, however individual children may experience mixed types [4]

The diagnosis of BHS is based on distinctive and stereotyped sequence of clinical events beginning with a provocation resulting in crying or emotional upset that leads to a noiseless state of expiration accompanied by color change and eventually loss of consciousness and postural tone [1, 4]. BHS can be mild or severe, severe breath- holding attacks are defined as those attacks resulting in loss of consciousness or convulsions, or both, while simple breath holding attacks is defined as those attacks occurring without loss of consciousness or jerking movements[7]

The mechanism of BHS remains controversial. The presence of autonomic nervous system imbalance with cerebral anoxia may be responsible in these spells [8].An association of BHS with anemia, particularly iron deficiency anemia, has been reported but is still poorly understood. A number of investigators have demonstrated the association of iron deficiency anemia with abnormalities of cognitive, developmental, and behavioral problems that may be reversible with early treatment of iron deficiency anemia. [9]

There are reports of an association between iron deficiency anemia and breath- holding episodes with a decrease or cessation of the episodes after iron therapy. [10]

AIM OF THE STUDY

This study was designed to evaluate the iron status in children with severe BHS.

PATIENTS AND METHODS

Forty six children (28 boys and 18 girls) with severe BHS aged from 6 - 36 `months, with a mean age of (19.16±8.75) attending pediatric outpatient department of Basra General Hospital during the period from September 2008 to April 2009 were enrolled in the study.

According to the age of onset of BHS the patients were divided into 4 sub-groups; 6-12 months, >12-18 months, >18-24 months, >24-30 months, and >30-36 months.

Fifty apparently healthy children (38 boys and12 girls) aged between 6-36months, with a mean age of (20.12±9.82) visiting the pediatric outpatient clinic for simple medical conditions such as cough and cold were taken as a control group.

Diagnosis of severe BHS was based on the history of BHS taken from the parents (three or more spells in 1 month), defined by the following clinical sequence: provocation followed by crying to a point of noiselessness and accompanying change of color (cyanotic, or pallid) and ultimately a loss of consciousness with an associated alteration in body tone.[5]The type of spells were classified according to skin color change of the child during the episode into pallid, cyanotic, and mixed (when there was no clear distinction between pallor and cyanosis).

Patients with history of febrile convulsions or epilepsies, clinically identified developmental delay, and severe malnutrition were excluded. Consent was taken from each patient's parent for inclusion in the study.

Each patient was subjected to a full medical evaluation. Relevant information obtained includes age at onset of BHS, type of attacks, and frequency of attacks.

The frequencies of BHS were classified into three groups (< 10/month, 10-30/month, and > 30/month). [4, 11]

In addition, the following blood indices were determined for each child in the study and control group: Hemoglobin level (Hb), Mean Corpuscular Volume (MCV), serum iron, Total iron binding capacity (TIBC), and serum ferritin.

The t- test was used for comparisons between two means of different groups. Comparisons between groups were made by using the one way analysis of variance (ANOVA). P value < 0.05 was considered statistically significant.

RESULTS

A total of 46 patients (28boys, 18girls) and 50 cases as a control group were enrolled in this study. The patient's age ranged from 6 to 36 months, with a meanage of 19.16±8.75.

In this study 60.87% of the studied patients were males. The onset of BHS before 12 month of age was seen in 58.7% % of patients. Most patients (60.8%) experienced less than 10 attacks each month. The spells were cyanotic in 47.8% of children, while pallid spells and mixed types were detected in 34.7% and 17.3 % of children respectively, (Table 1).

Blood indices in both study group and control group were studied and presented in Table 2.

The mean Hb level and MCV among children with BHS were significantly lower than those in the control group ($P<0.05$).

Children in the study group had a significantly lower mean serum iron and ferritin in comparison with the control group ($P<0.05$).

However, TIBC was higher in patients with the study group than in children with control group, and the difference was statistically significant ($P<0.05$).

The mean levels of studied blood indices (Hb, MCV, Serum Iron, Serum Ferritin, and TIBC) between different types of BHS(cyanotic, pallid, and mixed types) were not statistically significant ($P> 0.05$), (Table 3).

DISCUSSIONS

Breath - holding spells is a well-known event in infants and children in which the exact pathophysiology is not clearly understood, however numerous investigations have been carried out to study the association between iron deficiency anemia and BHS.

In this study the male to female ratio was found to be 1.5:1 which was similar to that reported by other studies. [1, 12]

The onset of breath-holding spells is rare in the first 6 months of life and questionable in the neonatal period. [8]

In this study, the onset of spells in 58% of the cases was within the first 12 month of life. The age of onset of BHS in most of the studies has been in the first 12 months of life. [1, 8, 10]

The frequency of spells varied widely among different studies from multiple episodes per day to as infrequently as once monthly. The majority of children (60.8%) in this study experienced fewer than 10 episodes per month.

In the study of Di Mario (25%) of the patients experienced more than 1 episode per day during peak frequency [5], While Mustaq et al. in India reported that only 18% of the patients had more than one episode of BHS per day and 64% of the patients had multiple episodes occurring every week at the time of peak frequency. [4]

In terms of clinical types of BHS, this study showed that 47.8% of spells were of the cyanotic, 34.7% of the pallid and 17.3% of the mixed type. Tonekaboni et al in their study demonstrated that 88.5% of the spells were cyanotic, 8.5% were pallid, and 3% were of mixed type.[8] However, Al rabaty reported that the cyanotic type of spell was detected in (64.2%), the pallid type in 13%, and the mixed type in 22.6% of patients.[13] Also, Mushtaq et al found that 62.7% of

patients had cyanotic spells, 11.8% had pallid spells, and 25.4% had both types [4]. This discrepancy may be due to misinterpretation of different investigators in distinguishing between types of BHS.

Various investigations have been conducted to determine the association between iron deficiency and BHS. In this study the hemoglobin level, MCV, and the conventional laboratory indices of iron status (serum iron level, total iron binding capacity, and serum ferritin) were used to evaluate iron deficiency in children with BHS.

The study revealed that children with severe BHS had lower hemoglobin levels, lower MCV, reduced serum iron, reduced serum ferritin, and increased total iron binding capacity than controls. The study results were consistent with other studies. Alrabaty observed that children with BHS had significantly lower hemoglobin, lower serum iron values, and higher TIBC than those of controls.[13] Also Mushtaq et al found that 59% of children with severe BHS were anemic on the basis of iron profile indices.[4]Handan et al also observed that 56% of children with BHS had iron deficiency. [14]

The study revealed that there were no significant differences between different types of BHS in terms of hemoglobin and other iron indices which are similar to that reported in other studies. [4, 11]

In addition, several workers have studied the role of iron in resolution of BHS and reported significant benefit from iron treatment. Tonekaboni et al documented a complete therapeutic response in 68.6% of children with BHS after 3 months of oral iron supplement therapy.[10] Also Khan et al reported a statistically significant fall in the frequency of breath holding spells after 12 weeks of iron therapy.[1]

It is not known how iron deficiency leads to BHS; however abnormalities in catecholamine metabolism and other neurotransmitters may explain association of BHS with iron deficiency anemia. The correction of spells with iron therapy may be related to the functional restoration of these neurotransmitters. [1] Furthermore, it has been suggested that the breath-holding attacks may relates to the interactions of cerebral erythropoietin (EPO), nitric oxide and interleukin-1. Increased brain erythropoietin production has a protective effect during breath holding attacks, but where this does not compensate for the severity of anoxic attacks, seizure may develop. In addition, it has been postulated that the enhanced erythropoiesis resulting from increased EPO secretion during hypoxia can induce a temporary state of iron-deficient erythropoiesis in iron-replete patients. As iron is consumed in erythropoiesis, a relative deficiency of iron stores occurs. Over time the child may become anemic and exhibit behavioral irritability, leading to further breath-holding attacks. [1, 7, 11]

Beside that there are some studies on iron-replete children with frequent and disabling breath-holding attacks who have responded to a course of oral iron supplementation although it is unclear why iron-replete children may respond to iron therapy. [15]

CONCLUSIONS

The data of this study documents that iron deficiency is a significant finding in children with severe BHS and may be the main underlying defect. The finding also recommends investigations and treatment, where appropriate, for iron deficiency anemia in children with severe BHS.

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APPENDICES

Table 1: Clinical Characteristics of Patients with BHS

Variable	N. (%)
Gender	
Male	28(60.87)
Female	18(39.13)
Total	46(100)
Age of onset (mo.)	
6-12	27(58.70)
>12-18	10(21.74)
>18-24	4(8.70)
>24-30	3(6.52)
>30-36	2(4.34)
Frequency of spells/month	
<10	28(60.87)
10-30	11(23.91)
>30	7 (15.22)
Type of spells	
Cyanotic	22(47.83)
Pallid	16(34.78)
Mixed	8(17.39)

Table 2: Blood Indices among Children with BHS and Control Group

Variable *	Patients	Control	P Value
Hemoglobin(g/dl)	9.26±0.64	11.2±1.05	0.021
Mean corpuscular volume(fl)	60±3.2	77.2±6.3	0.001
Total iron binding capacity (µmol/L)	83±8.54	50±2.26	0.012
Serum ferritin(ng/ml)	9.26±1.88	30±1.28	0.001
Serum iron(µmol/L)	7.83±3.68	20±1.5	0.001

Values are expressed as mean±SD**.** *

Table 3: Mean Value of Blood Indices in Different Types of BHS

Parameter	Cyanotic (N.22)	Pallid (N.16)	Mixed (N.8)	P Value*
Hemoglobin(g/dl)	9.19±0.56	8.99±1.12	9.00±0.91	0.452
Mean corpuscular volume(fL)	60.7±3.1	61.2±4.1	62.8±4.2	0.293
Total iron binding capacity(µmol/L)	84±7.3	82.3±8.1	85±5.2	0.642
Serum ferritin(ng/ml)	9.15±2.10	8.67±3.12	9.13±2.15	0.562
Serum iron(µmol/L)	7.78±3.54	8.21±2.13	7.89±3.62	0.371

ANOVA test was used*