EFFECTS OF ORAL IRON SUPPLEMENT ON BREATH-HOLDING SPELLS IN CHILDREN

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Abstract:
Objectives:
Breath holding spells are one of the most frequent and important diagnostic challenges in pediatrics. The aim of this study, conducted on pediatric patients referring to the pediatric neurology clinic in Hormozgan province, was to evaluate therapeutic effects of iron on breath holding spells.

Materials and Methods:
35 children (19 males and 16 females), aged between 3 to 60 months, with a history of breath-holding spells, were included in the trial. To obtain all relevant data a specifically designed questionnaire requiring information on sex, age, age of onset of spells, type of spells, frequency of attacks before and after treatment with oral iron supplement, and determinants of body iron stores was completed for all the patients, based on the mother’s statements. The patients were treated by an oral iron preparation for three months.

Results:
The age of onset of spells ranged between 6 to 24 months. The cyanotic type of spell was detected in 31 children, the pallid type in 3, and the mixed type in one child. There were 14 children with iron deficiency anemia and 20 children with reduced iron stores. Just one child had a normal iron profile. Complete therapeutic response was documented in 24 children, good response in 9, and poor response in one and in one child no change in frequency of spells was seen.

Conclusion:
Although no significant therapeutic difference was seen in the different response groups, it seems that iron supplement may play an important role in reducing breath holding spells in children.

Keywords: Iron, Breath holding spell, children, Iron deficiency Anemia

Introduction
Breath holding spells (BHS) are dramatic, involuntary episodes that occur in otherwise healthy children; the attacks, self-limited, are usually outgrown by school age (1). The spells are rare before the age of 6 months, peak around 2 years of age and abate by 5 year of age (2). There are two major types of BHS, the
cyanotic and the pallid type. Cyanotic BHS, the most common form is provoked by upsetting or scolding an infant, continues with a forced expiration, and is followed by apnea. There is rapid onset of generalized cyanosis and loss of consciousness that may be associated with clonic jerks and opisthotonus (2). Many studies have investigated different treatments for breath holding spells in children, with no definite therapy being documented and research continues. Earlier studies show the presence of concomitant iron deficiency in this group of patients; breath-holding episodes occur in up to 27% of children with iron-deficiency (3). Anemia, because of more rapid cerebral anoxia, exacerbates the likelihood of breath-holding episodes (3, 4). 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 (5). This study was undertaken to evaluate the efficacy of iron therapy in a group of children with BHS.

Materials & Methods:
This study is a clinical trial conducted on infants with a history of breath holding spells, referring to the Bandar Abbas Pediatric Neurology Clinic between April 1999 and April 2001. A pediatric neurologist diagnosed the subjects as having BHS. In this clinical trial, the frequency of spells before and after iron supplementation were investigated, recorded and compared.

Sex, age, age of onset of BHS, number of spells, family history, past medical history, developmental status, history of use of oral iron supplements and history of convulsions was documented; all related information was recorded in a questionnaire. Infants were categorized as cyanotic, pallid or mixed type according to criteria (2). Laboratory tests including (complete blood count, serum iron, total iron binding capacity, MCV, MCH, ferritin and transferrin saturation index (SI=serum iron/TIBC×100) were done for each patient; on the basis of these tests, patients were classified into three groups: 1) Normal subjects 2) Iron deficiency without anemia (serum ferritin <10 ng/ml, SI<12% for children under 4 years, <14% for children under 6 years, serum iron <50mg/dl and TIBC>400mg/dl) and 3) Iron deficiency anemia with Hb<10. All affected patients, regardless of iron status, were treated with oral iron (6 mg/Kg daily for 3 months). After three months of therapy, parents were questioned on frequency of spells. According to the data obtained on reduction in attacks, patients were classified into 4 groups: 1- Complete response (no spell) 2- Good response (>50% reduction in spells) 3- Poor response (10-50% reduction in spells) and 4- No response (6).

Results:
35 patients, [19 males (54.3%) and 16 females (45.7%)] were treated with oral iron supplements. Table-1 shows age of onset of spells. Most of the patients (66%) were aged between 6 to 24 months. In 5 patients there were positive family histories of BHS; 31 patients (88.5%) had the cyanotic type, 3 (8.5%) the pallid type and 1 patient (3%) had the mixed type.
14 patients (40%) had iron deficiency anemia, 20 patients (57.1%) had reduced iron stores and just one patient had a normal iron profile. Response to treatment was assessed after 3 months of treatment in 4 groups of patients and results are shown in tables 1 and 2 and in Fig 1.

Discussion
Breath holding spells (BHS), a well-known entity in infants and children has an average prevalence is about 4-5% (6). BHS is more common in males, the male to female ratio being around 1.3:1, as reported by many studies (7, 8); in our study the ratio was found to be about 1.2:1. In a study conducted in the Connecticut children’s hospital over a 9-year duration, there was no significant difference between genders (9); in this study of 95 children with BHS, median age of onset of spells was between 6-12 months with 15% presenting below the age of 6 months (9). Lombroso and Lerman found breath-holding spells in 4.6% of infants, with the majority of spells (76%) beginning in infants between 6-18 months of age (6). In the Bridge study conducted on 83 patients, age of onset of spells in 80% was under 18 months (7). In another study, 87% of patients manifested symptoms before 18 months and 100% before 22 months of life (10).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Age (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5</td>
</tr>
<tr>
<td>Absolute</td>
<td>8</td>
</tr>
<tr>
<td>Percent</td>
<td>22.9</td>
</tr>
</tbody>
</table>

Table 2: Effects of iron therapy on patients with BHS based on the severity of iron deficiency:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Iron deficiency anemia</th>
<th>Iron deficiency without anemia</th>
<th>Normal Iron Status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>frequency</td>
<td>Frequency</td>
<td>frequency</td>
<td>frequency</td>
</tr>
<tr>
<td></td>
<td>absolute</td>
<td>percent</td>
<td>absolute</td>
<td>Percent</td>
</tr>
<tr>
<td>Complete response</td>
<td>12</td>
<td>85.7</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Good response</td>
<td>2</td>
<td>14.3</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Poor response</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>No response</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>100</td>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>

Table1: Relative frequency of patients affected by breath holding spells based on age of onset of attacks:
deficiency, these spells are observed regardless of impact of family history (2,6).

In our study, 88.5% of spells were of the cyanotic, 8.5% of the pallid and 3% of the mixed type. In one large study of patients with BHS, 62% episodes were cyanotic, 19% were pallid and 19% were of the mixed type (6). This discrepancy may have been caused by misinterpretation of different investigators in distinguishing between the pallid and mixed types.

Various investigations have been conducted to determine the association between iron deficiency and BHS, resulting in several hypotheses. Holowach and Thurston were the first to identify increased frequency of BHS among iron deficient infants (4). Researchers have observed that infants with severe BHS had lower hemoglobin levels, reduced serum iron and increased total iron binding capacity vs. controls (4, 5). Breath-holding episodes have been reported in up to 27% of children with iron deficiency anemia (3). Iron plays an important role in regulation of neurologic functions; it may reduce the level of monoamine oxidase in the brain by increasing the urinary norepinephrine excretion, and since this enzyme regulates many brain activities, its deficiency may have an adverse effect on brain functions (2, 11). It also appears that supplementation of iron has an effect on improving the dysregulation of autonomic nervous system reflexes (12).

Several studies conducted investigating the effects of iron in treatment of BHS have all indicated that a strong association exists between BHS and iron deficiency (11-14). In our study, majority of children (68.6%) showed a complete response according to the standard definition and 25.7% had a good response to iron therapy; (6) these results were in agreement with published data (complete response + good response=94.3%). In a prospective study, 91 children (56 boys, 35 girls) aged between 6 and 40 months were followed for a median of 45 months. All patients were evaluated initially and during follow up for hematological indices. 63 patients were found to have iron deficiency anemia and were treated with iron (6mg/kg/day) for 3 months, after which there was a significant difference in frequency of cyanotic spells (84.1% vs. 21.4%) between children treated with iron and those who had not. In another study in Jordan, sixty-seven children with BHS were evaluated for effect of iron therapy on BHS; children divided into two groups, received iron or placebo. Those receiving iron showed significant reduction in the frequency of spells (88%), as compared with the frequency of spells (6%) in the placebo group (14).

A major difference between our trial and other studies may be the socioeconomic and cultural problems in Hormozgan province. Severe malnutrition, large families and lack of iron supplements may explain the apparently high frequency of iron deficiency in the BHS patients enrolled in this study. The prevalence of iron deficiency in Hormozgan province should however be determined in an epidemiologic study. It is noteworthy that patients with mild BHS, not basically iron deficient, had not been referred to our clinic, the only pediatric neurology clinic in the region. This prevented us from evaluating the effect of iron on nonanemic subjects with BHS.

**Conclusion:**

In conclusion, we recommend iron supplements for iron-deficient patients with BHS. Further studies with greater sample size are recommended to evaluate the impact of iron on reducing frequencies of spells and maybe even the effect of iron in subjects with normal iron status. Considering the benign nature of this disorder and availability of simple treatments such as oral iron supplements, physicians need to be cautioned against prescribing anticonvulsants for the treatment of breath holding spells.

**References:**