PATHOPHYSIOLOGY OF BREATH-HOLDING SPELLS

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Abstract

Objectives: The mechanism of breath-holding spells (BHS) is not fully understood and most probably multifactorial; So, this study was designed to clarify the pathophysiology of BHS through assessing laboratory parameters and electrocardiographic (ECG) changes which might be contributed to the occurrence of the attacks. Another aim of the study is to evaluate the differences in the pathophysiology between palilid and cyanotic types of BHS.

Methods: Seventy-six children aged 15-48 months were subjected to the study: 32 child with cyanotic BHS, 14 child with pallid BHS, and 30 healthy children as a control group. All children were subjected to: full history taking, clinical examination, laboratory work up in the form of CBC, serum iron, ferritin and zinc. Twenty-four hours ambulatory ECG (Holter) recording was also performed for all.

Results: No significant statistical difference was found between cyanotic and pallid groups regarding family history of BHS, severity and precipitating factors of the attacks. Frequent runs of respiratory sinus arrhythmia (RSA) during 24 hours ECG were significantly higher in children with BHS; the frequency of RSA was significantly correlated with the frequency (severity) of the attacks. Low serum ferritin was significantly associated with BHS groups but not correlated with the severity of the attacks.

Conclusion: Autonomic dysregulation evidenced by frequent RSA is the main cause of BHS in children and is correlated with the frequency of the attacks. Low serum ferritin is additional factor in the
pathophysiology. Both pallid and cyanotic BHS are types of the same disease sharing the same pathophysiology.

Key word: Breath-holding, reflex anoxic seizures, pallid, cyanotic, BHS.

Introduction

Breath holding spells (BHS) is a common problem in children, and particularly so in infants and is a frightening experience for the parents[1,2]. BHS is apparently due to acute cerebral hypoxia, and the child recovers spontaneously after a period of unconsciousness and sometimes opisthotonic posturing[3]. The diagnosis is based on stereotyped sequence of clinical events which begin with crying, trauma or emotional upset leading to noiseless state of expiration associated with color changes and ultimately loss of consciousness[4,5]. The spells begin most commonly during the first 12 months of life and almost always by 2 years of age. Most children outgrow those spells approximately at the age of 6 years[6]. Rarely BHS continue and replaced by vasovagal attacks[7].

Two types of BHS are present based on the color of the child during the apneic episode follow-

ing the end of prolonged expiration either pale (pallid attacks) or blue (cyanotic attacks); rarely both types may occur in the same child (mixed type)[1,4,8].

The mechanism of BHS is not fully understood and most probably multifactorial[7,9,10]. Iron deficiency anemia is claimed to be associated with the occurrence of BHS supported by the response of some cases to iron therapy; associated zinc deficiency may be additional factor[10,11]. Autonomic dysregulation that leads to alteration in cardiac function and simultaneous decrease in cerebral blood flow is important risk factor[12,13], so, electrocardiogram (ECG) should be strongly considered in any patient with BHS[14].

Objectives:

(1) To clarify the pathophysiology of breath-holding spells by assessing factors claimed to be associated with the attacks including laboratory parameters and continuous
ECG monitoring.
(2) To identify differences in the
copathophysiology between
pallid and cyanotic BHS.

Methods:
This cross-sectional study was
carried out in Pediatrics, Neurology and
Cardiology Departments of
Zagazig University Hospitals
(Egypt).

Seventy-six children aged 15-
48 months were included in the
study comprising 3 groups:
- Group I: 32 patients with cyano-
tic BHS.
- Group II: 14 patients with pal-
  lid BHS.
- Group III: 30 healthy children
  as a control group. Children
  with primary cardiac or cen-
  tral nervous system disease
  were not included as well as
  any child with uncertain his-
  tory of the type of BHS or
  suspected mixed type. Any
  child with possibility of set-
  tle were subjected to EEG
  assessment and children
  with abnormal EEG were
  also excluded. Initial basic
  ECG rhythm strip for 30 se-
  cond was done to exclude
  prolonged QT syndrome.

* All children were subjected
to:
- Full history taking including age,
gender, parental consanguinity
& thorough clinical examination.
- Detailed history of the attacks
  with stress on family history,
age of onset, triggering factors
  and severity; Severity of the at-
  tacks was assessed by determin-
  ing the average frequency of oc-
  currence:
  - Mild  →  < one attack/week
  - Moderate  →  1-3 attacks/week
  - Severe  →  >3 attacks/week
- Laboratory investigations includ-
ing RBC's count and hemoglobin
level (to assess anemia), serum
iron (by colorimetric chromazu-
ol B)(15), serum ferritin (by elec-
trochemiluminescence using
elecsys and cobas (2010) immu-
noassay analyzers)(16) and ser-
um zinc (by atomic absorption
spectrophotometer [GBC GF
3000])(17).

- Laboratory results were de-
scribed in the form of normal,
low or high according to their
reference range for each age.
- Electrocardiographic (ECG)
study: 24 hours ambulatory ECG recording was done for all children using (VX3 series E) recorders analyzed by H7000 Holter software for detection of changes in ECG during and in-between the attacks of BHS.

**Ethical considerations:** A permission was taken from the ethical committee of Zagazig University and the head of Pediatrics, Neurology and Cardiology Departments before the beginning of the study. An informed written consent was taken from the care givers of all children included in the study.

**Statistical analysis:**
Data management was done using SPSS version 14.

**Results**

Table (1): Characteristics of the studied population.

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Group I (n=32) Cyanotic BHS</th>
<th>Group II (n=14) Pallid BHS</th>
<th>Group III (n=30) Control group</th>
<th>Test of significance</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31.4±8.7</td>
<td>32.3±11.5</td>
<td>31.7±8.5</td>
<td>0.05</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>15-48</td>
<td>15-48</td>
<td>15-48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>18</td>
<td>9</td>
<td>17</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>14</td>
<td>43.7</td>
<td>5</td>
<td>0.23</td>
</tr>
<tr>
<td>Consanguineous marriage</td>
<td>+ ve</td>
<td>9</td>
<td>28.1</td>
<td>3</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>- ve</td>
<td>23</td>
<td>78.6</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Table (2): Features of BHS in cyanotic and pallid types.

<table>
<thead>
<tr>
<th>Onset of the attacks (months)</th>
<th>Group I (n=32)</th>
<th>Group II (n=14)</th>
<th>Test of significance</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.8±1.4</td>
<td>9.7±1.7</td>
<td>0.78</td>
<td>0.26</td>
</tr>
<tr>
<td>Positive family history</td>
<td>No</td>
<td>No</td>
<td>35.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>Mild</td>
<td>8</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Precipitating factors:</td>
<td>Moderate</td>
<td>13</td>
<td>40.6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>11</td>
<td>34.4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Head injury</td>
<td>6</td>
<td>18.8</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>11</td>
<td>34.4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Cry</td>
<td>24</td>
<td>75</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Fear</td>
<td>6</td>
<td>18.8</td>
<td>4</td>
</tr>
</tbody>
</table>
Table (3): Laboratory findings.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=32)</th>
<th>Group II (n=14)</th>
<th>Group III (n=30)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>No: 19, %: 59.4</td>
<td>No: 7, %: 50</td>
<td>No: 15, %: 50</td>
<td>0.66</td>
<td>0.72</td>
<td>NS</td>
</tr>
<tr>
<td>Low serum iron</td>
<td>No: 11, %: 34.4</td>
<td>No: 5, %: 35.7</td>
<td>No: 9, %: 30</td>
<td>0.2</td>
<td>0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Low serum ferritin</td>
<td>No: 17, %: 53.1</td>
<td>No: 8, %: 57.1</td>
<td>No: 7, %: 23.3</td>
<td>7.23</td>
<td>0.026**</td>
<td>Sig.</td>
</tr>
<tr>
<td>Low serum zinc</td>
<td>No: 8, %: 25</td>
<td>No: 6, %: 42.9</td>
<td>No: 6, %: 20</td>
<td>2.62</td>
<td>0.26</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table (4): Frequency of respiratory sinus arrhythmia (RSA) in 24 hours ECG monitoring among different groups**.

<table>
<thead>
<tr>
<th>RSA</th>
<th>Group I (n=32)</th>
<th>Group II (n=14)</th>
<th>Group III (n=30)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Few (&lt;5/24 hrs)</td>
<td>No: 5, %: 15.6</td>
<td>No: 2, %: 14.3</td>
<td>No: 21, %: 70</td>
<td>30.72</td>
<td>0.001*</td>
<td>Sig.</td>
</tr>
<tr>
<td>Moderate (5-10/24 hrs)</td>
<td>No: 19, %: 59.4</td>
<td>No: 4, %: 28.6</td>
<td>No: 7, %: 23.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent (&gt;10/24 hrs)</td>
<td>No: 8, %: 25</td>
<td>No: 8, %: 57.1</td>
<td>No: 2, %: 6.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** Significant run of RSA were found in group I and group II when compared with group III.

Table (5): ECG changes during the attack.*

<table>
<thead>
<tr>
<th>ECG findings</th>
<th>Group I (n = 7)</th>
<th>Group II (n = 3)</th>
<th>Total (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSA</td>
<td>3</td>
<td>1</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>1</td>
<td>-</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>1</td>
<td>1</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Asystole</td>
<td>-</td>
<td>1</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Prolonged Q-T</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Only 10 cases experienced a breath-holding attack during 24 hours ECG recording.

Table (6): Factors affecting severity of BHS:

6 (5): Relation between severity of the attacks and frequency of RSA in 24 hours ECG recording:

<table>
<thead>
<tr>
<th>RSA in 24 hours ECG monitoring</th>
<th>Few (&lt;5)</th>
<th>Moderate (5-10)</th>
<th>Frequent (&gt;10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Severity of the attacks:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>5</td>
<td>35.7</td>
<td>5</td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>64.3</td>
<td>9</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.00</td>
<td>8</td>
</tr>
</tbody>
</table>

\( \chi^2 = 14.08 \) \[ P = 0.007^* \] Significant

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6(b): Relation between severity of the attacks and low serum ferritin:

<table>
<thead>
<tr>
<th>Severity of the attacks:</th>
<th>Low serum ferritin</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>- Mild</td>
<td>7</td>
<td>33.3</td>
<td>7</td>
</tr>
<tr>
<td>- Moderate</td>
<td>10</td>
<td>47.6</td>
<td>8</td>
</tr>
<tr>
<td>- Severe</td>
<td>4</td>
<td>19.1</td>
<td>10</td>
</tr>
</tbody>
</table>

$X^2 = 2.46$  \hspace{1cm} $P = 0.29$  \hspace{1cm} NS

6(c): Correlation between severity of the attacks and other parameters.

<table>
<thead>
<tr>
<th></th>
<th>$r$</th>
<th>$P$</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 24 hours ECG recording</td>
<td>0.49</td>
<td>&lt;0.001*</td>
<td>NS</td>
</tr>
<tr>
<td>- Low serum ferritin</td>
<td>0.17</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 1: Respiratory Sinus Arrhythmia

Figure 2: Sinus tachycardia
Discussion

The pathophysologic mechanism of BHS remain controversial and no study had identified the exact etiology of the attacks. The present study included 46 children with BHS and 30 healthy children as a control group. The control group were age and gender matched to children with BHS with no statistical difference regarding consanguineous parental marriage (Table 1). The average age of onset of BHS was 9.8 and 9.7 months for cyanotic and pallid groups respectively (Table 2) which is not far from other studies which stated that most cases of BHS are manifested before the first birthday. Similar attacks of BHS in first degree relative (positive family history) were present in about one-third of cases of BHS (31.3-35.7%) (Table 3), which is consistent with multiple studies. DiMario, 1997 explained this considerable positive family history by the autosomal dominant inheritance with incomplete penetrance of BHS; However, as no specific gene had been identified for inheritance of BHS, the presence of family history may be related to the inheritance of the cause of BHS rather than BHS themselves.

Multiple precipitating factors were associated with the attacks (Table 2), of which, cry was the commonest event preceding cyanotic (75%) and pallid (50%) BHS; However, no single factor showed statistical significant association with either type of BHS.

Children with BHS showed non significant statistical difference
regarding anemia and low serum iron when compared with the control group (Table 3). Multiple studies had reported a high incidence of iron deficiency anemia in children suffering from BHS\(^6,9,11,12,21\). No other types of anemia were claimed to be associated with BHS in any study, so, it is obvious that the problem is related to "iron" and not to "anemia"; as body iron is better assessed by serum ferritin rather than serum iron which is affected by many factors\(^{25}\), our results still prove the role of iron deficiency in BHS pathogenesis alike other studies in the literature.

Low serum zinc was not associated with increased risk of BHS (Table 3). A single study performed by Gencgonul, et al in Turkey (2002) had suggested a role of zinc deficiency in the pathogenesis of BHS\(^{11}\); however, Gencgonul study only suggested a role of zinc deficiency in association with iron deficiency-and not zinc alone-in the pathogenesis of BHS; as zinc deficiency is a common association in iron deficiency anemia our results regarding this issue seem logic.

24 hours ECG monitoring was done for all children subjected to our study. Respiratory sinus arrhythmia (RSA) was the only significant finding in 24 hours ECG monitoring in cases with BHS; most cases of either cyanotic or pallid BHS showed higher runs of respiratory sinus arrhythmia compared with the control group (Table 4). Respiratory sinus arrhythmia was identified if PP intervals were present that exceeded the previous PP by more than 10\(^\%\)^{28}.

A study of DiMario, et al. 1998 had suggested the same association with pallid and not with cyanotic BHS\(^{22}\); the difference between the results of Di-Mario, et al and ours may be attributed to the fewer number of cases in their study (46 versus 76); also, the 24 hours ECG recording performed to our studied children is probably more accurate than Di-Mario, et al., study who performed a 5-min, ordinary ECG. In fact our study may be the only study that performed a Holter's monitoring for children with BHS and -to our knowledge- all published reviews of ECG interpretation in BHS de-
pend on ordinary short ECG strips.

Only 10 cases experienced an attack of BHS during 24 hours ECG recording and revealed RSA and sinus tachycardia to be the most common findings (Table 5), although statistical analysis could not be performed due to small sample size. Among the ten patients who experienced an attack during Holter ECG monitoring, no data of prolonged QT interval was obtained. Cases with persistent prolonged Q-T were not included in our study according to our exclusion criteria as prolonged Q-T syndrome associated syncope is a serious condition which may need interference up to pacemaker implantation[4,7,10,19,23]. On the other side, Akalin et al. (2004) had linked the BHS with increased QT dispersion in ECG[12] but their study didn’t exclude patients of prolonged QT syndrome which may extend their study outside the scope of BHS.

Our study revealed a significant correlation between the frequency of RSA in Holter monitoring and the frequency of BHS obtained from parental history (Table 6), which is an important evidence indicating the basic role of cardiac rhythm abnormality in the pathophysiology of BHS and strengthen the results of other studies which concluded that autonomic dysregulation is the primary abnormality in children with BHS that leads to defective cerebral blood flow followed by the sequence of events observed[12,13,22]. On the other side, low serum ferritin despite being significantly associated with BHS but was not correlated with the frequency of the attacks (Table 6) which may indicate that iron deficiency assessed by low serum ferritin is not the primary pathophysiology of BHS but an additional factor contributed to the etiology. The association of iron deficiency and BHS may be related to:

1) Iron deficiency is usually associated with irritability and excess crying[5,6] which is the commonest triggering factor for the attacks (Table 2).

2) Iron deficiency may lead to catecolamine disruption and subsequent autonomic dysregula-
tion(6,24) and this was proved by Orri et al.(2002) who reported an improvement of autonomic dysregulation after iron supply in three children with BHS(24).

Lastly, among all clinical, laboratory and ECG data obtained from the present study no significant difference was found between cyanotic and pallid BHS which indicates that both types of BHS share the same pathophysiologic mechanism i.e. pallid and cyanotic BHS are "one" and not "two" diseases. This conclusion is not in agreement with some studies which postulated that the pathophysiology of pallid and cyanotic spells is not the same(7,14,22). Again, the use of 24 hours ECG recording in our study which is more accurate than ordinary ECG may add more confidence to our results. Moreover, the presence of a considerable percentage of children who experienced both types of BHS i.e mixed type, may indicate that the pathogenesis of both types may be similar.

Differences between cyanotic and pallid BHS regarding sequence of events and color changes might be explained by the dominant autonomic dysregulatory component which may be sympathetic overactivity in cyanotic and parasympathetic in pallid BHS(4).

Conclusion
Both pallid and cyanotic BHS are types of the same disease sharing the same pathophysiologic mechanisms. The main etiology of BHS is autonomic dysregulation manifested by frequent respiratory sinus arrhythmia in ECG recording; this heart rate disturbance was positively correlated with the frequency of breath-holding spells. Defective body iron assessed by low serum ferritin is an additional factor which may contribute to the etiology of BHS to lesser extent as low serum ferritin was not correlated with the frequency of the attacks. Positive family history was present in one-third of cases but it is not known whether this family history is an indicator of inheritance of BHS or inheritance of autonomic dysregulation responsible for the attacks.

References
1. Subbarayan A., Ganesan


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