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Clinico-laboratory profile of breath-holding spells in children in Sohag University Hospital, Upper Egypt

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Abstract

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. Breath-holding spells are usually caused by either a change in the usual breathing pattern or a slowing of the heart rate. In some children, BHSs may be related to iron deficiency anemia. The aim of the work was to study the clinical and laboratory profile of BPHs in children presented to the Neuropediatric Clinic at Sohag University Hospital.

Methods: An observational prospective study was done at Sohag University Hospital over a period of one year on children diagnosed as having BHSs by clinical history and laboratory evaluation, including complete blood count (CBC), serum iron, serum ferritin, total iron binding capacity, and Electroencephalography (EEG).

Results: During the period of study (one year), we reviewed data of 32 children who had been diagnosed as having BHSs. We found that cyanotic spells (71.88%) predominated over pallid spells. There were positive family histories (31.25%) and consanguinity (53.135) in the studied patients. We found a high incidence of iron deficiency anemia (62.5%) in association with BHS. Abnormal EEGs were found in (65.63%) of studied children.

Conclusion: BHS is a common, important problem associated with iron deficiency anemia, which is, in turn, a common nutritional problem in our country.

Keywords: breath holding spells, cyanotic spells, pallid spells, iron deficiency anemia

1. Introduction

A breath-holding spell is an involuntary pause in breathing, sometimes accompanied by loss of consciousness. It usually occurs in response to an upsetting or surprising situation (1). Breath-holding spells occur in 5% of otherwise healthy children. They can occur in children between six months and six years of age, but they vary in how often they occur and how severe they are. Some children have them once a year, while others may have several spells within one day (2). Breath-holding spells usually are caused by either a change in the usual breathing pattern or a slowing of the heart rate. These reactions may be brought on by pain or by strong emotions, such as fear or frustration. In some children, BHS may be related to iron deficiency anemia, a condition in which the body does not produce a normal number of red blood cells (3). There are two clinical types of breath holding spells, i.e., cyanotic

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(blue) and pallid (pale) spells. BHS should be differentiated from epilepsy, congenital heart disease, vasovagal syncope, prolonged QT interval, and hyperactive carotid sinus. BHS is a clinical diagnosis. EEGs are not needed for diagnosis, but they are done sometimes, especially when the semiology of the disease is unclear. The interictal EEG is normal. If a breath-holding spell is captured on an EEG, initially there is a slowing of the EEG's background. As the child become bradycardic, further slowing and suppression of the EEG's background become apparent at the time subsequent or concomitant asystole. As the child regains consciousness, there is a rapid return of the EEG's background to normal (4). It is not known exactly how ID causes breath-holding spells, but it has been proposed that iron has a role in catecholamine metabolism and in the functioning of enzymes and neurotransmitters in the central nervous system. Iron has an important role in the regulation of neurologic functions, and it may reduce the level of monoamine oxidase in the brain and since this enzyme regulates many brain activities, a deficiency may have adverse effects on the brain's functions (5).

2. Material and Methods

This study was a descriptive, hospital-based study done in the Neuropediatric Outpatient Clinic at Sohag University Hospital over a one-year period. 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 pediatrician 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. The spells were classified into cyanotic and pallid spells. The study was approved by the Research Ethics Committee at Sohag Faculty of Medicine, and verbal consent was obtained from the children's guardians. The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. 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. The following laboratory investigations were conducted for the studied group: 1- complete blood count (CBC) was done by Abbott Cell Dyn Ruby analyzer, Abbott Diagnostic, Abbott Park, IL, USA; 2- 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; electroencephalogram (EEG) was done for all eligible patients. Clinical, laboratory, and EEG data were entered into the SPSS software package, version 10, for descriptive statistics. The results of the study were expressed as mean with standard deviation and range for continuous variables and as percentages for discrete variables.

3. Results

During the period of study (one year), 32 children were diagnosed with breath holding spells by clinical and laboratory evaluation in the Neuropediatric Outpatients' Clinic at Sohag University Hospital. The mean age was 19.95 months with an age range from four months to four years. Concerning the gender distribution, 19 of the children were males (59%), and 13 were females (41%) (Table 1).

Table 1. Characteristics of the studied children

Characteristics		Summary statistics
Age (months); Mean ± SD		19.95 ± 12.17
Gender; n (%)	Female	13 (40.63)
	Male	19 (59.38)
Type of HBS; n (%)	Cyanotic	23 (71.88)
	Pallide	9 (28.13)
Provocating factors	Anger	1 (3.13)
	Anger & crying	4 (12.5)
	Crying	27 (84.38)
Duration in minutes; Mean ± SD		3.74 ± 3.34

Concerning the type of BHS of the studied children, 23 of them had cyanotic BHS (71.88%), and nine of them had pallide BHS (28.13%). Provocating factors were crying in 27 patients (84.38%), anger and crying in four patients (12.50%), and anger only in one patient (3.13%). The duration of the spells ranged from 0.17 to 15 minutes (mean 3.74 minutes) (Table 1). Delayed motor milestones were noted in six patients (18.75%). Delayed speech was noted in 21 patients (34.38%) (Table 2). A family history of similar condition was present in 10 patients (31.25%) and a

history of consanguinity was present in 17 patients (53.13%) (Table 2). Iron deficiency anemia was observed in 20 patients (62.5%) as detected by low hemoglobin concentration (Hb), low hematocrite value (HCT), low mean corpuscular volume (MCV), low mean corpuscular hemoglobin (MCH), low serum iron, low serum ferritin, and high total iron binding capacity (TIBC). The mean Hb concentration was 10.24 g/dl, and it ranged from 8.5 to 12.5 g/dl. Mean hematocrite value was 33.40, and it ranged from 28 to 39.6. Mean MCV was 70.09 fl, and the range was from 51.80 to 86.40 fl. The mean MCH was 21.72 pg/ml, and it ranged from 14.90 to 28.90 pg/ml. Mean serum ferritin was 12.27ng/ml, and it ranged from 2.21 to 77.40 ng/ml. Mean serum iron was 52.75 µg/dL, and it ranged from 21 to 100 µg/dL. Mean iron binding capacity was 340.47 µg/dL, and it ranged from 200 to 440 µg/dL (Table 3). EEG was normal in 11 patients (34.38%) and abnormal in 21 patients (65.63%). Abnormalities that were detected were focal epileptic discharge in 20 patients (62.5%) and generalized cerebral dysrhythemia in one patient (3.13%).

Table 2. Developmental history and family history of the studied patients

Characteristics		Summary statistics
Language development; n (%)	Normal	11 (65.63)
	Delayed	21 (34.38)
Motor development; n (%)	Normal	26 (81.25)
	Delayed	6 (18.75)
Family history; n (%)	No	22 (68.75)
	Yes	10 (31.25)
Consanguinity	No	15 (46.88)
	Yes	17 (53.13)

Table 3. Laboratory investigations of studied children

Test	Mean ± SD
HB	10.24 ± 1.13
HCT	33.4 ± 3.48
MCV	70.09 ± 7.43
MCH	21.72 ± 3.23
Serum iron	52.75 ± 34.43
Serum ferritin	12.72 ± 15.32
Iron binding capacity	340.47 ± 75.42

4. Discussion

In this study, we performed a clinical and laboratory analysis of the data of 32 children that had BHS. We focused on determining the type of BHS and its relationship with iron deficiency anemia, with special consideration for the presence of abnormal EEG findings and the analysis of neurodevelopmental status. Diagnosis of BHS was made clinically by a pediatrician based on the history given by the mothers and personal observation of the spells. Spells were defined as the child's breathing stopping during expiration after a deep inspiration while crying. Anemia was evaluated by CBC, serum ferritin, serum iron, and total iron binding capacity (TIBC). The mean age of the studied patients was 19.95 months with an age range from four months to four years, which was in good agreement with several other studies (4, 6-8). However, in a study done by Olsen (9), the age onset range was between six and 24 months, but cases with onset in the neonatal period and as late as 48 months have been described. In a study by Tonekaboni et al. (10), the ages of most of the patients (66%) were between six and 24 months. In a study by Subbarayan et al. (11), 40% of the patients had the onset of BHS within first six months of life, 23.3% of them had onset between seven and 12 months of age, and 26.7% had their first experience between 13 and 24 months. The onset of BHS after two years of age constituted only 10%. Concerning the gender of the studied children, 59% were males, and 41% were females. BHS were observed more frequently in boys than in girls, and this also has been reported in other studies (6, 12, 13). Concerning the type of BHS of the children that were studied, cyanotic BHS was detected in 71.88%, and these results also were in good agreement with other studies (7, 14). However, these results were lower than that of some other studies, e.g., Anil et al. (13) (94%), Bhatia et al. (15) (96%), and Tonekaboni et al. (10) (88.5%). However, in a study done by Zehetner et al. (16), 49/95 (51%) had cyanotic spells, 27/95 (29%) only had pallid spells, and 19/95 (20%) had both types with one predominating over the other. A provocating factor was noticed in all patients. Crying was the most common triggering factor (84.38%), similar to the study of Bhatia et al. (15) in which anger and frustration were the common triggering factors in 90.0% of the

cases. In Ashrafi et al.'s study (7), anger and pain were the common triggering factors (65.1%). Other studies reported that BHS was provoked by frustration, anger, fear, or pain, i.e., Goraya et al. (17), Daoud et al. (18), and Evans Owen (19). Consanguinity was present in 53.13% of patients, and these results were much higher than those of Ashrafi et al.'s study (7) (30%) or Hilal Mocan et al.'s study (20) (8.7%). This can be explained by the fact that relatives often marry in the high ranges in our country, especially in Upper Egypt where our study was conducted. In a study done by Daoud et al. (18), positive consanguinity was detected in 70% of the studied cases. Concerning family history, a positive family history was present in 31.25%, which was in agreement with many several similar studies, e.g., Paul et al. (14) (35%), Zehetner et al. (16) (30%), and Bhat et al. (12) (34%) . However, it was less than those of Ashrafi et al.'s (7) study (51.2%) and Daoud et al.'s study (18) (47.5%). However, in the study done by Handan Gençgonül et al. (8), positive family history was detected in 22% of the studied cases. Family pedigree analysis of children with BHS suggested an autosomal dominant pattern of inheritance with reduced penetration (7). In a study conducted in the Hartford Center in the USA, family pedigrees of 57 proband were examined, of which 27% of proband parents and 21% of proband siblings had severe current or prior BHS.

Iron deficiency anemia was observed in 62.5% of the studied patients, as detected by low Hb, low HCT, low MCV, low MCH, low serum iron, low serum ferritin, and high total iron binding capacity (TIBC), and these results were in good agreement with those of Tonekaboni et al. (10) (68.6%) and Hudagolu et al. (4) (62.5%). The mechanism that links BHS and IDA is not clear. It has been postulated that decreased oxygen concentrations in the lungs (1) and in the brain (15) in IDA caused BHS. It has been proposed that iron has an important role in the regulation of the neurologic function, it may reduce the monoamine oxidase in the brain by increasing the urinary norepinephrine, and since this enzyme regulates many brain activities, its deficiency may have an adverse effect on brain function (5). This result was slightly higher than that of Ashrafi et al. (7) (53%) and that of Handan Gençgonül et al. (8) (56%). This can be explained by low socioeconomic status and bad nutritional habits, especially at time of weaning, and the lack of iron supplements. But our results were lower than those of Hilal Mocan et al. (20) (69.2%). This can be explained by the marked improvement of formula production in the last few years. Most types of formula are enriched with iron and vitamins. As reported previously, a low serum ferritin may be the earliest laboratory finding of IDA (18). Concerning the EEG findings, the EEGs were normal in (34.38%) of the studied patients and abnormal in (65.63%) of them. The abnormalities that were detected were focal mild epileptic discharge in 20 patients (62.5%) and generalized cerebral dysrhythemia in one patient (3.13%). In a study by Hudagolu et al. (4), 37.5% had epileptogenic EEG abnormalities, 12.5% had benign EEG variants, and (50%) had completely normal EEGs. The focal epileptiform discharge that was detected in the patients originated from the centrotemporal and centroparietal regions. There was no statistically significant difference between patients with epileptiform EEG changes and patients with normal EEGs. In Hilal Mocan et al.'s study, abnormal EEGs were detected in 20% of the studied patients in the form of slight or moderate EEG abnormalities (20). In the study done by Ashrafi et al., all of the patients had normal EEGs (7).

5. Conclusions

BHS is a common and important problem that is encountered in the Neuropediatric Clinic, and the cyanotic type was more common than the pallid type. BHS commonly was associated with iron deficiency anemia, which, in turn, is a common nutritional problem in our country. The EEGs showed significant abnormalities in this disorder.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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