INTRODUCTION

Breath-holding spells (BHS) are among the common benign paroxysmal non-epileptic disorders occurring in healthy otherwise normal children.\(^1\) The prevalence has been estimated between 0.1% and 4.6% in the general population.\(^2,3\)

The diagnosis is usually made by description or observation of typical attacks which are characterized by a sequence of clinical events, beginning with a provocation such as minor trauma or emotional upset, followed by a noiseless state of expiration accompanied by color change in the skin as paleness or cyanosis, and finally loss of consciousness and postural tone. Two types are recognized clinically as pallid and cyanotic on the basis of skin color change observed during spells, the former being more common.\(^4\) Although BHS are often very stressful for the parents observing
an episode, these attacks are mostly self limited, and spontaneous resolution without sequelae is anticipated in nearly all cases by school age. On the other hand, these spells may rarely be an initial symptom of long QT syndromes or paroxysmal cardiac rhythm abnormalities in some patients. Therefore performance of an electrocardiogram to evaluate for prolonged QT syndrome is strongly considered. Severe pallid spells and less commonly, cyanotic spells may be complicated by myoclonic jerks and generalized seizures, following the crying period. Iron deficiency anemia (IDA) may be a factor contributing to BHS by reducing the oxygenation of CNS. Correction of iron deficiency may eliminate these spells.

The aim of the present study was to evaluate the value of neurologic and cardiologic assessment and also to determine the frequency of iron deficiency anemia in children with BHS in daily clinical practice.

**METHODS**

A total of 166 children diagnosed with BHS at the child neurology out-patient clinics at Dr. Behcet Uz Children’s Hospital between 2011 and 2013 were included into the study. Children with a primary neurologic, cardiac or hematologic disease were excluded. The study protocol was approved by the ethical committee of the hospital. Details of the children with BHS and controls are presented in Table-I.

Data from these files were collected, including information on age at admission and at onset of symptoms, sex, perinatal problems (i.e. asphyxia, hypoglycemia, infection, and respiratory distress), developmental history, blood tests, electroencephalography (EEG), electrocardiography (ECG) and echocardiography results and family history among first degree relatives regarding BHS, epilepsy and febrile convulsions. The spells were classified into cyanotic, pallid or mixed types according to the skin color change during episodes. Data on BHS included the type, severity and frequency of attacks, and total number of spells. Two hundred children with a diagnosis of simple febrile convulsions in the similar age and sex group followed-up in the same child neurology out-patient clinic served as controls.

**Table-I: Demographic and clinical characteristics for children with breath holding spells and controls with febrile convulsions.**

| Parameters                                      | BHS n = 165, (%) | Controls n = 200, (%) | p value |
|--------------------------------------------------|------------------|-----------------------|---------|
| Sex                                              |                  |                       |         |
| Female                                           | 75 (45.5)        | 83 (41.5)             | 0.448   |
| Male                                             | 90 (54.5)        | 117 (58.5)            |         |
| Median Age at onset, months                       | 9                | 14                    |         |
| Mean Age at onset, months, ±S.D., (range)        | 10.6±9.6 (0-50)  | 11.9±4.2 (2-29)       | 0.099   |
| <6 month                                         | 64 (38.8)        | 17 (8.5)              |         |
| 7-12 months                                      | 51 (30.9)        | 101 (50.5)            |         |
| 12-24 months                                     | 39 (23.6)        | 81 (40.5)             |         |
| >24 months                                       | 11 (6.7)         | 1 (0.5)               |         |
| Median Age at diagnosis, months                  | 17               | 20                    |         |
| Age at diagnosis, months, ±S.D., (range)         | 21.3±14.69 (1-68)| 21.6±10.55 (3-60)     | 0.817   |
| <6 month                                         | 17 (10.3)        | 6 (3.0)               | 0.014   |
| 7-12 months                                      | 26 (15.8)        | 26 (13.0)             |         |
| 12-24 months                                     | 70 (42.4)        | 108 (54.0)            |         |
| >24 months                                       | 52 (31.5)        | 60 (30.0)             |         |
| Mean interval to diagnosis                       |                  |                       |         |
| Disease duration, months, ±S.D., (range)         | 11.2±14.25 (1-90)|                       |         |
| Perinatal problems 165                          | 16 (9.7)         | 24 (12.2)             | 0.452   |
| Prematurity                                      | 7 (4.2)          | 8 (4.1)               | 0.750   |
| Perinatal asphyxia                               | 7 (4.2)          | 11 (5.6)              |         |
| SGA                                              | 2 (1.2)          | 5 (2.5)               |         |
| Neonatal convulsions                             | 1 (0.6)          | 0                     | 0.274   |
| Delayed psychomotor development                  | 2 (1.2)          | 2 (1.0)               | 0.858   |
| Parental consanguinity                           | 22 (13.4)        | 26 (13.3)             | 0.967   |
| BHS in first degree relatives                    | 22 (13.3)        |                       |         |
| Epilepsy in first degree relatives               | 20 (12.1)        | 29 (14.8)             | 0.460   |
| Febrile convulsion in first degree relatives     | 3 (1.8)          | 42 (21.4)             |         |

BHS = breath-holding spells, S.D. = standard deviation, SGA = small for gestational age.
Hemoglobin concentration, mean corpuscular volume (MCV), serum iron (SI), and total iron binding capacity (TIBC) were measured at the time of the diagnosis. Electrocardiography and echocardiography in all children and EEG in selected cases were carried out for exclusion of organic disease. The QT interval was accepted as the interval between the beginning of the QRS complex and the end of the T wave. The Bazett formula\textsuperscript{9} was used for calculation of corrected QT (QTc), which was recorded in milliseconds (ms), or on a normal–abnormal scale on the charts of the patients. The abnormalities on EEG were divided into background abnormalities without epileptic activity and epileptic abnormalities when it is clearly epileptic.

In order to study the relation of BHS with IDA, complete blood count and SI, TIBC, and ferritin levels were measured at the time of the diagnosis. The diagnosis of IDA was made according to the age-specific criteria for the diagnosis of anemia.\textsuperscript{10} Patients with IDA were treated with ferrous sulphate solution 6 mg/kg/day orally for three months.

**Statistics:** All data were descriptively analysed with SPSS 20.0, Chicago, IL, USA. For qualitative data, Pearson Chi-square test was employed. For comparison of quantitative data of two groups, Student’s \textit{t} test and Mann-Whitney U-tests were used for parametric and nonparametric data respectively. P <0.05 values were considered significant.

**RESULTS**

In one child with a typical BHS history and a normal initial EEG, the frequency and severity of spells increased over time and the attacks began to occur without any provocation. After obtaining a second EEG which revealed clearly epileptic activity, a diagnosis of epilepsy was made and the patient was excluded from the rest of the analysis. A total of 165 children with BHS and 200 children with febrile convulsions as a control group were studied. Demographic and clinical characteristics of the patients and controls are shown in Table-I and characteristics of BHS are presented in Table-II.

Results of EEG, ECHO and EEC investigations of children with clinical diagnosis of BHS are shown in Table-III. Eighteen patients (25.7\%) had EEG abnormalities without epileptic activity and 4 (5.7\%) patients had EEG abnormalities with epileptic activity. Echocardiography revealed patent foramen ovale in two patients, pulmonary stenosis in one patient and mitral valve prolapsus in one patient. Electrocardiography was normal in all patients. Corrected QT intervals were recorded in msec in 62 patients, and the mean QTc interval was 397±19.8 msec. In the remainder, QTc interval was recorded as normal. Mean QTc interval was not significantly different between patients with cyanotic and pallid BHS, between the patients with simple and complicated BHS, and also between the patients with and without iron deficiency anemia.

Table-II: Characteristics of breath holding spells.

| Parameters                  | \(n = 165\), (%) |
|-----------------------------|-----------------|
| Duration of spell, seconds  | 41.20±25.38 (10-180) |
| Type of BHSs                |                 |
| Cyanotic                    | 148 (89.7)      |
| Pallid                      | 11 (6.6)        |
| Mixed                       | 6 (3.6)         |
| Severity of spells          |                 |
| Simple                      | 78 (47.3)       |
| Complicated                 | 87 (52.7)       |
| Frequency of spells         |                 |
| >30 per month               | 22 (13.3)       |
| 10-30 per month             | 19 (11.5)       |
| <10 per month               | 124 (75.2)      |

BHS = breath-holding spells

Table-III: Results of EEG, echocardiography and electrocardiography in the patients with breath holding spells and a control with febrile convulsions.

| BHS n/Na, (%)          | Controls n/Na, (%) | \(p\) value |
|------------------------|--------------------|-------------|
| Abnormal electroencephalography | 18/70 (25.7) | 40/142 (28.2) | 0.706 |
| Background abnormalities | 14/70 (20.0) | 25/142 (17.6) | 0.493 |
| Epileptic abnormalities | 4/70 (5.7) | 15/142 (10.6) |
| Abnormal electrocardiography | 0/84 |              | 0.653 |
| QTc, ms, ±S.D., (range) n = 62 | 397±19.8 (350-430) | 5/97 (5.1) | 0.10 |
| Patent foramen ovale     | 3/97 (3.1)        |             |      |
| Pulmonary stenosis       | 1/97 (1.0)        |             |      |
| Mitral valve prolapsus   | 1/97 (1.0)        |             |      |

BHS = breath-holding spells; ms = millisecond; QTc = corrected QT; S.D. = standard deviation

\(p\) value

a Number of patients with outcome variable/total number of patients.
Table IV: Mean values of blood indexes in the patients with breath holding spells and a control group with febrile convulsions.

|                      | BHS n/Na, (%) | Controls n/Na, (%) | p value |
|----------------------|---------------|--------------------|---------|
| Hemoglobin (mg/dl), ±S.D., (range) | 11.08±1.20 (6.4-13.6) | 11.53±0.99 | 0.001   |
| Frequency of low Hb, (%) | 60/145 (41.4) | 32/134 (23.9) | 0.002   |
| MCV (fl), ±S.D., (range) | 75.74±7.60 (50-89) | 79.26±5.50 |         |
| Frequency of low MCV, (%) | 46/145±31.7 | 19/134 (14.2) | 0.001   |
| Iron (µg/dl), ±S.D., (range) | 50.00±28.18 (7-122) | |         |
| Frequency of low iron, (%) | 32/115 (27.8) | |         |
| Total iron binding capacity, ±S.D., (range) | 377.5±57.2 (185-506) | |         |
| Ferritin (µg/L), ±S.D., (range) | 28.06±26.32 (1-149) | |         |
| Frequency of low ferritin (%) | 11/104 (10.6) | |         |
| Iron deficiency anemia (%) | 69/144 (47.9) | 40/134 (29.9) | 0.002   |

DISCUSSION

Breath-holding spells represent an age-limited disorder. It usually begin between the ages of 6 and 24 months of life, peaking in frequency by around 2 to 3 years, and 90% or more of patients have their initial spells by age 2 years. It may begin as early as during neonatal period, and almost never after the age of 5 years. About half of the children stops experiencing spells by age 4 years, and almost all by age 6 years, beyond which their occurrence is extremely uncommon. In accordance with previous reports, we found that the mean age of occurrence of BHS was 10.6 months in our series. The mean interval between the onset of spells and admittance to physician was 11.2 months. Although statistically not significant, this interval was longer in patients with a family history of BHS. In consistent with previous studies we found a higher

Table V: Comparisons of mean values of blood indexes and corrected QT intervals between various groups of patients with breath holding spells.

|                      | Patients without IDA | Patients with IDA | p value |
|----------------------|----------------------|-------------------|---------|
| Hemoglobin (mg/dl), ±S.D. | 11.9±0.61 | 10.1±0.98 | 0.730   |
| MCV (fl), ±S.D. | 79.3±3.73 | 71.9±7.89 | 0.001   |
| Iron, (µg/dl), ±S.D. | 57.8±25.3 | 40.0±27.8 | 0.426   |
| Total iron binding capacity, ±S.D. | 364±52.5 | 389±59.1 | 0.789   |
| Ferritin, (µg/L), ±S.D. | 32.0±28.8 | 22.5±21.4 | 0.568   |
| Iron deficiency anemia (%) | 397±20.1 | 396±19.7 | 0.422   |
| QTc (ms), ±S.D. | 64/130 (49.2) | 5/15 (33.3) | 0.698   |

BHS = breath-holding spells; S.D. = standard deviation; ms = millisecond; QTc = corrected QT; MCV = mean corpuscular volume.
incidence of BHS in males compared to females with a ratio of 1.2:1. As reported previously there were no significant differences in perinatal data including perinatal asphyxia, premature or SGA birth, and neonatal convulsions when comparing the patients with BHS to the control group.

A genetic causative factor may be responsible for the disease, and autosomal-dominant inheritance is suggested. A positive family history of the disease, and autosomal-dominant inheritance may affect QT interval. Lengthening of the QT interval either. However we cannot suggest that it is unnecessary to obtain ECG in the assessment of a child with BHS, since previous reports draw attention to the importance of performing an ECG, at least in children with pallid BSH, in order to identify prolonged QT-syndrome or other cardiac arrhythmia. One of these studies investigating long term prognosis for children with BHS has reported that a patient suddenly died due to ECG-verified Wolf-Parkinson-White block with a short PQ-interval, slightly broadened QRS-complexes and delta waves. ECG had not been performed during the time the patient was first admitted to hospital for BHS. Therefore; the persistence of spells into late childhood should be accepted as an alarming sign to search an underlying cardiac disorder.

Occasionally, patients may experience a seizure-like activity, a true epilepsy or even status epilepticus following either a cyanotic or pallid BHS. In a previous study, 95 children with BHS were followed prospectively, and 15 of them were found to have hypoxic convulsions. In our series, an infant with an initial history of typical cyanotic BHS and a normal EEG, was subsequently diagnosed with epilepsy. In addition, 4 patients had vertex spikes on their interictal EEGs and two of them experienced convulsive seizures following anoxic periods. Iron therapy ablated spells in one patient and decreased considerably in the other. Thus it appears imperative to rule out other causes of loss of consciousness and EEG investigation appears useful in patients with BHS, when the pattern of attacks changes over time in breath-holders.

Parents are under a great degree of emotional stress of the thought of danger of death during the spells. Physicians; on the other hand, refer these children to pediatric neurology and pediatric cardiology clinics because of the fear of missing an underlying serious cardiac or neurological disorder. However none of the patients in our series had any relevant cardiac pathology and epilepsy diagnosis was made in only one patient who had an initial diagnosis of BHS.

Treatment of BHS consists mostly of providing reassurance to the parents and attempting behavioural modification. Besides iron treatment has been shown to be effective. An association between anemia and BHS has been demonstrated previously. It has been demonstrated that children with BHS had significantly lower hemoglobin concentrations than those of controls, and from 65% to 69% of patients with BHS had IDA. Similarly, 69 (47.9%) patients had IDA in our series, and Hb and MCV indices were significantly lower when compared with controls with febrile convulsions.
In conclusion, referral of children with a clinical diagnosis of BHS to pediatric neurology or cardiology clinics is unnecessary, and routine electroencephalography and echocardiography are not appropriate investigations in initial evaluation of patients with BHS.

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Unsal Yilmaz, Tuba Sevim Yilmaz, Tanju Celik, Onder Doksoz, Gulcin Akinci had primary responsibility for protocol development, patient screening, enrolment, data analysis and writing the manuscript. Timur Mese supervised the design and execution of the study, performed the final data analyses.